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

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IOM
WORKING FOR A HEALTHY AND SUSTAINABLE WORLD

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Question	Main questions addressed in perspectives manuscript
1	Which exposure assessment methods (EAMs) are used in pesticide occupational epidemiological studies?
2	How well do study participants recall their exposure to pesticides (and other exposure determinants)?
3	What is the relationship between self-reported exposure modifying factors and urinary pesticide biomarkers?
4	How do different EAMs perform when applied against the same health outcomes?

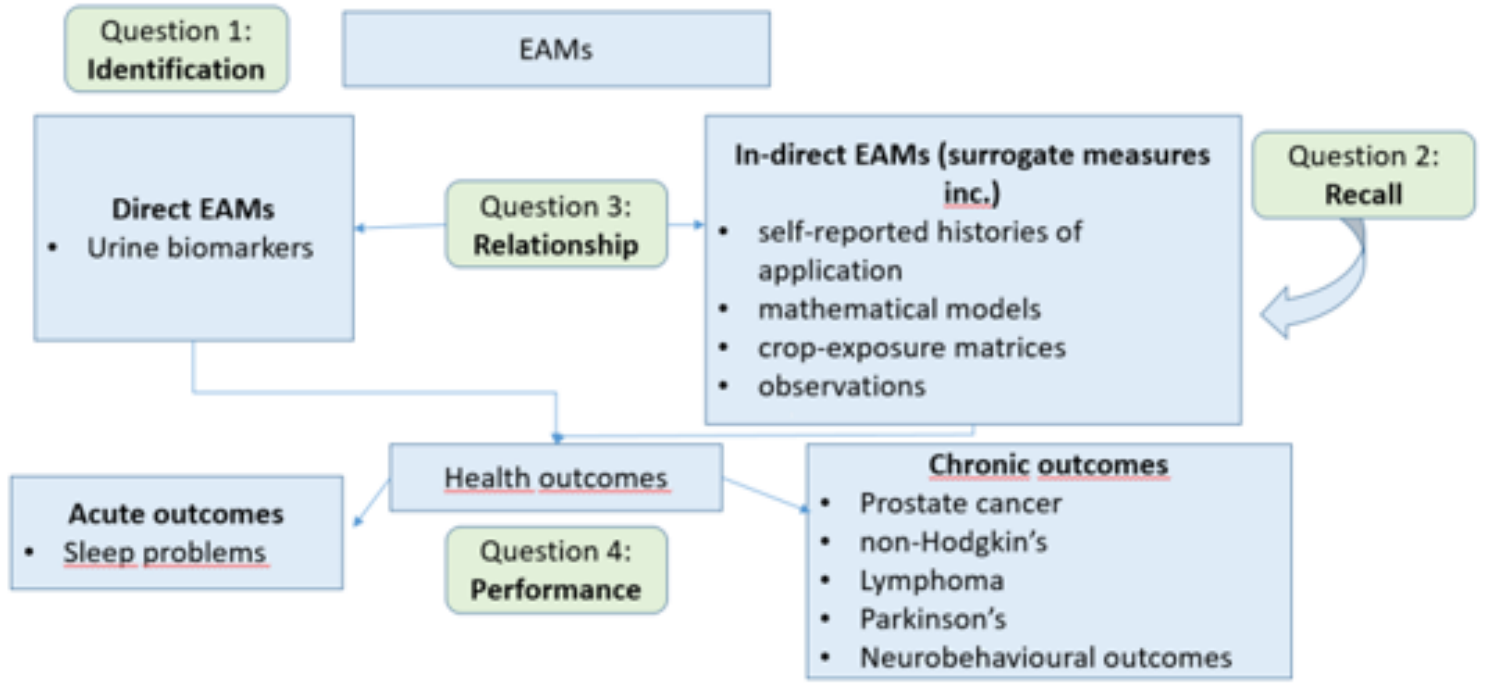
Tools and data considered:

Desk work:

- Systematic literature review
- Metanalysis

Existing & new data from studies

- Prospective Investigation of Pesticide Applicators' Health (PIPAH), UK
- Pesticide Users Health Study (PUHS), UK
- Study of Health in Agricultural Work (SHAW), UK
- Pesticide Use in Tropical Settings (PESTROP), Uganda
- Malaysia farm workers, Malaysia



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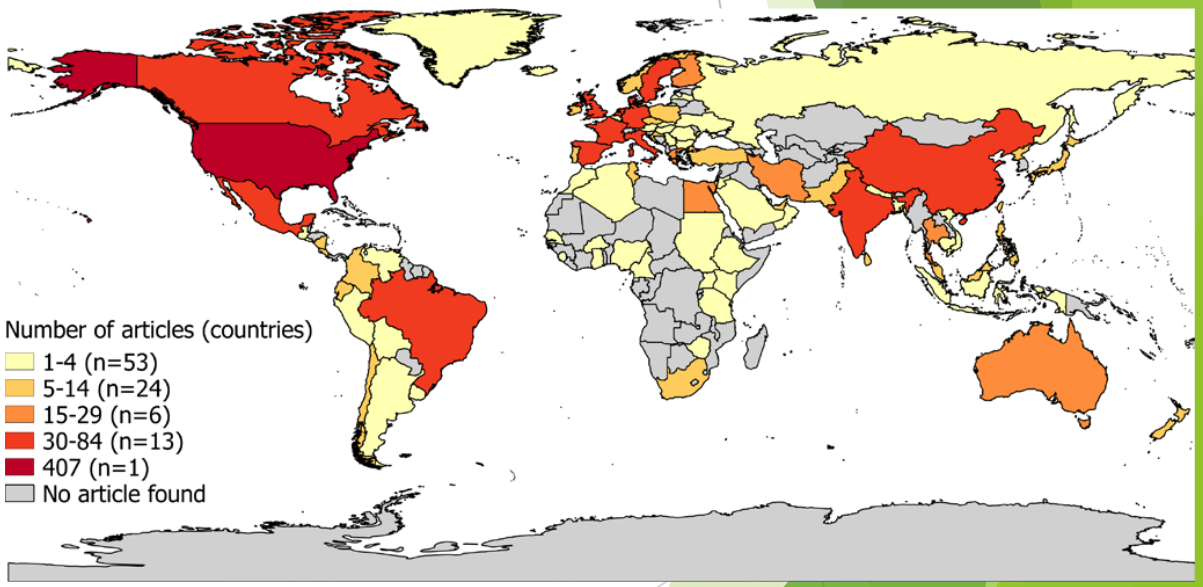
What EAMs are being used?

- Searched for articles reporting observational epidemiological studies in MEDLINE and Embase published 1993 to 2017.
- Relative frequency of EAM analysed according to EAM type (direct and indirect methods), health outcome, study design, study location (country) and specificity of assessment.
- Temporal trends in EAM were analysed.
- 1271 articles concerned studies performed in 97 countries reviewed

Systematic review of methods used to assess exposure to pesticides in occupational epidemiology studies, 1993–2017

Johan Ohlander [1], Samuel Fuhrimann [1], Ioannis Basinas [2], John W Cherrie [2,3], Karen S Galea [2], Andrew C Povey [4], Martie van Tongeren [4], Anne-Helen Harding [5], Kate Jones [5], Roel Vermeulen [1], Hans Kromhout [1]



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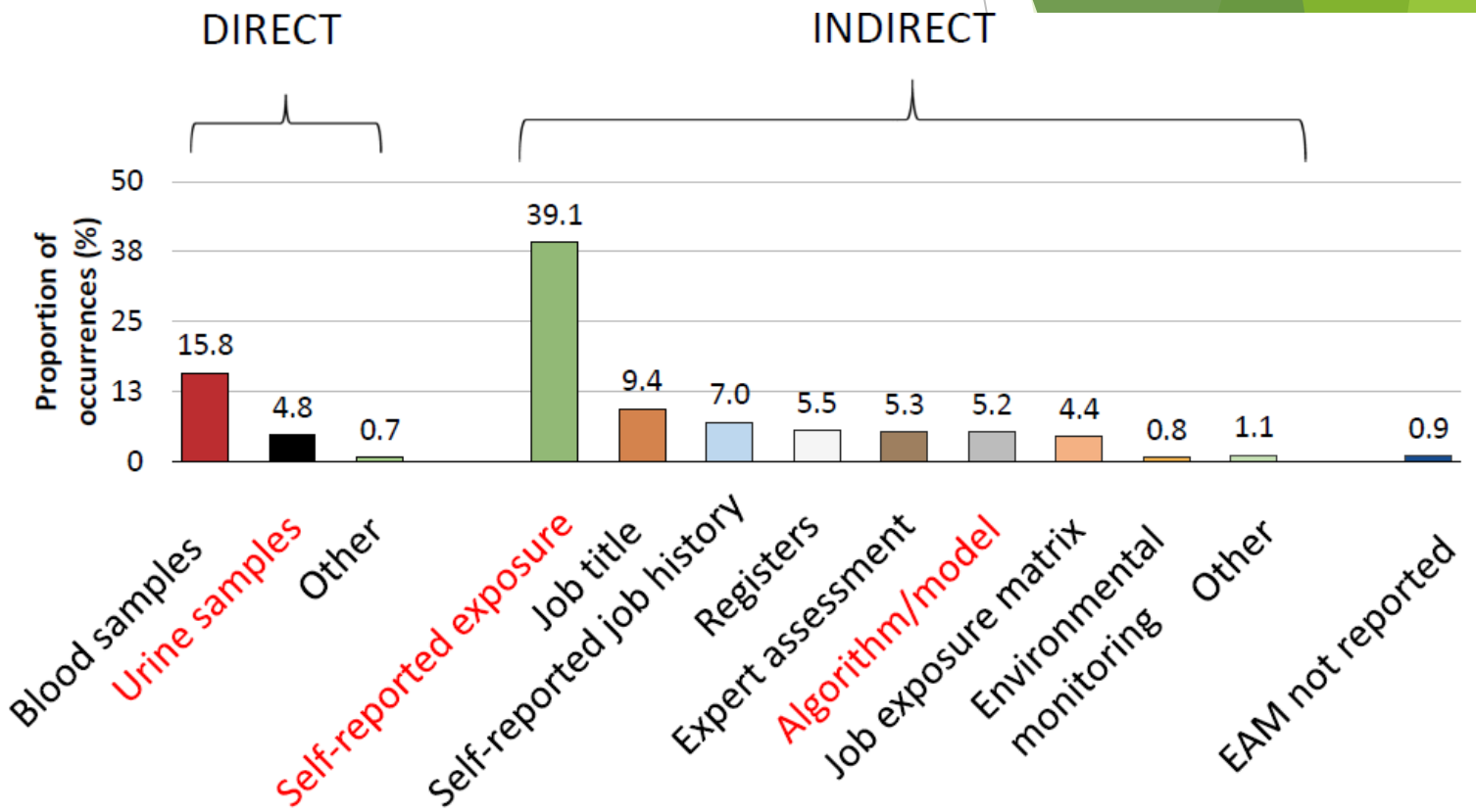
What did our review tell us?

- Majority of EAM indirect, based on self-reported exposure
- During last 25 years (1995-2020) ratio of indirect: direct EAM (5:1) was relatively constant
- For indirect EAM, increasing use of self-reported exposures and declining use of exposure assignment by job title and expert (case-by-case) assessment
- Epidemiological study design and endpoint studied have limited influence
- Modelled quantitative exposure data, exposure algorithms and their use in combination with more traditional methods are (still) very scarce



Evaluation of recall of exposure

- Objectives:
  - Assess recall of exposure modifying factors across different time periods
    - Frequency of pesticide use
    - Crops
    - PPE worn
    - Hygiene practices
    - Application methods
    - Active ingredients (Uganda only)
  - Examine differences /biases in recall ability by demographic characteristics

Evaluation of two-year recall of self-reported pesticide exposure among Ugandan smallholder farmers

William Mueller [a,*], Aggrey Atuhaire [b], Ruth Mubeezi [c], Iris van den Brenk [d], Hans Kromhout [d], Ioannis Basinas [a,e], Kate Jones [f], Andrew Povey [e], Martie van Tongeren [e], Anne-Helen Harding [f], Karen S. Galea [a], Samuel Fuhrimann [d,g,h]

Recall of exposure in UK farmers and pesticide applicators: trends with follow-up time

William Mueller[1,*], Kate Jones[2], Hani Mohamed[3], Neil Bennett[2], Anne-Helen Harding[2], Gillian Frost[2], Andrew Povey[3], Ioannis Basinas[1,3], Hans Kromhout[4], Martie van Tongeren[3], Samuel Fuhrimann[4] and Karen S. Galea[1]

Study	Country	Year of baseline questionnaire	Time to recall (years)	Follow-up survey/baseline survey (n)	Response rate
Pesticide Use in Tropical Settings – **PESTROP**	Uganda	2017	2	255/302	84%
Prospective Investigation of Pesticide Applicators' Health Study – **PIPAH**	UK	2016	3	336/730	46%
Pesticide Users' Health Study – **PUHS**	UK	2006	13	268/767	35%
Study of Health in Agricultural Work – **SHAW**	UK	2006-2008	12-14	39/234	17%

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What did we learn? In brief…

- UK farmers:
  - Results indicate that recall ability may deteriorate over a longer period.
  - Although low-response rates may require these findings to be interpreted with caution, 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.

- Uganda farmers:
  - Smallholder farmers in Uganda could better recollect after a 2-year period the total number of years using pesticides, as well as certain active ingredients and personal protection equipment (PPE), compared to poorer recall of specific crops.
  - More research is needed on recall in poorly educated agriculture communities in low- and middle-income settings to confirm these results.

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Factors influencing occupational exposure to pyrethroids and glyphosate: An analysis of urinary biomarkers in Malaysia, Uganda and the United Kingdom

William Mueller [a,*], Kate Jones [b], Samuel Fuhrimann [c], Zulkhairul Naim Bin Sidek Ahmad [d,e], Craig Sams [b], Anne-Helen Harding [b], Andrew Povey [d], Aggrey Atuhaire [f], Ioannis Basinas [d], Martie van Tongeren [d], Hans Kromhout [c], Karen S. Galea [a]

Relationship between self-reported exposure modifying factors and urinary pesticide biomarkers

- Studies
  - Malaysian Farm Workers Study (n=81) Malaysia
  - Pesticide Use in Tropical Settings Project (PESTROP) (n=84) Uganda
  - Prospective Investigation of Pesticide Applicators' Health (PIPAH) (n=106) UK

- Collection of same day pre & post-activity (mixing/spraying) urine samples
- Diaries to record duration, application methods, active ingredients used, hygienic behaviour, and use of personal protective equipment
- Multi-level censored (Tobit) regression models by cohort and active Ingredient
- Dependent variable: Urinary concentrations of 3-PBA (pyrethroids) and glyphosate
- Independent variables: exposure modifying factors, age, sex, education/literacy, creatinine

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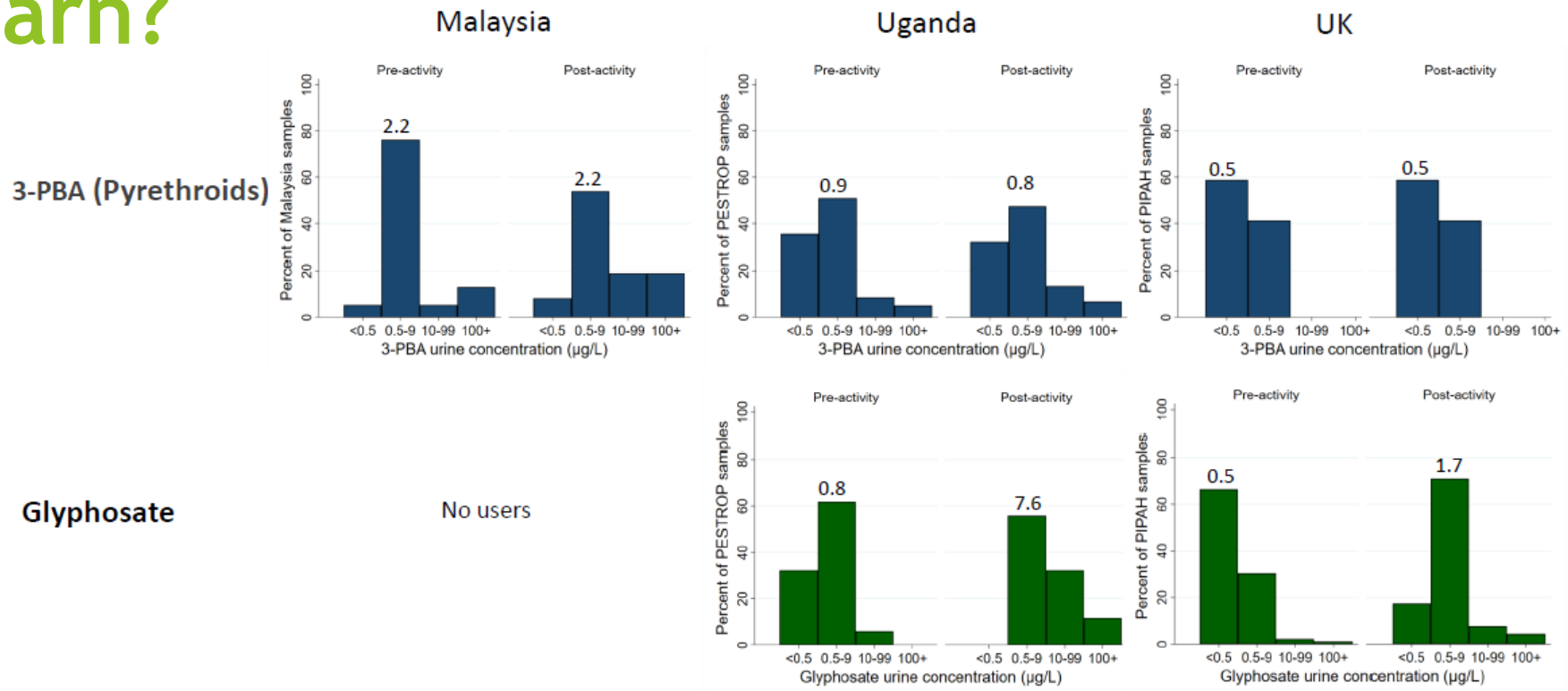
What did we learn?



- Duration of use, PPE, education level, 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 EMFs as the relevance of exposure routes, levels of detection, and farming systems/practices may be very context specific.

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How do different EAMs perform when applied the same health outcome?

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

Johan Ohlander [1], Samuel Fuhrimann [1], Ioannis Basinas [2,3], John W Cherrie [2,4], Karen S Galea,[2] Andrew C Povey,[3] Martie van Tongeren [3], Anne-Helen Harding,[5] Kate Jones [5], Roel Vermeulen [1], Anke Huss,[1] Hans Kromhout [1]

- We conducted three meta-analyses to specifically investigate how the type of EAM influenced summary risk estimates of prostate cancer (PC), non-Hodgkin's lymphoma (NHL) and Parkinson's disease.
- Influence of EAM type on the summary risk ratio (sRR) of PC (25 articles), NHL (29 articles) and PD (32 articles) was investigated.
- EAM 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.

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What did the meta-analyses tell us?

- EAM 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 EAM.
- Overall, study design, publication year and geographic region where the study was conducted, showed larger effects on estimated sRRs than EAM.
- When performing systematic reviews and meta-analyses 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.
- EAM is of less importance but shouldn't be forgotten given that they are closely linked to study design

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Exposure to Glyphosate, Mancozeb and neurobehavioral outcomes

Paper accepted and in publication

- Original EAMs based on information collected in 2017 indicating exposure for previous year:
  - Application status (yes/no)
  - Number of application days
  - Average exposure-intensity scores of an application (EIS) derived from a semi-quantitative exposure algorithm
  - Number of EIS-weighted application days
- Recalled information collected in 2019 resulted in two additional measures:
  - Re-called application status
  - Re-called EIS

What did the study tell us?

- Observed relationships between different measures of increasing exposure to glyphosate and a worse performance among four neurobehavioural 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.

Exposure to glyphosate and mancozeb and sleep problems

- 253 smallholder farmers studied in Uganda in 2017
- Questionnaire-based exposure measures
  - Any pesticide last week (never, 1-2; >2 days)
  - Glyphosate and mancozeb-specific measures:
    - Application during last 12 months (yes/no)
    - Application timing (never, last 7 days, last 12 months but not last 7 days)
    - Number of application days last year
    - Average exposure-intensity scores (EIS) derived from a semi-quantitative exposure algorithm
    - EIS-weighted application days last year
- Estimated exposure based urinary biomarkers
  - Glyphosate and mancozeb-specific measures
  - Post-workday urinary glyphosate/Pre-workday urinary ETU

Self-reported and urinary biomarker-based measures of exposure to glyphosate and mancozeb and sleep problems among smallholder farme in Uganda

Samuel Fuhrimann [a,b,c,*], William Mueller [d], Aggrey Atuhaire [e], Johan Ohlander [a], Ruth Mubeezi [f], Andrew Povey [g], Ioannis Basinas [d,g], Martie van Tongeren [g], Kate Jones [h], Craig Sams [h], Karen S. Galea [d], Hans Kromhout [a]

What did the study tell us?

- Positive (statistically significant) associations with 6-item sleep problem index
  - Self-reported any pesticide application in last 7 days
  - Self-reported glyphosate application in last 7 days
  - Self-reported mancozeb application in last 12 months
  - Estimated average urinary glyphosate concentrations showed an exposure-response association
  - Estimated average urinary ETU concentration

- •No associations with 6-item sleep problem index
  - Other glyphosate and mancozeb exposure measures based on self-reports

- Active ingredient-specific short-term and long-term exposure measures based on either self-reported information or based on urinary biomarkers can be used when studying the association with (acute) sleep problems

  But,

- Performance of exposure measures will be largely depending on contrast in exposure in the studied population and when studying acute (health) effects whether the exposure measure covers biologically relevant time window of exposure
- Perform pilot exposure studies to improve EA and have informative studies on pesticides and health effects

Take home messages

- Exposure assessment is a critical component of pesticide epidemiological studies
- EAMs used 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
- No EAM is *a priori* superior to others, but careful choices and exposure validation studies are a pre-requisite for informative epidemiological studies on health effects from pesticides

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IMPRESS peer-reviewed publications

- Fuhrimann S, et al. Occupational exposure to pesticides and neurobehavioral outcomes. Impact of different original and recalled exposure measures on the associations. Ann Work Expo Health. 2024. In press.
- Fuhrimann S, et al. Self-reported and urinary biomarker-based measures of exposure to glyphosate and mancozeb and sleep problems among smallholder farmers in Uganda. Environ Int. 2023 Dec;182:108277. doi: 10.1016/j.envint.2023.108277.
- Jones K, et al. Improving Exposure Assessment Methodologies for Epidemiological Studies on Pesticides: Study Protocol. JMIR Res Protoc. 2020 Feb 28;9(2):e16448. doi: 10.2196/16448.
- Mueller W, et al. Factors influencing occupational exposure to pyrethroids and glyphosate: An analysis of urinary biomarkers in Malaysia, Uganda and the United Kingdom. Environ Res. 2024 Feb 1;242:117651. doi: 10.1016/j.envres.2023.117651. Epub2023 Nov 22.
- Mueller W, et al. Evaluation of two-year recall of self-reported pesticide exposure among Ugandan smallholder farmers. Int J HygEnviron Health. 2022 Mar;240:113911. doi: 10.1016/j.ijheh.2021.113911.
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- Ohlander J, et al. Systematic review of methods used to assess exposure to pesticides in occupational epidemiology studies, 1993-2017. OccupEnviron Med. 2020 Jun;77(6):357-367. doi: 10.1136/oemed-2019-105880. Epub2020 Feb 25.
- Ohlander J, et al. 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. OccupEnviron Med. 2022 Aug;79(8):566-574. doi: 10.1136/oemed-2021-108046.

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Funding and project governance

Funding source:

Project Governance:

- Independent Advisory Board provides independent and impartial expert advice
- All completed Conflict of Interest forms
- Project governance document stating agreed roles, responsibilities and interactions of those involved
- Freedom to publish our project findings

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The IMPRESS team!