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Short communication

How can exposure assessment for pesticides in epidemiological studies be improved? Insights from the IMPRESS project

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ABSTRACT

The IMPRoving Exposure aSSessment Methodologies for Epidemiological Studies on Pesticides (IMPRESS) project (http://www.impress-project.org/) aimed to further the understanding of the performance of pesticide exposure assessment methods (EAMs). To achieve this the IMPRESS project used two approaches to assess EAM performance, using existing and newly collected data from five studies from three different countries and use of published secondary data to undertake three *meta*-analyses for selected chronic health outcomes. Based on the findings of the IMPRESS project we provide in this paper insights on the overarching research question “How can exposure assessments for pesticides in epidemiological studies be improved”? Exposure assessment is a critical component of pesticide epidemiological studies. EAMs used and epidemiological practices employed need to reflect the changing nature and complexities of pesticide exposure in various occupational settings. To properly assess the association between exposure and selected health outcomes, the choice of EAM should provide a clear exposure contrast within the study population. Acquiring a practical understanding of the pesticide use practices is crucial to determine whether factors such as frequency or intensity of exposure have to be considered in planned analyses. Biomonitoring may be more beneficially applied intensively in a focussed exposure assessment analysis of a particular cohort, which can be used to determine the most relevant exposure factors within that cohort-specific context. Overall, improving pesticide exposure assessment in epidemiological studies requires a multi-disciplinary approach. A next step for the wider scientific community may be to consider the development of a decision tree to aid the selection of suitable EAMs. Such a decision tree would need to consider and be based on multiple parameters including, but not limited to, study type, health endpoint, socio-demographic context, farming system, pesticide used, and application methods.

1. Introduction

Occupational exposure to pesticides has been linked to chronic ill-health including neurological effects, cancers and respiratory disorders (Ohlander et al., 2020). Determining the role of pesticides in the development of chronic diseases requires historical exposure assessment. This is typically based on surrogate information e.g., self-reported histories of pesticide application, job-exposure matrices, mathematical models (Ohlander et al., 2020), as exposure measurement data are rarely available to adequately cover the entire relevant exposure period. Self-reported exposure measures have limitations, e.g., due to the inability of a person to remember all their jobs, which may bias the conclusions of a study (Althubaiti, 2016). Modelling approaches are challenging due to the large number of active ingredients and mixtures involved, different toxicokinetics, seasonality of use, and a broad range of application characteristics. Measurements can be hampered by large spatial and temporal variability in exposure levels, and by logistic and cost issues. The influence of meteorological conditions can also lead to large

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temporal variability. Dermal exposure can be a dominant route of exposure, which adds another source of variability to the exposure assessment (Vermeulen et al., 2002). Understanding the performance of surrogate measures in exposure assessment is important when evaluating health related risks associated with occupational exposure to pesticides.

The IMPRoving Exposure aSSessment Methodologies for Epidemiological Studies on Pesticides (IMPRESS) project aimed to improve our understanding of the performance of pesticide exposure assessment methods (EAMs) used in previous epidemiological investigations and to use this information to recommend enhancements in practice for future studies (Jones et al., 2020). The IMPRESS project results have been published in seven research papers in the peer reviewed literature (Fuhrimann et al., 2023, 2024, Mueller et al., 2022a,b, 2023, Ohlander et al., 2020, 2022). In this paper the IMPRESS team provide their insights on the overarching research question "*How can exposure assessments for pesticides in epidemiological studies be improved?*". These insights are based on our study findings and are intended to advance discussions within relevant scientific and stakeholder communities.

2. Overview of the IMPRESS project

The IMPRESS project assessed the reliability and accuracy of measures used to assign exposure. It also evaluated the extent of recall bias on the misclassification of pesticide exposure as this can affect the magnitude and direction of epidemiological estimates of exposure. We first carried out a systematic review to identify EAMs typically used in occupational epidemiological studies of pesticide exposure (Ohlander et al., 2020). The IMPRESS project used two approaches to assess EAM performance:

1. The use of existing and newly collected data from five existing studies from three different countries (UK, Uganda and Malaysia), that members of the IMPRESS team were responsible for (Table 1). Additional information on these studies is reported elsewhere (Jones et al., 2020). The aims and objectives of these studies had already been determined and data collection activities had commenced. Consequently, the IMPRESS team had to be cognisant of working within these parameters.
2. The use of published secondary data. Three *meta*-analyses were undertaken to investigate the influence of EAMs, and other parameters such as geographical area, study design, and time-period, on the standardised risk ratio (sRR) of prostate cancer, non-Hodgkin's lymphoma and Parkinson's disease (Ohlander et al., 2022).

A detailed overview of the IMPRESS project activities and related outputs is provided in Table 2.

3. Which EAMs are used in pesticide occupational epidemiological studies?

We systematically reviewed peer-reviewed literature published during 1993–2017 for EAMs used in original observational epidemiological studies describing analyses of occupational exposure to pesticides in association to any health outcome (Ohlander et al., 2020). In 1271 reviewed articles, 1483 EAM occurrences were documented, summarised in Table 3. Over 80 % were indirect EAMs, based on, e.g., job title, self-reported exposures and job histories by self- or interview-administered questionnaires, records and registers. Self-reported exposure accounted for almost 40 % of EAMs reported. The use of self-reported exposures and job exposure matrices increased, and expert-assessments and job title assessments decreased over this time period. The use of algorithms and predictive models showed no temporal trend.

Table 1
Short summary of existing studies used in IMPRESS.

Study	Country	Original study aims	Year established	EAMs used in existing study	IMPRESS study questions study helped answer
Prospective Investigation of Pesticide Applicators' Health (PIPAH)	UK	Investigate evidence of a link between working with pesticides and ill-health	2013	Questionnaire	How well do study participants perform at recalling their exposure to pesticides (and other exposure determinants)? What is the relationship between exposure modifying factors and urinary biomarkers of exposure to pesticides?
Pesticide Users Health Study (PUHS)	UK	Monitor long-term health of individuals potentially exposed to low levels of pesticides on a long-term basis	Late 1990 s	Questionnaire	How well do study participants perform at recalling their exposure to pesticides (and other exposure determinants)?
Study of Health in Agricultural Work (SHAW)	UK	Whether low-dose pesticide exposure was associated with neuropsychiatric disorders in UK farmers	2002	Questionnaire	How well do study participants perform at recalling their exposure to pesticides (and other exposure determinants)?
Pesticide Use in Tropical Settings (PESTROP)	Uganda	Deepen the understanding of the environmental, health and regulatory dimensions of pesticide use in agriculture in low/middle income countries (LMICs)	2017	Questionnaire, erythrocytic acetylcholinesterase activity, urine, hair, and toenail samples	How well do study participants perform at recalling their exposure to pesticides (and other exposure determinants)? What is the relationship between exposure modifying factors and urinary biomarkers of exposure to pesticides? How do different EAM methods perform when applied against the same health outcomes?
Malaysia farm workers	Malaysia	Prospective study of farmer's ill health in the pesticide spraying season in the Sabah region of Malaysia	2018	Questionnaire, Diary, Video, Urine samples	What is the relationship between exposure modifying factors and urinary biomarkers of exposure to pesticides?

Table 2
Summary of IMPRESS project results. EAM=exposure assessment methods.

IMPRESS question addressed	Data considered	No. participants / samples considered (if applicable)	Main findings	Conclusions / recommendations	Reference
Which EAMs are used in pesticide occupational epidemiological studies?	1483 EAMs used in 1271 peer-reviewed original articles published between 1993–2017	NA	• Over 80 % EAM were indirect methods (e.g., job title, expert case-by-case assessment). ~40 % were self-reported exposure (self- or interviewer–administered questionnaires). Indirect EAM highest in case-control studies (96 %), in high-income countries (87 %) and in studies with doctor-diagnosed health outcomes (>85 %). Direct EAM were used in 21 % of studies, predominantly in cross-sectional studies (~30 %), in LMICs (~41 %) and in studies of neurological (50 %) outcomes. Use of self-reported exposures and job exposure matrices increased over time, while job titles and registers use decreased. Use of algorithms and predictive models showed no temporal trends.	• Strengths and limitations of each EAM need to be clearly understood and considered within each study-specific context before the most appropriate EAM can be applied.	(Ohlander et al., 2020)
What is the relationship between exposure modifying factors and urinary biomarkers of exposure to pesticides?	New data from Malaysia farm workers study (Malaysia), PESTROP (Uganda) and PIPAH (UK) – urine metabolite results and questionnaire data	From the Malaysia, Uganda, and UK studies, 81, 84, and 106 study participants provided 162, 384, and 212 urine samples.	• Urinary biomarker concentrations higher in applicators in Malaysia and Uganda than in UK. Duration of use, PPE, education level, Active Ingredient (AI) use, associated with biomarker concentrations, but no factor consistently associated with exposure across different biomarkers and cohorts. Moderate correlations between pyrethroid biomarker concentrations and exposure algorithm scores in PIPAH study only. No other such associations observed.	• Urinary biomarkers can provide indicators of exposure to pesticides, but results suggest a need for AI-specific interpretation of exposure-modifying factors as the relevance of exposure routes, levels of detection, and farming systems/practices may be very context specific.	(Mueller et al., 2023)
How well do study participants perform at recalling their exposure to pesticides (and other exposure determinants)?	New and original questionnaire data from three UK studies (PIPAH, PUHS and SHAW) (3–14 year period)	643 individuals completed both the baseline and follow-up surveys across the three studies with response rates ranging from 17 to 46 %.	• Strong correlation between baseline and recalled years working with pesticides. Stronger agreement in two of the cohorts for recalled days compared to hours per year that pesticides were used. Recall for number of exposure determinants across short and longer-term recall periods entailed overall agreement of > 70 %, though some differences: e.g., sensitivity for long-term recall of crops was poor (<43 % in PUHS), whereas short-term recall of hygiene practices good in PIPAH.	• Recall ability may deteriorate over a longer period but recall for a number of exposure determinants appeared reliable, such as crops and hygiene practices within 3 years, as well as days per year working with pesticides.	(Mueller et al., 2022a)
	New and original questionnaire data from PESTROP (Uganda) study (2 year period)	255 individuals completed both the baseline and follow-up surveys, response rate 84 %	• Instances of better recall for the use of some AIs, commonly used PPE items, and washing clothes after application, whereas only 13 % of participants could correctly recall their three major crops. Observed trend of over reporting of use of AIs and under reporting of the use of PPE items.	• We found better agreement in the recall of years working with pesticides compared to hours per day or days per week in the field, with no apparent systematic over or under reporting by demographic characteristics. While some recall assessment findings provided consistency with those from high-income countries, more research is needed on recall in more poorly educated agriculture communities in LMICs to confirm the results observed.	(Mueller et al., 2022b)
How do different EAM methods perform when applied against	Data from peer-reviewed literature – three *meta*-analyses investigated	NA	• EAM applied appears to not have significant effect on risk estimates for the chronic diseases investigated.	• In future systematic reviews of chronic health effects of occupational exposure to	(Ohlander et al., 2022)

(*continued on next page*)

Table 2 (*continued*)

IMPRESS question addressed	Data considered	No. participants / samples considered (if applicable)	Main findings	Conclusions / recommendations	Reference
the same health outcomes?	influence of EAM on summary eisk ratio (sRR) of prostate cancer, non-Hodgkin's lymphoma and Parkinson's disease.		All investigated EAMs analysed (apart from biomonitoring) performed equally well, and showed sRRs above 1 for non-Hodgkin's lymphoma and Parkinson's disease (also when analysing solely case-control studies). A majority of observed study heterogeneity was driven by study design rather than by differences in applied EAM.	pesticides, epidemiological study design, publication year and geographic location, should primarily be considered.	
	New and original questionnaire data from PESTROP (Uganda) study focussed on neurobehavioral outcomes	246 smallholder farmers	• Observed relationships between different measures of increasing exposure to glyphosate and a worse performance among four neurobehavioral tests (Benton visual retention, digital symbol, finger tapping dominant hand and trail making A). The finger tapping non-dominant hand and semantic verbal fluency tests showed no association with glyphosate exposure. Glyphosate exposure based on information recalled 2 years following the survey did not show associations with any neurobehavioral outcome. For mancozeb none of the exposure measures were related to the neurobehavioral outcomes.	• The exposure – response relationship between self-reported glyphosate exposure and neurobehavioral test scores pointed in the same direction across the different exposure measures tested. However, exposure estimates based on recalled information drove the associations towards the null, even though the recall period was only two years.	(Fuhrimann et al., 2024)
	New and original questionnaire data from PESTROP (Uganda) study and urine metabolite results focussed on sleep problems	253 smallholder farmers	• Observed relationships between any pesticide application days in last 7 days and all three sleep problem indices. Self-reported glyphosate application in last 7 days and mancozeb application in last 12 months were associated with the 6-item sleep problem index. The modelled urinary glyphosate and ethylenethiourea (ETU) concentrations both showed positive associations with the 6-item sleep problem index For the other glyphosate and mancozeb exposure measures based on self-reports, no significant associations were observed.	• Self-reported and urinary biomarker-based exposure measures of glyphosate and mancozeb showed similar directions in associations with sleep problems. Using estimated average biomarker concentrations based on measured urinary pesticide biomarkers and self-reported exposure information improved the exposure assessment. Results also suggest that different pesticide-AIspecific short- and long-term exposure measures are relevant when studying the association with (acute) sleep problems	(Fuhrimann et al., 2023)

Regarding the use of direct EAMs (i.e. methods that rely on direct measurements by biomonitoring or personal sampling of the workers' breathing zone or skin), no large changes were seen over time. The review showed that the specificity of pesticide assessment increased, since studies assessing exposure by job title as a proxy declined meanwhile assessments by type of pesticide increased.

The IMPRESS team evaluated the dominant EAMs (Ohlander et al., 2020): exposure assessed by either self-administered or interview-administered questionnaires. Regarding direct EAMs, the IMPRESS team used urine samples, as some of our included studies (Table 1) were already completed or ongoing and had used this EAM. Whilst blood samples were the most commonly used sampling matrix for direct EAMs (Ohlander et al., 2020) (perhaps partly due to an observed increased focus on investigating genetic biomarkers and, historically, more persistent and organophosphate pesticides being used during the review period), urine samples are generally more practical to collect as they can be considered as non-invasive, requiring no specialist staff (e.g. phlebotomist), allowing multiple sampling and self-sampling; transport and storage is also more straightforward (World Health Organisation, 2015).

Through undertaking the *meta*-analyses for selected health outcomes (Ohlander et al., 2022), we were also able to assess the influence of other EAM types on the risk of selected health outcomes.

4. How well do study participants recall their exposure to pesticides (and other exposure determinants) and how can this be improved?

We investigated the ability of participants to recall pesticide exposure determinants (e.g., due to different pesticides, application methods, and personal protective equipment (PPE) being used, over a range of time frames in two very different exposure situations: UK farmers and applicators over short (3 years) and long (12–14 years) time periods (Mueller et al., 2022a) and Ugandan smallholder farmers after two years (Mueller et al., 2022b).

Recall ability in UK farmers and applicators may deteriorate over a longer time period (12+ years), with recall over the 3-year period being better for certain parameters, such as crops and hygienic practices and days per year working with pesticides (Mueller et al., 2022a). In the

Table 3
Exposure assessment methods (EAMs) in epidemiological studies of occupational pesticide exposure in relation to any health outcome published 1993–2017 (Ohlander et al., 2020).

	1993–2017	
	N	%
Number of articles	1271	
Number of EAM occurrences in articles	1483	100.0
Indirect EAM	1219	82.2
Direct EAM	253	17.1
EAM not reported	11	0.7
Indirect EAM:		
Job title	182	12.3
Expert case-by-case	84	5.7
Self-reported exposure: Self-administered or interview administered questionnaire		
Self-reported job history: Self-administered or interview administered questionnaire		
Registers	85	5.7
Job Exposure Matrices	69	4.7
Crop Exposure Matrices	3	0.2
Task Exposure Matrices	1	0.1
Algorithm/model	80	5.4
Index *	6	0.4
Score **	1	0.1
Metric ***	1	0.1
Environmental monitoring	12	0.8
Geographic information systems (GIS)	2	0.1
Direct EAM:		
Biomonitoring:		
Blood	175	11.8
Urine	69	4.7
Dermal	2	0.1
Hair	1	0.1
Adipose tissue	3	0.2
Personal air sampling	3	0.2

* An index combines multiple exposure related factors into a single composite measure of exposure (e.g. to categorize workers into low, medium, high exposure).

** A score is a (oftentimes semi-quantitative) measure that categorizes or ranks exposure scenarios and is often used where relative comparisons is more important, or only available as precise quantification of exposure is not possible within a study context.

*** A metric is a specific quantitative assessment of the exposure (e.g. cumulative exposure: concentration*duration*frequency over time).

Ugandan cohort, reporting practices using longer units of time (i.e., years) appeared more reliable than recalled hours per day or days per week (Mueller et al., 2022b). We also found higher levels of agreement for the recall of PPE items and certain active ingredients, whereas we observed difficulties remembering crop types (Mueller et al., 2022b). In the UK studies with longer recall intervals, we found evidence of overestimation for the total years and hours per year worked (Mueller et al., 2022a). Regardless of recall period, our results suggest less reliable recollection for dynamic (e.g., crops in tropical settings) or less intuitive (e.g., hours per year) measures of exposure. Although there is some consistency in our findings between low and high-income countries, more research is needed on recall bias in LMICs' agricultural communities to confirm these results. We considered education / literacy levels in our recall evaluation and observed no apparent systematic bias due to these demographic characteristics in either study.

In our investigation of the association between neurobehavioral problems, both historical self-reported data (Fuhrimann et al., 2021) and more recent recollections of the same historic exposure from Ugandan smallholder farmers were used (Fuhrimann et al., 2024). The original reported associations between glyphosate exposure with behavioral test scores seemed reliable. However, when based on re-recalled exposure, the associations with the original exposure measures disappeared. It was recommended that in future studies relying on self-reported exposure, researchers should critically evaluate the potential for bias, especially when using recalled data.

These findings reiterate that there are issues associated with use of EAMs relying on recall. Ideally, EAMs would not rely on participants' recall of their use of pesticides and other essential exposure determinants. The implemention of prospective, harmonised, systematic recording systems (recording e.g, application date and methods, AI amount and concentration, re-entry intervals), with due consideration of ethics and data protection, would be a step forward. Whilst legal requirements to maintain spray records are in place in some countries, e.g., in the UK they must be held for a minimum of 3 years (Statutory Instrument, 2011), the reality of such systems being achieved and used globally, particularly LMICs, is challenging. Conducting qualitative interviews before the study to understand the context, referring to known major cultural or landmark events (Glasner et al., 2012) and local rainy seasons (instead of calendar years) or developing context-specific visual aids (Booker et al., 2021) (e.g. to visualize units, showing pictures of pesticide products, application equipment or PPE) next to structured questionnaires are feasible approaches to decrease reporting bias. Increasing education and literacy levels and supporting professionalism of practices (e.g, using licensed products correctly, better recording of pesticide applications) within LMIC smallholder farming systems would also place less reliance on recall.

Researchers should ensure that questionnaires are appropriately designed to collect the required information. A particular feature is that the study design addresses a contextual exposure contrast. For example, if all farmers use handheld application devices, one should know details about the frequency or intensity of the application. If a comparison is made by application method (e.g. handheld vs tractor), exposure contrast will largely be determined by the two methods of application. A realistic understanding of the context of pesticide use is needed *a priori* to understand if frequency or intensity of exposure (or both) must be considered and which exposure pathways are relevant.

It is difficult to prescribe a set time-period for retrospective data collection as the IMPRESS project only considered limited follow-up periods. Nevertheless, a 2–3 year follow-up period generated reliable results related to application experience and frequency on an annual basis, and PPE items. We suggest that prospective studies should continue to collect detailed information but that thorough checks/ multiple sources of evidence should be used, where possible, to confirm any assumptions made when significant gaps in follow-up occur (e.g., 10 years or more).

5. What is the relationship between self-reported exposure modifying factors and urinary pesticide biomarkers and how useful is biomonitoring as an individual-based exposure assessment method for pesticides?

Biomonitoring is well established for exposure assessment and there is evidence of use in epidemiological investigations (Ohlander et al., 2020). Currently used pesticides generally have short biological half-lives, being rapidly excreted in urine (Norén et al., 2020); as such, biological samples may be used to reflect exposure that day or week. There is a lack of biomonitoring guidance values to determine whether exposures are adequately controlled but results can be compared to standard practices (as reported in the literature) or to Biological Equivalents (BE) and other reference ranges. The challenge when using biomonitoring in epidemiology studies is relating the marker of exposure (usually excreted over hours or days) with the development of health effects (acquired over months or years).

For example, in the IMPRESS study, the measured day exposure for glyphosate varied quite substantially (e.g., post-shift levels up to 317 μg/L [233 μg/g creatinine] for the Uganda cohort and up to 191 μg/L [87 μg/g creatinine] for the UK were recorded), similar to or exceeding maximum levels reported in other cohorts (e.g. Ireland: 7.4 μg/L (Connolly et al., 2019), Thailand: 240 μg/g creatinine (Bootsikeaw et al., 2021) and 170 μg/g creatinine (Kohsuwan et al., 2022). These levels were still well below the derived BE (5400 μg/L) based on the Acceptable Daily Intake (ADI) (Hays et al., 2023). Of course, this does not imply safe exposure levels, unless we assume a consistent exposure pattern, as the measurements reflect only a single day's exposure and we found that within worker variability can be greater than between worker variability (Fuhrimann et al., 2023). Such variability highlights the challenges of separating day-to-day variables (such as the amount of pesticide used) from systemic characteristics such as the level of education, which we demonstrated to influence exposure (Mueller et al., 2023; Fuhrimann et al., 2023).

Our analyses demonstrated evidence from the individual IMPRESS studies that higher urinary biomarker concentrations for glyphosate and pyrethroids can be associated with mixing/application of the active ingredient on the day of urine sampling, longer duration of mixing/application, lower PPE protection, and less education/literacy (Mueller et al., 2023). However, and importantly, no factor was consistently associated with exposure across biomarkers in the three studies. We concluded that while urinary biomarkers can indeed provide indicators of exposure to pesticides, our results suggest a need for active ingredient specific interpretation of exposure-modifying factors such as the relevant exposure routes, levels of detection, and farming systems/practices. Therefore, as part of the study design there is a need for researchers to thoroughly consider what the active ingredients of interest are for the study (rather than simply assessing 'pesticides in general'). The resulting enhanced specificity of the pesticide exposure assessment and reduced exposure misclassification will contribute to increased precision of estimated exposure–response relationships in epidemiological studies of occupational exposure.

The IMPRESS project leveraged existing cohorts as a cost and time-effective means of conducting the study. While we were able to standardise urine sample collection and the analysis of samples, we were unable to harmonise the accompanying questionnaires used as these were already established. Relatively few parameters could therefore be tested across all cohorts; within each cohort there was limited contrast as most recruits in each cohort used similar work practices.

One of the well-recognised challenges of chemical exposure assessment is the extent of combined exposures to multiple chemicals e.g., (OECD., 2018). Within the IMPRESS project, workers often reported using up to six or more AIs per day. Analysis was restricted to the most frequently cited AIs to achieve statistic robustness which makes exploring potential mixture interactions difficult. Although there is some limited evidence in volunteers (Sams and Jones, 2011) that mixed exposures (within the ADIs) are unlikely to interact, these data do not represent real-life exposures of multiple and changing mixtures.

Pesticide metabolite half-life excretion is an important sampling strategy consideration. Glyphosate and synthetic pyrethroids (measured as 3-phenoxybenzoic acid) have relatively short half-lives (∼7 h, Mueller et al., 2023), with urine samples mostly reflecting that day's exposure, although skin uptake will result in delayed absorption and excretion. A questionnaire can be designed to cover this exposure window in reasonable detail. However, AIs such as mancozeb, excreted as ETU, have a much longer half-life (up to 100 h, Kurttio et al., 1990), therefore relating a questionnaire response to a biomarker result is more complicated as the result reflects various exposures over the last month or so. On the other hand, it is more indicative of their long-term exposure and may therefore be more relevant to the development of health effects. Whilst extensive and repeated collection of biomonitoring samples over extended time periods of time may help resolve some of the issues highlighted, there is the question of whether such extensive biomonitoring programmes are feasible from practical, financial, ethical and participant acceptability perspectives.

Another complicating factor is the presence of background levels of the biomarkers. In the IMPRESS study, significant levels of ETU were detected in urine, even in those who reported not to have sprayed with mancozeb in the last 12 months (up to 78.7 μg/g creatinine in a post-work sample). For comparison, the NHANES data for ETU (2007/08, https://www.cdc.gov/exposurereport/data_tables.html) reported a 95th percentile for adults of 0.8 μg/g creatinine. The cause of this discrepancy is unknown but it has a significant bearing when associating health effects, biomarker levels and pesticide usage. As ETU is not specific to mancozeb, exposure to other pesticides registered for use in Uganda (such as maneb, ziram or ETU itself) could account for the raised background (Atuhaire et al., 2017) although their use was not reported by the cohort. Also, as ETU was excreted at almost a steady state in this cohort, this limits the ability for the biomarker to detect an increase in exposure due to occupational activities on a given day.

6. How do different EAMs perform when applied against the same outcomes and how can we use this information to plan future epidemiological studies?

In our *meta*-analysis (Ohlander et al., 2022) we examined whether EAMs play a significant role in explaining observed differences in risk in different studies regarding prostate cancer, non-Hodgkin's lymphoma, Parkinson's disease. We found that different EAMs were not associated with significantly different summary risk estimates for these three health outcomes (no large impact of EAM on heterogeneity in results was seen) (Table 2). Instead, study design (cancer studies), publication year (non-Hodgkin's lymphoma) and geographic region (prostate cancer) had a larger effect on the sRRs. Consequently, these factors are key drivers of study heterogeneity and may provide critical insight into the observed variation in risk estimates. We therefore recommend that systematic reviews focussing on chronic health effects associated with occupational pesticide exposure should prioritize the evaluation of specific factors such as study design, publication year, and geographic location.

Further, we used published data from Ugandan smallholder farmers (Fuhrimann et al., 2021) to investigate and compare the association between different EAMs (self-reported and measured exposure) and two health outcomes: neurobehavioral (chronic) and sleep (acute) problems. The EAMs studied ranged from self-reported methods e.g. application status (yes/no) or recent application status (never, last 7 days, last 12 months), to those based on semi-quantitative algorithms, e.g. average exposure-intensity scores. For neurobehavioral problems two EAMs based on recall after two years were also studied: application status and average exposure-intensity scores. In relation to sleep problems, the EAMs of individual urinary biomarker concentrations for glyphosate and mancozeb and estimated urinary biomarkers for these (based on modelled urinary biomarkers and self-reported information) were investigated. For neurobehavioral outcomes, the exposure–response relationship between self-reported exposure and neurobehavioral test scores was similar across the original EAMs tested. There was no association between EAMs based on data recalled after two years and neurobehavioral outcome. For sleep problems, comparisons of different exposure measures of glyphosate showed that using more detailed exposure measures based on self-reported exposure methods (e.g., exposure algorithms) or estimated urinary biomarker concentrations revealed the same associations with sleep problems as those solely based on reported frequency of application over the last week or year. These results suggest that for sleep problems, the use of less sophisticated self-reported EAMs may be just as effective as those based on more details.

7. Conclusions

Exposure assessment is a critical component of pesticide epidemiological studies. The IMPRESS project was novel in that it allowed the following insights to be obtained: which EAM have been used (over time); farmers' recall of pesticides used and other pertinent exposure parameters; the effect of poor recall on exposure–response association; the impact of EAM choice on the risk of the health outcome of a study; and that the EAM and other factors (including region, time period, and study design) should be taken into account in any systematic review of human observational studies on health effects of occupational pesticide exposure.

Pesticides differ greatly in their mode of action, uptake by the body, metabolism, elimination from the body, and toxicity to humans. Currently used pesticides are likely to be replaced by other active ingredients and mixing and application methodologies may change. EAMs and epidemiological practices used need to be informed by such developments and be refined to accurately capture the complexities of pesticide exposure in occupational settings.

Whilst biomonitoring is a valuable tool it has its limitations. It will always be near-impossible to determine long-term exposure from a single sample with sufficient confidence. Repeat sampling is therefore valuable (and tools based on pharmacokinetic modelling simulations can help researchers determine the approximate number of urine samples needed (Verner et al., 2020) but the practicality of doing so with sufficient frequently is difficult. Biomarker samples will need questionnaires to accompany them that collect contextual information that is representative of the relevant exposure window. From an epidemiological perspective, biomonitoring may be more beneficially applied intensively in a focussed exposure assessment analysis of a particular cohort, which can then be used to determine the most relevant exposure factors within that cohort-specific context. Questionnaires, job-exposure matrices, algorithms etc. can then be developed to capture the relevant information in an epidemiological study. This approach too has its limitations as we know that the pesticide application setting is prone to many variables that will never be static over the time frames entailed in epidemiology. What this study (and others) have shown is that factors such as education and exposure control measures can reduce exposures significantly and efforts to improve these aspects need to continue and advance.

The absence of a standardized framework for exposure assessment in occupational pesticide epidemiology is demonstrated by the variety of indirect and direct methods used. This may be due to the different research questions, study designs, and health outcomes that are being investigated, and the different agricultural systems and pesticides applied. As no single 'perfect' epidemiological study exists, it is imperative that all data is collected with a clear, focussed purpose, and that results are reported transparently. There is also value in the implementation and use of prospective, harmonised, recording systems as well as harmonisation of data and sample collection initiatives to aid study comparisons and data pooling.

As mentioned previously, a particular feature is that the study design and research questions are implemented that allow a contextual exposure contrast to be addressed. Acquiring a practical understanding of the pesticide use practices is crucial before commencing an epidemiological study. This understanding is necessary to determine whether factors such as frequency or intensity of exposure (or both) have to be considered in planned analyses. Additionally, elucidating which exposure pathways are relevant is vital. Improvement of pesticide exposure assessment in epidemiological studies requires a multi-disciplinary approach. A next step for the wider scientific community may be to consider the development of a decision tree to aid the selection of suitable EAMs. Such a decision tree should consider multiple parameters including, but not limited to, study type, health endpoint (also considering if acute or chronic health effect), socio-demographic context, farming system, pesticide used, and application methods. Within the constraints of the IMPRESS project it was not possible to develop such a decision concept, however it is hoped that the insights gained from the IMPRESS project will help stimulate discussion and that there may be future collaborative endeavours by research groups to move this forward.

8. Author statement

All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the following appropriate institutional committee(s):

- PUHS and PIPAH: Ethical approval for the study has been obtained from the University of Sheffield's Research Ethics Committee (REC) for the assessment of recall bias (Reference Number HSL28) and the exposure assessment (Reference Number HSL29).

  The Greater Manchester Central REC gave approval for the PUHS to share individual-level data collectedas part of the 2004-2006 Survey of Pesticide Usage with the PIPAH study (REC Reference number 14/NW/1042).
- SHAW: Ethical approval has been obtained from the University of Manchester RECs (2019-5987-9976).
- Uganda: Ethical approval will be sought from Utrecht University in the Netherlands and the Higher Degrees Research and Ethics Committee at Makerere University in Uganda.
- Malaysia: Ethical approval for the study has been obtained from the University of Manchester RECs (2017-0439-3979) and a Malaysian Medical REC (NMR-17-424-34635[IIR]).

The privacy rights of human subjects have been observed and informed consent was obtained from human subjects.

CRediT authorship contribution statement

Karen S. Galea: Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **William Mueller:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Samuel Fuhrimann:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Kate Jones:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Johan Ohlander:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ioannis Basinas:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization. **Andrew Povey:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Martie van Tongeren:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization. **Hans Kromhout:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

We are reflecting on data that we have already published as part of the IMPRESS project

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