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Impact of occupational pesticide exposure assessment method on risk estimates for prostate cancer, non-Hodgkin's lymphoma and Parkinson's disease: results of three meta-analyses

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ABSTRACT

Assessment of occupational pesticide exposure in epidemiological studies of chronic diseases is challenging. Biomonitoring of current pesticide levels might not correlate with past exposure relevant to disease aetiology, and indirect methods often rely on workers' imperfect recall of exposures, or job titles.

We investigated how the applied exposure assessment method influenced risk estimates for some chronic diseases. In three meta-analyses the influence of exposure assessment method type on the summary risk ratio (sRR) of prostate cancer (PC) (25 articles), non-Hodgkin's lymphoma (NHL) (29 articles) and Parkinson's disease (PD) (32 articles) was investigated. Exposure assessment method types analysed were: group-level assessments (eg, job titles), self-reported exposures, expert-level assessments (eg, job-exposure matrices) and biomonitoring (eg, blood, urine). Additionally, sRRs were estimated by study design, publication year period and geographic location where the study was conducted.

Exposure assessment method types were not associated with statistically significant different sRRs across any of the health outcomes. Heterogeneity in results varied from high in cancer studies to moderate and low in PD studies. Overall, case–control designs showed significantly higher sRR estimates than prospective cohort designs. Later NHL publications showed significantly higher sRR estimates than earlier. For PC, studies from North America showed significantly higher sRR estimates than studies from Europe. We conclude that exposure assessment method applied in studies of occupational exposure to pesticides appears not to have a significant effect on risk estimates for PC, NHL and PD. In systematic reviews of chronic health effects of occupational exposure to pesticides, epidemiological study design, publication year and geographic location, should primarily be considered.

INTRODUCTION

Retrospective assessment of occupational pesticide exposure in epidemiological studies of chronic diseases is challenging. The most specific exposure assessment method is biomonitoring, which primarily relies on sampling of biomarkers or metabolites in blood, urine or skin, or on personal sampling of workers' breathing zone or skin.[1] However, (bio)monitoring is complicated; exposures vary over time and in space,[2] many pesticides have short half-lives and multiple types of pesticides are often applied simultaneously.[3] Consequently, besides the case of persistent pesticides (mainly organochlorines), biomonitoring of current exposures may not correlate well with past exposures relevant to chronic disease aetiology. Therefore, long-term pesticide exposure might be better assessed using indirect methods such as assessments by job titles, workers' self-reported exposure or job-exposure matrices (JEMs). The choice of exposure assessment method is further heavily influenced by the type of study design and the composition and size of the study population.

We showed recently in a systematic review of epidemiological studies on occupational pesticide exposure that indirect methods comprise the majority of applied exposure assessment methods, and that prostate cancer (PC), non-Hodgkin's lymphoma (NHL) and Parkinson's disease (PD) are the most frequently studied health outcomes.[4] Thus, occupational pesticide exposure in relation to chronic diseases is assessed by several different, often indirect exposure assessment methods, complicating the interpretation of synthesised study results.

In meta-analyses of PC,[5–11] NHL[12–19] and PD,[20–27] bias resulting from heterogeneity associated with the use of different pesticide exposure assessment methods is often discussed, although seldom systematically quantified and analysed in relation to disease risk. Nevertheless, regarding PC, Lewis-Mikhael *et al*[9] reported that group-based exposure assessment methods yielded much higher risk estimates than measured serum pesticide levels. In contrast, Van Maele-Fabry and colleagues[5] found in studies of pesticide manufacturing workers that biomonitoring of serum, blood, fat and/or urine yielded the highest estimated risks, followed by assessments based on job title/work area. Smith and colleagues[19] evaluated NHL risk associated with 2,4-D exposure in (mainly) occupational studies, and found higher risks by expert assessments (informed by job titles, records, questionnaires and hygiene monitoring) compared with use of self-reported exposures. Regarding PD, van der Mark *et al*[24] found that job title assessments (including additional

Key messages

What is already known about this subject?

⇒ Retrospective assessment of occupational pesticide exposure in epidemiological studies of chronic diseases is challenging.
⇒ Exposure assessments are occasionally made using direct measurements by biomonitoring, but more frequently by indirect exposure assessment methods, such as assessments based on job titles and job-exposure matrices.
⇒ Previous studies have suggested that exposure assessment method might be related to different risk estimates of chronic diseases.

What are the new findings?

⇒ We conducted three meta-analyses to specifically investigate how the type of exposure assessment method influenced summary risk estimates of prostate cancer (PC), non-Hodgkin's lymphoma (NHL) and Parkinson's disease.
⇒ Exposure assessment method was not associated with significantly different summary risk estimates for any of the analysed health outcomes.
⇒ Study design (for cancer studies), publication year (for studies on NHL) and geographic region where the study was conducted (for PC), showed a larger effect on the summary risk estimates than the applied exposure assessment method.

How might this impact on policy or clinical practice in the foreseeable future?

⇒ These meta-analyses will inform researchers in the field of occupational pesticide epidemiology about the potential dependence of chronic disease risk estimates on different exposure assessment methods applied.
⇒ The results will guide the methodological improvement of studies on chronic disease in relation to occupational exposure to pesticides, and inform about potential sources of heterogeneity (including epidemiological study design, time period of publication and region where the study was conducted) regarding systematic reviews and meta-analyses.

incorporation of JEMs and expert assessments) resulted in the highest risks in occupational and non-occupational populations, and Yan *et al*[22] reported no difference in PD risk for exposures assessed by questionnaires and face-to-face interviews.

Thus, synthesised data suggest that occupational pesticide exposure assessments informed by workers' job title generally yield the highest risk estimates for PC, NHL and PD. We aimed to further analyse how the applied exposure assessment method influences assessed risks of these three chronic diseases.

METHODS

Within the IMPRESS project (www.impress-project.org) we conducted separate meta-analyses to systematically investigate how exposure assessment method applied in studies of strictly occupational pesticide exposure influences risk estimates of PC, NHL and PD, respectively. The meta-analyses were informed by articles retrieved in a recent systematic review performed by the authors, described elsewhere,[4] plus by a few new articles. Briefly, within the IMPRESS project a systematic review of articles on associations between occupational pesticide exposure and any type of health outcome published from 1 January 1993 to 31 December 2017 was performed (search syntax and retrieved articles were published as supplementary material).[4] The systematic review resulted in 1271 articles from which the lead author of this manuscript (JO) extracted exposure assessment method(s), study design, study location (country), health outcome, authors of article, year of publication and journal.[4] A second independent reviewer (HK) assessed a random selection of 5% of included articles for eligibility and extracted data, and a random selection of 1% of excluded articles for eligibility.[4]

Article selection

For the meta-analyses we extracted from the systematic review all articles on PC, NHL and PD or Parkinsonism. Additionally, the search syntax from the systematic review was reapplied (without limiting searches to articles published between 1 January 1993 to 31 December 2017) to retrieve relevant articles published before 1993 and after 2017 until end of 2020. Moreover, relevant articles in the bibliography of retrieved articles and published meta-analyses on named health outcomes were considered. The following eligibility criteria were applied to each article for inclusion into the meta-analyses:

- Peer-reviewed original publications on at least one of the three named chronic diseases in relation to occupational pesticide exposure.
- Case–control or cohort studies (prospective, retrospective). Cross-sectional and ecological studies were excluded to limit bias of pooled risk estimates in the meta-analyses.
- A reported relative risk (RR), HR, standardised incidence ratios (SIR), or OR associated with a defined exposure assessment method. Articles reporting (cause-specific) mortality rates were excluded as mortality rates might not properly reflect disease risk.
- Analyses based on at least five exposed cases.

Data extraction from articles

In addition to data from the systematic review, we extracted for the meta-analyses from each article the reported risk estimate, study population, sample size, number of cases and controls, type of pesticide(s) and type of exposure variable (eg, cumulative exposure). Included articles and extracted data are provided in online supplemental file 1. References to included articles and applied exposure assessment method(s) are described in online supplemental file 2.

For data extraction the following a priori determined criteria were applied:

- We extracted risk estimates corresponding to all applied exposure assessment methods in the included articles. As some articles reported risk estimates for more than one exposure assessment method the number of extracted risk estimates exceeds the number of included articles.
- The most fully adjusted risk estimate(s) in each article were preferred to less adjusted or crude risk estimates.
- We extracted risk estimates according to the following hierarchy of exposure variable categorisation: (a) cumulative exposure (including duration of exposure as a surrogate for cumulative exposure); (b) level of exposure by categories, for example, none/low/medium/high; (c) dichotomised exposure categories based on level, for example, low/high; (d) dichotomised categories based on prevalence of exposure, for example, never/ever.
- Where exposure assessment methods produced multiple risk estimates for different levels of (cumulative) exposure, we extracted the result for the highest exposure group, as this was based on the highest exposure contrast and, hence, most likely identify any effect of exposure, and less likely result

from chance, bias or confounding. Additionally, exposure assessment methods that generate risk estimates by level of exposure, for example, JEM, would lose an intrinsic methodological feature had risk estimates by different exposure levels been collapsed according to pesticide exposure (never/ever).
- We preferred risk estimates based on an unexposed control group instead of a low-exposed control group.
- For case–control studies, we preferred estimates based on population controls over hospital controls.
- When several risk estimates originated from the same study population, we selected the estimate based on the highest number of cases (often corresponding to the most recent publication).
- When risk estimates were reported by several different pesticide categories, risk estimates based on the exposure category 'pesticides in general/any pesticide' were preferred over estimates based on pesticide types (eg, insecticides), pesticide classes (eg, organochlorines) and specific pesticides. This approach maximised our number of exposed cases per exposure assessment method. If multiple risks by pesticide types, chemical classes or specific pesticides were reported we extracted the highest risk estimate.

Statistical analysis

Meta-analyses were performed using the R-package 'Metagen'. Risk estimates were pooled using the inverse variance method, expressed as a summary risk ratio (sRR). Heterogeneity was quantified using I^2 with its recommended cut-offs 25% (low), 50% (moderate) and 75% (high),[28] and with Cochran's Q statistics. Due to a relatively large heterogeneity of the results for most health outcomes (PC I^2=87.3%, NHL I^2=66.8%, PD I^2=42.4%) we used random effects models for pooling effects, according to DerSimonian and Laird.[29]

The influence of exposure assessment method on the sRR of selected health outcomes was investigated using subgroup analyses by exposure assessment method type in the meta-analyses. The following categories of exposure assessment method types were applied in the analyses:
- Group-level assessments (job titles, self-reported job histories, exposure registers, registers of licensed pesticide appliers).
- Self-reported exposures (by questionnaires or interviews).
- Expert level assessments (expert case-by-case assessments, JEMs, crop-exposure matrices (CEM), algorithms).
- Biomonitoring (blood, urine, adipose tissue).

Exposure assessment methods were categorised by the level of specificity of exposure assessment. Thus, although job titles inform for example, JEM assignments, these were considered different types of exposure assessment method. Further, categorisation was made by the highest level of specificity of exposure assessment applied, meaning that, for example, expert-based exposure assessments based on self-reports were categorised as expert-level assessments. For the subgroup analyses a mixed-effects model was applied; random effects for pooling effects within each subgroup, and fixed effects for comparing sRR between subgroups. Additionally, sRR estimates were calculated by study design (prospective cohort studies, retrospective cohort studies and case–control studies), time period of publication (before and after the median publication year per health outcome) and by study location (Europe, North America or other countries).

As exposure assessment method and study design are closely related[4] we additionally analysed the influence of exposure assessment method type on sRR estimates within case–control studies only. The sample size was insufficient to conduct (meaningful) similar analyses in prospective and retrospective cohort studies, respectively.

For PD, sensitivity analyses were made through excluding some few eligible articles that did not report on the number of exposed cases. Moreover, as a sensitivity analysis for NHL, we excluded articles that used a combination of NHL and chronic lymphocytic leukaemia as health outcome. Finally, to analyse the impact of each study on the overall sRR we performed for each health outcome leave-one-out analyses among all included studies.

RESULTS

Prostate cancer

In total 25 articles were included in the meta-analysis of occupational pesticide exposure and PC (online supplemental files S1 and S2). Of these, 17 originated from our systematic review, 1 article was published after 2017[30] and 7 articles were not previously retrieved in the systematic review (these were not captured by the search algorithm as they did not mention pesticide-related terms in title/abstract or index terms, or were previously not accessible to the authors).[31–37] The articles were published between 1995 and 2019 and described prospective cohort studies (n=5), retrospective cohort studies (n=8) and case–control studies (n=12). The included articles reported studies from North America (n=12), Europe (n=11) and other countries (n=2).

In the 25 articles, a total of 27 risk estimates for PC were reported for the following exposure assessment methods (online supplemental file 2): job titles (n=5), self-reported job histories (n=1), exposure registers (n=3), records of pesticide licenses (n=4), self-reported exposures (n=5), JEM (n=2), expert assessments (n=6) and biomonitoring of blood (n=1).

Sub-group analyses and sensitivity analyses

Subgroup meta-analysis of the 27 risk estimates of PC by exposure assessment method showed no statistically significant differences in sRR (table 1, online supplemental figure S3.1). The heterogeneity in risk estimates was high for all exposure assessment methods.

Subgroup analyses by study design showed a significantly higher sRR for case–control studies compared with prospective cohort studies (sRR=1.63 vs sRR=1.08) (table 1, online supplemental figure S3.2). There was no difference in sRR estimates between studies from earlier years compared with later years (sRR=1.12 vs sRR=1.11) (table 1, online supplemental figure S3.3). Studies from North America showed a significantly higher sRR compared with studies from Europe (sRR=1.28 vs sRR=1.03) (table 1, online supplemental figure S3.4).

Within case–control studies of PC, no significant differences in sRR estimates by exposure assessment method were observed (table 1).

In the publication period 2007–2019, the sRR by expert-level and self-reported assessments were higher than the sRR estimate by group-level (sRR=2.00 and sRR=1.57 vs sRR=1.08) (table 1).

The leave-one-out analysis showed throughout all iterations a similar significant increased overall sRR (data not shown).

Table 1 Pooled risk estimates for prostate cancer by exposure assessment method, study design, publication year period and geographic region, based on meta-analysis of articles on occupational pesticide exposure published between 1995 and 2019.

	Number of risk estimates	sRR	95% CI	Heterogeneity measures			
				I^2 (%)	P value	Q	P value
Exposure assessment method						3.28	0.35
Group-level	13	1.09	1.00 to 1.20	92	<0.01		
Self-reported exposure	5	1.35	0.95 to 1.94	76	<0.01		
Expert-level	8	1.41	0.99 to 2.01	79	<0.01		
Biomonitoring	1	1.32	0.75 to 2.33	.	.		
Study design						7.59	<0.02
Cohort (prospective)	5	1.08	1.03 to 1.14	64	<0.01		
Cohort (retrospective)	8	1.09	0.90 to 1.31	95	<0.01		
Case–control	12	1.63	1.22 to 2.18	79	<0.01		
Publication year period						0.01	0.93
1995–2006	14	1.12	0.94 to 1.35	92	<0.01		
2007–2019	13	1.11	1.04 to 1.19	77	<0.01		
Geographic region						9.15	<0.01
Europe	12	1.03	0.96 to 1.11	66	<0.01		
North America	13	1.28	1.13 to 1.45	92	<0.01		
Other	2	2.17	0.42 to 11.4	86	<0.01		
Case–control studies only							
Exposure assessment method						1.15	0.56
Group-level	1	2.37	1.22 to 4.61	.	.		
Self-reported exposure	4	1.53	0.89 to 2.62	68	0.02		
Expert-level	7	1.63	1.11 to 2.40	79	<0.01		
Exposure assessment method during publication year periods							
1995–2006							
Exposure assessment method						0.53	0.91
Group-level	7	1.16	0.87 to 1.55	95	<0.01		
Self-reported exposure	2	1.02	0.45 to 2.33	67	0.08		
Expert-level	4	1.04	0.69 to 1.57	70	0.02		
Biomonitoring	1	1.32	0.75 to 2.33	.	.		
2007–2019							
Exposure assessment method						5.8	0.05
Group-level	6	1.08	1.02 to 1.14	73	<0.01		
Self-reported exposure	3	1.57	0.96 to 2.56	85	<0.01		
Expert-level	4	2.00	1.07 to 3.75	76	<0.01		

I^2=percentage of variation across studies due to heterogeneity
Q=Cochran's Q.
sRR, summary risk ratio.

NON-HODGKIN'S LYMPHOMA

In total 29 articles were included in the meta-analysis of NHL (online supplemental files S1 and S2). Of these 24 articles originated from our systematic review, 2 articles were published before 1993[38 39] and 3 studies were not retrieved in our systematic review (these were not captured by the search algorithm as they did not mention work-related terms in title/abstract, or were previously not accessible to authors).[40–42] The articles were published between 1987 and 2017 and described prospective cohort studies (n=5), retrospective cohort studies (n=3) and case–control studies (n=21).

The 29 articles reported in total 40 risk estimates according to the following exposure assessment methods (online supplemental file S2): job titles (n=10), self-reported job histories (n=4), exposure registers (n=3), self-reported exposures (n=13), JEM (n=2), CEM (n=1), expert assessments (n=6) and exposure algorithm (n=1).

Subgroup analyses and sensitivity analyses

Subgroup meta-analysis of the 40 NHL risk estimates by exposure assessment method did not show significant differences in sRR estimates (table 2, online supplemental figure S3.5). However, expert-level assessments showed the highest sRR (sRR=1.74), followed by self-reported exposure (sRR=1.49) and group-level assessment (sRR=1.21). The sRR for all exposure assessment methods were significantly raised, and showed no heterogeneity for expert-level assessments, and moderate to high heterogeneity for group-level assessments and self-reported exposures (I^2=0%–76%). Case–control studies of NHL had a significantly higher sRR than prospective cohort studies (sRR=1.66 vs sRR=1.04) (table 2, online supplemental figure S3.6). The sRR for NHL in studies published as of 2006 was significantly higher than for studies published before 2006 (sRR=1.59 vs sRR=1.15) (table 2, online supplemental figure S3.7). Geographical region showed no statistically significant differences in sRR; all regions had sRR estimates that were significantly raised varying between (sRR=1.27–1.77) (table 2, online supplemental figure S3.8).

Within case–control studies the sRR estimates by exposure assessment method were very similar (table 2).

In the period 2006–2017, the sRR by expert-level and self-reported assessments were slightly higher than the sRR estimate by group-level (sRR=1.88 and sRR=1.94 vs sRR=1.35) (table 2).

All results remained largely unaffected when excluding two studies that analysed NHL and chronic lymphocytic leukaemia combined (data not shown). The leave-one-out analysis showed throughout all iterations a significant increased overall sRR.

Parkinson's disease

In total 32 articles were included for the meta-analysis of exposure assessment method and risk of PD (online supplemental files S1 and S2). Of these 23 originated from our systematic review, 2 articles were published before 1993,[43 44] 2 were published after 2017,[45 46] 4 articles were not retrieved in our systematic review (these were not captured by the search algorithm as they did not mention occupational terms in title/abstract, or any pesticide related terms in title/abstract or index terms)[47–50] and 1 article was at the time of systematic review analysis not accessible to the authors in full text.[51] Included articles were published between 1990 and 2020 and described prospective cohort studies (n=7), retrospective cohort studies (n=1) and case–control studies (n=24).

Table 2 Pooled risk estimates for non-Hodgkin's lymphoma by exposure assessment method, study design, publication year period and geographic region, based on meta-analysis of articles on occupational pesticide exposure published between 1987 and 2017.

	Number of risk estimates	sRR	95% CI	Heterogeneity measures			
				I^2 (%)	P value	Q	P value
Exposure assessment method						6.23	0.07
Group-level	17	1.21	1.05 to 1.40	63	<0.01		
Self-reported exposure	13	1.49	1.16 to 1.91	76	<0.01		
Expert-level	10	1.74	1.39 to 2.19	0	0.68		
Study design						22.1	<0.01
Cohort (prospective)	8	1.04	0.96 to 1.13	23	0.24		
Cohort (retrospective)	4	1.11	0.89 to 1.39	11	0.34		
Case–control	28	1.66	1.39 to 1.98	57	<0.01		
Publication year period							
1987–2005	19	1.15	1.00 to 1.32	21	0.2	8.5	<0.01
2006–2017	21	1.59	1.34 to 1.87	78	<0.01		
Geographic region						3.89	0.14
Europe	18	1.42	1.13 to 1.77	55	<0.01		
North America	18	1.27	1.10 to 1.47	70	<0.01		
Other	4	1.77	1.31 to 2.39	38	0.18		
Case–control studies only							
Exposure assessment method						0.1	0.95
Group-level	9	1.63	1.20 to 2.21	61	<0.01		
Self-reported exposure	11	1.67	1.21 to 2.31	71	<0.01		
Expert-level	8	1.73	1.33 to 2.27	0	0.47		
Exposure assessment method during publication year periods							
1987–2005							
Exposure assessment method						2.30	0.32
Group-level	8	1.04	0.83 to 1.28	31	0.18		
Self-reported exposure	8	1.26	1.05 to 1.51	0	0.51		
Expert-level	3	1.37	0.86 to 2.17	0	0.51		
2006–2017							
Exposure assessment method						4.68	0.1
Group-level	9	1.35	1.11 to 1.64	74	<0.01		
Self-reported exposure	5	1.94	1.14 to 3.30	91	<0.01		
Expert-level	7	1.88	1.45 to 2.24	0	0.7		

I^2=percentage of variation across studies due to heterogeneity. Q=Cochran's Q. sRR, summary risk ratio.

Table 3 Pooled risk estimates for Parkinson's disease by exposure assessment method, study design, publication year period and geographic region, based on meta-analysis of articles on occupational pesticide exposure published between 1990 and 2020.

	Number of risk estimates	sRR	95% CI	Heterogeneity measures			
				I^2 (%)	P value	Q	P value
Exposure assessment method						1.20	0.55
Group-level	6	1.34	1.16 to 1.54	0	0.54		
Self-reported exposure	22	1.45	1.18 to 1.76	56	<0.01		
Expert level	9	1.56	1.21 to 2.01	18	0.28		
Study design						2.82	0.24
Cohort (prospective)	8	1.28	0.95 to 1.73	63	<0.01		
Cohort (retrospective)	1	1.14	0.77 to 1.68	.	.		
Case–control	28	1.54	1.34 to 1.77	27	0.09		
Publication year period						1.49	0.22
1990–2006	19	1.58	1.32 to 1.89	36	0.06		
2007–2020	18	1.34	1.12 to 1.62	48	0.01		
Geographic region						1.92	0.38
Europe	14	1.47	1.21 to 1.79	37	0.08		
USA	19	1.53	1.24 to 1.88	51	<0.01		
Other	4	1.17	0.85 to 1.62	30	0.23		
Case–control studies only							
Exposure assessment method						0.60	0.74
Group-level	3	1.48	1.02 to 2.15	0	0.39		
Self-reported exposure	20	1.51	1.24 to 1.83	42	0.02		
Expert level	5	1.70	1.31 to 2.2	0	0.88		
Exposure assessment method during publication year periods							
1990–2006							
Exposure assessment method						1.24	0.54
Group-level	3	1.57	1.09 to 2.27	37	0.20		
Self-reported exposure	13	1.52	1.2 to 1.93	37	0.09		
Expert level	3	2.38	1.12 to 5.03	28	0.25		
2007–2020							
Exposure assessment method						0.62	0.73
Group-level	3	1.23	0.93 to 1.62	0	0.83		
Self-reported exposure	9	1.34	0.95 to 1.88	70	>0.01		
Expert level	6	1.42	1.12 to 1.81	0	0.49		

I^2=percentage of variation across studies due to heterogeneity. Q=Cochran's Q. sRR, summary risk ratio.

In the 32 articles in total 37 risk estimates for PD were reported for the following exposure assessment methods (online supplemental file S2): job titles (n=4), self-reported job histories (n=2), self-reported exposures (n=22), JEM (n=7) and expert assessments (n=2).

Sub-group analyses and sensitivity analyses

Subgroup meta-analysis of the 37 PD risk estimates by exposure assessment method showed no significant differences in sRR estimates (table 3, online supplemental figure S3.9). The sRR for all exposure assessment methods were significantly raised (varying between 1.34 and 1.56), and showed low to moderate degrees of heterogeneity (I^2=0%–56%).

Type of study design, publication year period and geographic region showed no significant differences in sRR estimates for PD (table 3, online supplemental figures S3.10–S3.12).

Further, no difference in sRR estimates by exposure assessment method was found when analysed by publication year periods.

Within case–control studies the sRR were similar for the different exposure assessment methods, with slightly higher sRR for expert-level assessments (sRR=1.70) compared with self-reported exposure (sRR=1.51) and group-level assessments (sRR=1.48) (table 3).

All results remained largely unaffected (data not shown) when excluding the four PD studies that did not report the number of exposed cases (online supplemental file S1). The leave-one-out analysis showed throughout all iterations a significantly increased overall sRR (data not shown).

DISCUSSION

In three meta-analyses of the association between occupational exposure to pesticides and PC, NHL and PD, we found no statistically significant differences in sRRs estimates for applied exposure assessment methods. The heterogeneity in risk estimates varied from high in cancer studies, to moderate and low in PD studies. For cancer studies, study design appeared to be the most significant source of heterogeneity, with significantly higher sRR in case–control studies compared with prospective cohort studies. Further analyses by publication year periods showed higher sRR estimates in later NHL publications, and analyses by geographic location where the study was conducted showed significantly higher sRR estimates for PC studies conducted in North America compared with those conducted in Europe. Finally, slightly higher sRRs for PC and NHL were found for self-reported exposures and expert-level assessments in the later publication year periods.

Prostate cancer

Based on 25 studies (27 risk estimates) published 1995–2019 we found no significant differences in sRRs for PC by different exposure assessment methods. In contrast, Lewis-Mikhael *et al*[9] reported based on 25 studies published between 1985 and 2014 that group-based exposure assessments resulted in the highest risk (pooled OR=2.24 95% CI 1.36 to 3.11). Our group-level estimate (sRR=1.09 95% CI 1.00 to 1.20) was, however, based on 12 studies (13 risk estimates), whereas that of Lewis-Mikhael was based on only three studies. Our results also differ from those of Van Maele-Fabry,[5] who in 18 studies of pesticide manufacturing workers published between 1984 and 2004 found the highest risk by biomonitoring of serum, blood, fat and/or urine (sRR=1.59 95% CI 1.05 to 2.41), followed by assessments by job title/history of work area (sRR=1.22 95% CI 0.86 to 1.72), JEM (sRR=1.19 95% CI 0.86 to 1.67) and model-based estimates of cumulative dose (sRR=1.1 95% CI 0.3 to 2.8). Nevertheless, comparability with our results is limited as we included also pesticide applicators in agriculture. Additionally, we used a different categorisation of exposure assessment methods, and excluded studies analysing mortality rates of which many were biomonitoring studies.

Further, PC studies conducted in North America showed higher sRR than those conducted in Europe. This difference might be partly attributable to the large difference in bans of specific pesticides in the USA and the European Union (EU). Donley[52] showed that pesticides banned in the EU accounted for more than 25% of agricultural pesticides applied in the USA in 2016. These included, for example, terbufos which has been linked to increased PC risks.[53]

Non-Hodgkin's lymphoma

For NHL, we found based on 29 articles (40 risk estimates) published between 1987 and 2017 the highest and uniform sRR in studies applying expert-level assessments (sRR=1.74 95% CI 1.39 to 2.18). Overall, however, differences in sRR by exposure assessment method were not statistically significant. In their meta-analysis of 23 studies of occupational and non-occupational 2,4-D exposure, Smith and colleagues[19] also reported the highest pooled risk from expert assessments (informed by job titles, records, questionnaires and hygiene monitoring) (pooled RR=2.17 95% CI 1.03 to 4.58), followed by self-reported exposures (pooled RR=1.47 95% CI 0.89 to 2.44). Interestingly, our meta-analysis and that of Smith *et al*[19] produced sRR estimates based on the highest level of exposure available in each included article. In individual studies, Nanni *et al* compared self-reported exposures with assessments by CEM and found almost the same risk estimates of NHL and CLL for the two methods (OR=1.74 vs. OR=1.70).[54]

Parkinson's disease

Also for PD we found, based on 32 studies (37 risk estimates), no difference in sRR estimates by exposure assessment method. In contrast, van der Mark *et al*[24] reported in a meta-analysis of 39 studies of occupational and non-occupational pesticide exposure and PD the highest sRR in studies that assigned exposure informed by job titles (applied exposure assessment methods were expert assessments, and JEM) (sRR=2.50 95% CI 1.54 to 4.05). However, their finding[24] was based on three studies whereas our estimate was based on seven studies. Moreover, the sRR estimates in our meta-analysis for PD varied the least with respect to exposure assessment method. The lower heterogeneity might be related to that, in contrast to PC and NHL, we found no significant influence by study design, publication year periods or geographic location in PD studies. Regarding individual studies, van der Mark *et al*[55] compared PD risk in a hospital-based case–control study by JEM (assessing pesticides in general, and classes of pesticides), exposure algorithm (assessing classes of pesticides) and CEM (assessing specific pesticides), and found generally no significant differences in risk estimates. Rugbjerg *et al*,[56] however, found in a population-based case–control study that PD risk based on self-reported exposures were reduced when restricted to subjects considered exposed according to hygiene-reviews.

Exposure misclassification

Cancer studies applied most frequently group-level assignments. Generally, one would expect a lower degree of exposure misclassification in studies that apply higher quality assessment, such as JEM.[57] However, whether for example, group-level assignments will misclassify workers' exposure depends on factors including analysed exposure, completeness of job histories and type of group-level assessment applied.[58] For example, exposure misclassification resulting from assessments based on registers of licensed pesticide users should be lower compared with using farm-related job titles, which might over-estimate workers' exposure.[59] Generally, differential exposure misclassification is assumed to be relatively low when assessments are informed by job titles, which is mainly the case for group-level assessment and expert-level assessments. Thus, the overall lack of statistically significant differences in sRR between group-level assessment and expert-level assessments might be partly related to that assessments informed by job titles on average quite well capture and classify long-term pesticide exposure

relevant for the development of analysed chronic diseases. In PD studies self-reported exposures were most frequently applied. In the Agricultural Health Study, self-reports regarding use and use duration have been shown to assign accurate, somewhat underestimated, exposures.[60] However, recall bias from self-reports particularly in case–control studies within the general population might generate false-positive associations, or, particularly in PD studies, possibly also false-negative associations as cases might under-report exposure due to cognitive deficits.

Analyses by study design

Regarding all analysed health outcomes, a large part of the observed study heterogeneity was driven by study design rather than by differences in applied exposure assessment method. For PC and NHL, case–control studies showed significantly higher sRR estimates than prospective cohort studies. For NHL, similar results were found in studies of organophosphate pesticides with increased risks in case–control studies (pooled OR=1.44 95% CI 1.14 to 1.81) and nested case–control studies (pooled OR=1.57 95% CI 1.04 to 2.39), but not in cohort studies (pooled OR=1.00 95% CI 0.85 to 1.17).[18] Similarly, in occupational and some non-occupational studies of organochlorine pesticides and NHL consistently higher pooled risks estimates were found in case–control studies (pooled OR=1.40 95% CI 1.22 to 1.59) and in nested case–control studies (pooled OR=1.54 95% CI 1.27 to 1.87), compared with case-cohort designs (pooled OR=1.13 95% CI 0.82 to 1.55).[61] Generally, the lower sRR estimates in prospective cohort studies compared with case–control studies might result from agricultural cohort studies (66% of our analysed prospective cohort studies) not having completely unexposed control groups, as indicated by generally higher risks of, for example, PC compared with the general population,[62] which potentially dilutes the pooled effect in agricultural cohort studies. Additionally, the higher sRR in case–control studies might be related to recall bias resulting from cases' potential over-reporting of exposure compared with controls.

Sensitivity analyses in case–control studies

Throughout all health outcomes, no significant differences in sRR by exposure assessment method were seen in case–control studies only. However, although not significant, expert-level assessments yielded for PD case–control studies a higher sRR estimate than self-reported exposures. This difference might be related to the aforementioned low degree of differential exposure misclassification associated with assessments informed by job titles (eg, in expert-level assessments). JEM, for example, assign exposure in a standardised group-based approach with exposure misclassification expected to be non-differential, and due to Berkson-type error classification will result in little or no bias in risk estimates.[58] Thus, the comparatively higher sRR estimates from expert-level assessments should not result from bias away from the null. Instead, as suggested by van der Mark,[24] who reported similar results in studies of PD, the comparatively lower sRR estimate from self-reported exposures might rather result from workers' inability to reliably remember and report exposure (especially at the level of specific pesticides), which is expected to result in non-differential misclassification of exposure and bias towards the null.[24] The lower sRR by self-reported exposures might also be related to PD cases' potential underestimation of exposure due to aforementioned cognitive deficits.

Analyses by publication year periods

Studies of NHL showed higher sRR estimates in later publication years. Additionally, slightly higher sRR for PC and NHL were found for self-reported exposures and expert-level assessments in later publication years. These changes are not explained by concurrent changes in type of study design; case–control studies, which showed the highest sRR regardless health outcome, were less frequently applied in later NHL studies and equally applied in early and late PC publications (results not shown). Publication year will partly correlate with years of pesticide exposure, and might thus reflect changes in used active ingredients and levels of exposure over time (although year of banning certain pesticides differ between countries[52]). Nevertheless, publication year correlates better with time of outcome assessment for chronic diseases (particularly for case–control studies). As the disease classification system for NHL changed in 2000 to cover subtypes of NHL,[63] the inclusion of more specific health outcomes in recent studies might have enabled the detection of associations previously undiscovered. Moreover, in present analyses later NHL studies applied less frequently group-level assessments and/or self-reported exposures, and more frequently expert-level assessments. Thus, higher sRR estimates seen in later NHL publications might partly reflect an increased probability of less error-prone (expert-level) exposure assessment methods to yield less towards-the-null biased associations. However, the superiority of expert-level assignments is dependent on the (quality of) exposure information available.

Study strengths

Presumably, this is the most comprehensive analysis of how estimated chronic disease risk depends on exposure assessment method applied in epidemiological studies of occupational exposure to pesticides, comprising three frequently analysed chronic diseases and four types of exposure assessment methods. As the objective of this meta-analysis was not to re-analyse the estimated risk of PC, NHL and PD, respectively, associated with occupational pesticide exposure, we extracted all risk estimates associated with all exposure assessment methods documented in the selected publications. This maximised the contrast in our subgroup analyses by exposure assessment method type. As the sRR in subgroup-analyses by exposure assessment method types were based partly on risk estimates generated from the same study population, these should be less influenced by between-study characteristics that evidently contribute to heterogeneity of results in meta-analyses. Additionally, we extracted risk estimates associated with the highest level of exposure, a method less prone to chance findings.[64] Assessment and classification of workers by level of (cumulative) exposure is a feature related to exposure assessment method, and is more common in more refined methods (mainly in those applying expert-level assessments). We did not collapse risk estimates within a study into pesticide exposure (never/ever), as this would have omitted an inherent methodological advantage of more refined exposure assessment methods.

Study limitations

The level of specificity at which each exposure assessment method assesses exposure, and its effect on the association between exposure assessment method type and risk of chronic disease, was not specifically considered in our analyses. We extracted primarily risk estimates according to populations exposed to 'pesticides in general'/'any

pesticide', which enabled analyses of more exposed cases than had we extracted risk estimates by categories of pesticide exposure, for example, by specific pesticides. Nevertheless, inclusion of studies that assessed exposure at different levels of specificity might have contributed to a more representative estimate of how, for example, the exposure assessment method 'self-reported exposures' is associated with chronic disease risk. Further, we only included one study that assigned exposure based on biomonitoring. This partly resulted from biomonitoring studies being almost only applied in cross-sectional studies, and rarely in studies of cancer or doctor-diagnosed neurological health outcomes (notably PD).[4]

CONCLUSION

The method for assigning workers' occupational pesticide exposure appears not to result in different sRR estimates for PC, NHL and PD. Overall, study design, publication year and geographic region where the study was conducted, showed larger effects on estimated sRRs than exposure assessment method. When performing systematic reviews of studies on chronic health effects of occupational pesticide exposure, epidemiological study design, publication year and region where the study was performed, should primarily be considered.

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