Environmental Research 242 (2024) 117651

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

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

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ARTICLE INFO

Keywords:
Pesticides
Exposure assessment
Occupational epidemiology
Biomarkers

ABSTRACT

Background: Long-term exposure to pesticides is often assessed using semi-quantitative models. To improve these models, a better understanding of how occupational factors determine exposure (e.g., as estimated by biomonitoring) would be valuable.

Methods: Urine samples were collected from pesticide applicators in Malaysia, Uganda, and the UK during mixing/application days (and also during non-application days in Uganda). Samples were collected pre- and post-activity on the same day and analysed for biomarkers of active ingredients (AIs), including synthetic pyrethroids (via the metabolite 3-phenoxybenzoic acid [3-PBA]) and glyphosate, as well as creatinine. We performed multilevel Tobit regression models for each study to assess the relationship between exposure modifying factors (e.g., mixing/application of AI, duration of activity, personal protective equipment [PPE]) and urinary biomarkers of exposure.

Results: From the Malaysia, Uganda, and UK studies, 81, 84, and 106 study participants provided 162, 384 and 212 urine samples, respectively. Pyrethroid use on the sampling day was most common in Malaysia (n = 38; 47%), and glyphosate use was most prevalent in the UK (n = 93; 88%). Median pre- and post-activity 3-PBA concentrations were similar, with higher median concentrations post-compared to pre-activity for glyphosate samples in the UK (1.7 to 0.5 μg/L) and Uganda (7.6 to 0.8 μg/L) (glyphosate was not used in the Malaysia study). There was evidence from individual studies that higher urinary biomarker concentrations were associated with mixing/application of the AI on the day of urine sampling, longer duration of mixing/application, lower PPE protection, and less education/literacy, but no factor was consistently associated with exposure across biomarkers in the three studies.

Conclusions: Our 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 and AI-specific.

1. Introduction

The global average pesticide use per area of cropland has increased by almost 50% since the 1990s (1.2–1.8 kg/ha) (FAOSTAT, 2022). The occupational use of pesticides has been linked to many adverse health outcomes including cancers (e.g., multiple myeloma, bladder cancer,

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https://doi.org/10.1016/j.envres.2023.117651
Received 31 May 2023; Received in revised form 17 October 2023; Accepted 10 November 2023
Available online 22 November 2023

non-Hodgkin's lymphoma, prostate cancer, leukaemia, and breast cancer) (Pedroso et al., 2022), respiratory illnesses (e.g., asthma, chronic obstructive pulmonary disease, impaired lung function) (Ye et al., 2017), cognitive impairment (Lucero and Muñoz-Quezada, 2021), and acute poisoning (Dhananjayan and Ravichandran, 2018).

A systematic review on occupational pesticide exposure found that in nearly 1300 papers, approximately five times as many studies were based on indirect (e.g., self-reported) compared to direct (e.g., [bio] monitoring) exposure assessment methods (EAMs) (Ohlander et al., 2020). The reliability of self-reported data can vary depending on the exposure parameter (Mueller et al., 2022a) and can also lead to exposure misclassification, particularly over time (Mueller et al., 2022b). Direct EAMs, such as the analysis of urinary biomarkers, tend to be more costly and resource intensive, which is especially challenging for low- and middle-income country (LMIC) settings (Fuhrimann et al., 2020) and only reflect a defined, limited exposure window. Risk estimates of certain health outcomes (e.g., prostate cancer, non-Hodgkin's lymphoma and Parkinson's disease) have been shown to depend more strongly on the study design and geographic location than the EAM used (i.e., direct/indirect); however, study design and exposure assessment are often closely related and thus difficult to disentangle (Ohlander et al., 2022).

For long-term health outcomes, it is impractical to have continuous monitoring, so an exposure model is often needed, especially in LMICs (e.g., Negatu et al., 2016). To improve these models, a better understanding is needed of how occupational factors determine exposure (e.g., as estimated by biomonitoring). Interpretation of results from urinary biomarkers to determine occupational pesticide exposure is complex, as results will depend on application practices, biological half-life of metabolites, exposure from other sources (e.g., food and drinking water), and ability to detect low urinary concentrations (Barrón Cuenca et al., 2020; Oerlemans et al., 2021).

The "IMPRoving Exposure aSSessment methodologies for epidemiological studies on pesticides" (IMPRESS) project (www.impress-project.org), aimed to improve understanding of the performance of pesticide EAMs used in epidemiological investigations, and to recommend enhancements in scientific practice (Jones et al., 2020). The present study aimed to evaluate the associations between different exposure-modifying factors (i.e., individual behaviours, workplace characteristics, and work tools that may affect one's exposure to a given active ingredient [AI]) and urinary biomarker concentrations based on three studies of farmers in Malaysia, Uganda, and the UK. These diverse study settings allowed an examination of these factors across different populations and pesticides (i.e., pyrethroids and glyphosate using the urinary biomarkers 3-phenoxybenzoic acid [3-PBA] and glyphosate, respectively), which can help inform and improve pesticide exposure models.

2. Methods

2.1. Study descriptions

Our analysis was based on data from three existing epidemiological studies aligned within the IMPRESS project: the Malaysian Farmers study, the Pesticide use in tropical settings (PESTROP) study in Uganda, and the Prospective Investigation of Pesticide Applicators' Health (PIPAH) in the UK.

The Uganda farmers study (PESTROP) consists of 300 smallholder farmers that were recruited in 2017 (Staudacher et al., 2020). The study aims to generate a deeper understanding of the environmental, health, and regulatory dimensions of pesticide use in Uganda. For the current study, all 300 farmers were contacted via mobile telephone and selected if they planned to spray in the upcoming spraying season; 86 participants provided repeat urine samples in 2020.

The Malaysian farmers study was a prospective study of farmer's ill-health in the pesticide spraying season in the Kelantan state of Malaysia (bin Sidek Ahmad et al., 2023). Participants were interviewed to provide baseline information on socio-demographic and occupational factors, as well as their health. During the spraying season, urine samples were collected by the farmers, activities were video recorded by a trained researcher, and dermal exposure was estimated using the DREAM (dermal exposure assessment method) tool's ranking of tasks. The DREAM tool is a semi-quantitative dermal exposure assessment method that estimates exposure levels on the outside clothing layer and skin (Van Wendel de Joode et al., 2003). Participants also kept a diary on pesticide use and health symptoms. Data collection took place between September 2018 and February 2019 and involved 150 participants.

The PIPAH study was established by Great Britain's Health and Safety Executive (HSE) to investigate working with pesticides and health (Harding et al., 2017). PIPAH involves over 5700 men and women in the UK who are certified pesticide users, aged 17 to over 80 years. All subjects who completed the 2016 exposure questionnaire and were still working with pesticides (n = ~1500) were invited to participate; 106 participants provided urine samples between 2019 and 2020.

2.2. Field data collection

We used common urine sample collection and analytical methods, which were described in the IMPRESS study protocol (Jones et al., 2020). Briefly, pre- and post-activity urine samples were collected on the same day during pesticide application in all three studies, as well as during non-application days in PESTROP (Uganda). Activities included mixing and application. For non-application days, sample collection was attempted within 7 days of crop spraying. Sampling occurred irrespective of the pesticide involved except for the PIPAH (UK) participants, who were asked to collect samples when a pesticide from a list of preselected substances was applied (Jones et al., 2020). However, if none of these products were routinely used, these participants were asked to provide samples on any day involving contact with pesticides and to record the product or AIs in their activity diary. PIPAH (UK) and the Malaysian Farmers (Malaysia) study participants provided samples on one day only, whereas participants were visited up to three times in the PESTROP (Uganda) study.

Clear instructions on how to provide the urine samples in a manner to minimise potential cross-contamination were given in a written (PIPAH, UK) or verbal (PESTROP, Uganda & Malaysian Farmers, Malaysia) and semi-pictorial form (all). Field blanks were collected to assess any contamination of sample bottles by the worker. These comprised empty vials, filled with tap or bottled water by the participants themselves, and were included in approximately 10% of the samplings, with selection being made at random by the researcher. Further details are provided in Supplementary Material 1.

As the three studies were initiated prior to the IMPRESS project, some of the data collection questionnaires were not standardised. Researcher-led (PESTROP, Uganda and Malaysian Farmers, Malaysia) or self-administered (PIPAH, UK) diaries were used to collect information on factors considered important for determining the workers' level of pesticide exposure. This information included contextual data (e.g., activities involved and time spent on them), pesticide application and mixing methods, equipment used, where activities took place (indoor or outdoor), cleaning tasks, products, AIs and quantities used, and use of personal protective equipment (PPE). For PESTROP (Uganda), the urine sample collection coincided with participant recall evaluation, which necessitated the use of the same original questionnaire (Mueller et al., 2022a). In the Malaysian Farmers study (Malaysia), the urine sample collection and questionnaire administration had been completed earlier than the core IMPRESS study. To ensure quality control, all field researchers were fully trained to collect samples and administer data collection tools. Questionnaires were similar to those completed previously by study participants, who have demonstrated consistent responses (Mueller et al., 2022a, 2022b).

Urine samples were immediately stored in the participant's

refrigerator before being either collected by researchers in the field and then frozen by the local research teams within 24 h prior to courier shipment to the UK for analysis (Malaysian Farmers, Malaysia & PESTROP, Uganda) or posted by participants to the HSE laboratory (PIPAH, UK). On receipt, samples were stored frozen (<-15 °C) within five days of collection (the length of the stability trial; see Supplementary Material 1.4) until analysis. Overseas samples were shipped with temperature loggers, and all samples remained frozen during transit.

2.3. Analysis of biomarkers

Analysis of collected urine samples was based on the AI applied on the day of urine collection. A minimum of 20 pre- and post-activity samples during non-application days were analysed as well, except for glyphosate in the UK (n = 19 pairs). Based on the reported AIs and frequencies of use across participants in the three studies, we report on the urine sample analysis of synthetic pyrethroids and glyphosate. The number of samples analysed is presented in Table 1. The methods of biomarker analysis were established previously: the synthetic pyrethroids' method was adapted from Galea et al. (2015) and the glyphosate method was described in Connolly et al. (2017, 2018). Briefly, the pyrethroid method involved solid phase extraction (SPE, C18 phase) after enzyme hydrolysis followed by liquid chromatography with tandem mass spectrometry analysis (LC-MS/MS) using negative electrospray ionisation. The glyphosate method involved SPE (strong anion exchange) followed by LC-MS/MS, again using negative electrospray ionisation. These analyses have sufficient sensitivity to detect exposures in non-occupationally exposed individuals. The limit of quantification (LoQ), the minimum concentration at which the compound can be measured reliably, was set at 0.5 μg/L for both compounds. The methods are described in further detail in Supplementary Material 1. HSE's laboratory has established internal quality control systems for the methods and, in addition, has successfully participated in external quality assurance at environmental levels (www.g-equas.de).

Table 1
Characteristics of participants and urine samples in each study.

Characteristics	Malaysian farmers (Malaysia)	PESTROP (Uganda)	PIPAH (UK)
Number of individual farmers	81	84	106
Number of analysed days	81	192	106
Number of analysed urine samples			
3-PBA	147	216	64
Glyphosate	40	384	212
Mixing/application of Active Ingredient on sampling day: n (%)			
Pyrethroids	38 (47)	59 (31)	17 (16)
Glyphosate	0 (0)	34 (18)	93 (88)
Detection of biomarker in analysed urine samples[a]: n (%)			
3-PBA	137 (93)	130 (60)	29 (45)
Glyphosate	N/A	163 (42)	123 (58)
Sex: n (%)			
Male	81 (100)	65 (77)	106 (100)
Female	0 (0)	19 (23)	0 (0)
Age (years): mean (SD)	46.2 (15.6)	46.4 (11.5)	57.5 (8.1)
Duration[b] (hours): mean (SD)			
Pyrethroids	1.3 (0.58)	2.7 (2.4)	2.2 (2.8)
Glyphosate	N/A	3.4 (3.4)	4.1 (4.4)
Completion of hygiene habits (any) following Active Ingredient use: n (%)	N/A	177 (92)	65 (61)
Application method: n (%)			
Manual	81 (100)	192 (100)	39 (37)
Tractor-based	0 (0)	0 (0)	67 (63)

N/A: Not applicable; SD: Standard deviation.
[a] Includes pre- and post-activity samples.
[b] Mixing/spraying/finishing for PIPAH, spraying/mixing for PESTROP (Uganda), spraying for Malaysian farmers (Malaysia).

All samples were analysed within two years of collection. Published data, quality control, or sample stability data show that all analytes are stable at < -15 °C for more than two years (e.g., Leng et al., 1997; Galea et al., 2015; Noren et al., 2020).

2.4. Statistical analysis

Pre- and post-activity median urinary concentrations were calculated for each AI in each study, including the number of measurements below the LoQ (<0.5 μg/L). To determine associations between exposure modifiers and the urine metabolites, we performed multilevel Tobit regression models to account for left-censored data where concentrations were <LoQ (Lubin et al., 2004). Multilevel Tobit models have the ability to account for the presence of correlations between multiple observations from the same individual (Wang and Griswold, 2016).

We developed models separately for each study and AI given the distinct exposure situations and (differences in) availability of information (Table S2.1). The use of an AI was defined as mixing, application, and/or finishing (e.g., cleaning) activities. For PPE protection, we developed categories separately for each study to maximise variation, which accounted for the reported use of a tractor cab or wearing gloves/facemask (UK) or the number of body parts protected (Malaysia/Uganda) (see Supplementary Material 3 for sensitivity analyses). Specific model parameters are provided below for each study. Distributions of biomarker concentrations were skewed right and were natural log-transformed as the dependent variable in regression models. Regression residuals were assessed using kernel density estimations and quantile-quantile plots (Meuleman et al., 2015). Model outputs (i.e., exponentiated coefficients) represent the fold-change of biomarker concentrations for the presence of a given determinant. We also compared the correlation of biomarker concentrations to scores generated by selected semi-quantitative exposure models (Coble et al., 2011; Negatu et al., 2016) (see Supplementary Material 4). We used Stata (v18) for statistical analysis.

2.4.1. Malaysian Farmers (Malaysia)

Due to the limited use of glyphosate by the participating farmers, the analysis focussed only on 3-PBA. The Tobit regression models for the Malaysian Farmers dataset relating to 3-PBA concentrations included a random intercept for participant and parameters for pre- or post-activity sample time; PPE protection; duration of spraying; a binary indicator for mixing pesticides; age; education; and creatinine concentration.

PPE worn during spraying activities was categorised by the number of the following body parts protected: hands, feet, and face. Two or more body parts protected was the reference category (see individual items in Table S2.2). A variable was generated for the reported hours of duration spraying pyrethroids on the sampling day. Sex was excluded, as all participants were male. Age was included as a continuous measure representing 10-year intervals. Education was classed as 'beyond secondary' or 'primary/no formal' with 'secondary' as the reference group. Information on hygiene practices was not included in the activity diary.

Sensitivity analyses were undertaken to include the method of manual application (i.e., backpack, power sprayer, or blower), the specific pyrethroid used (i.e., cypermethrin, deltamethrin, lambda-cyhalothrin, cyfluthrin), and the reported exposure of specific body parts (i.e., head, arms, chest, legs, feet). As well, semi-quantitative DREAM dermal exposure estimates were included in the model based on spraying and mixing activities (Van-Wendel-de-Joode et al., 2003).

2.4.2. PESTROP (Uganda)

The Tobit regression models for the PESTROP (Uganda) dataset relating to glyphosate and 3-PBA concentrations included random intercepts for participant and visit (to account for multiple sampling days); a binary indicator either for the formulation/application of glyphosate or pyrethroids on the sampling day; pre- or post-activity sample time; duration of formulation/application; PPE protection; completion of any

hygiene activities; age; sex; literacy ability; and creatinine concentration.

Duration of formulation/spraying was calculated as the sum of the difference of reported start and stop times of mixing and/or spraying separately for products containing glyphosate or pyrethroids. A parameter for entering treated fields was not included in the model, since there was only n = 1 such instance after spraying pyrethroids in the previous week and n = 4 after spraying glyphosate. PPE protection categories were based on the protection of 5–6 (reference), 3–4 and 0–2 body parts, including the following: eyes, mouth/nose, upper body, hands, legs, feet (see Table S2.3). Hygiene was based on an indicator for undertaking any of the following habits: cleaning spraying equipment, washing hands during/after work, bathing after work, or changing clothes after work. Age in 10-year increments was included as a continuous variable as above. Binary variables were included for sex and self-reported literacy (as an indicator for education).

We performed several sensitivity analyses. The use of products containing glyphosate or pyrethroids in the past week and year was incorporated into models to check the robustness of associations with pesticide formulation/spraying on the day urine samples were provided. Cypermethrin was used as a proxy for pyrethroid formulation/spraying in the prior year. The quantity of a product mixed/applied (where values reported could be standardised to ml) was examined. Nearly all participants who used glyphosate reported the use of 'Weedmaster' (n = 2 reported 'Muddosate' and 'Weedban'), so it was not possible to examine the influence of different formulations for that AI. However, we did compare the formulation/spraying of different pyrethroid-based products. We also examined associations with the individual hygiene habits, as listed above.

2.4.3. PIPAH (UK)

The Tobit regression models for the PIPAH (UK) dataset relating to glyphosate and 3-PBA concentrations included a random intercept for participant; a binary indicator either for mixing/application of glyphosate or pyrethroids on the sampling day; pre- or post-activity sample time; duration of mixing/spraying/finishing; pesticide application method; PPE protection; any hygiene activities; age; education; and creatinine concentration (to correct for hydration status) (Barr et al., 2005).

Duration of mixing/application/finishing was calculated by summing the reported hours for each activity separately for glyphosate and pyrethroids, which was capped at 18 h (this maximum was applied to two individuals). PPE protection categories were defined by the use of a tractor cab for each activity performed (reference category), the use of either gloves or a facemask for all activities, and neither of these scenarios. A parameter was included to identify boom (i.e., tractor-based) or manual pesticide application methods. For hygiene activities, a binary variable was included to indicate if the individual had at any time subsequent to handling pesticides showered or changed their gloves, clothes, or mask. Age in 10-year periods was included as a continuous variable, and education was linked to an earlier study questionnaire (Mueller et al., 2022b) and was classed as 'higher'/'vocational' or 'other'/'no formal' with 'secondary' as the reference group.

Several parameters were omitted from these models. Sex was excluded since all participants were male. Only two individuals reported activities related to the entry of fields treated within one week prior to sampling, so this parameter was not included. While the quantity of product used was included in the PIPAH (UK) survey, reported amounts were often in the form of a rate per area; however, without consistent information on the total area on which a product was applied, it was not possible to calculate the overall quantity of product used. Sensitivity analyses were conducted to examine statistical associations with individual hygiene practices and the formulation/spraying of glyphosate on the previous day (not pyrethroids, since only n = 3 mixed/applied this AI on the previous day).

3. Results

From the Malaysia, Uganda, and UK studies, 81, 84, and 106 study participants provided 162, 384 and 212 urine samples, respectively. Eighty-five (80%) of PIPAH (UK) participants had a secondary or higher education or vocational degree with n = 5 participants missing these data. Seventy three (87%) of the PESTROP (Uganda) participants self-reported to be literate. Fifty-four (67%) of the Malaysian Farmers (Malaysia) study participants had a secondary education or university degree. For PPE protection categories in the Malaysian Farmers (Malaysia) study, there were 45 (56%) and 28 (35%) participants with at least two and one body part protected, respectively. In PESTROP (Uganda), 17 (7%) and 61 (32%) had 5-6 and 3–4 body parts protected, respectively, and in PIPAH (UK), 19 (18%) and 74 (70%) reported the use of a cab and gloves/facemask, respectively. Table 1 presents descriptive characteristics for each study.

3.1. Analysis of urinary 3-PBA concentrations

Median urinary 3-PBA concentrations in pyrethroid users were similar in the pre- and post-activity samples in the three studies and were highest in the Malaysian Farmers (Malaysia) study (2.2 μg/L) (Fig. 1).

In the Malaysian Farmers (Malaysia) study, the use (i.e., mixing/applying) and duration of spraying of pyrethroids were highly correlated (*rho* = 0.96) (Fig. S2.1); duration of spraying was used due to better model fit based on the lower value of its Akaike Information Criterion (AIC) (i.e., 348.6 vs 359.5). Only the duration of spraying pyrethroids (per hour) was associated with higher concentrations (1.41 [95% CI: 1.07–1.86]) (Fig. 2i). Sensitivity analysis did not identify any clear associations with the type of manual application or dermal exposure (DREAM) scores for mixing or spraying. 3-PBA concentrations were higher for users of cypermethrin (2.22 [95% CI: 1.49–3.31]), but not other pyrethroids (0.65 [95% CI: 0.38–1.14]); due to a high correlation with the use of specific pyrethroid products (*rho* = 0.92), duration of spraying pyrethroids was excluded from this analysis.

For the PESTROP (Uganda) analysis, the binary use (i.e., mixing/applying) and duration of activity with pyrethroids were highly correlated (*rho* = 0.98) (Fig. S2.1); duration was included based on a lower AIC value (i.e., 521.2 vs 522.6). No parameter indicated a strong association with urinary 3-PBA concentrations (Fig. 2ii). A sensitivity analysis found higher concentrations with pyrethroid use in the previous 7 days (1.49 [95% CI: 1.01–2.19]), but not with use within the past year. There was no association with individual hygiene practices, quantity of product, or use of specific pyrethroid products (data not shown).

In the PIPAH (UK) study, most exposure parameters did not indicate a clear relationship with urinary concentrations (Fig. 2iii). The binary use (i.e., mixing/applying) and duration of activity with pyrethroids were highly correlated (*rho* = 0.92) (Fig. S2.1); the binary variable was ultimately included due to better model fit based on the lower value of its AIC (i.e., 116.9 vs 118.3). Only the use of gloves/facemask compared to a cab was associated with two-fold higher biomarker concentrations (2.10 [95% CI: 1.04–4.23]). A sensitivity analysis with individual hygiene practices in separate models identified three-fold lower concentrations with changing gloves only (0.31 [95% CI: 0.12–0.80]). See Table S2.4 for fold-ranges across the three studies.

There were moderate correlations (*rho* = 0.34 to 0.55) between urinary biomarker concentrations and exposure algorithm scores for pyrethroids in the PIPAH (UK) study only, with no apparent correlations (*rho* = −0.04 to 0.17) in the PESTROP (Uganda) or Malaysian Farmers (Malaysia) studies (Figs. S4.2-S4.4).

3.2. Analysis of urinary glyphosate concentrations

Median urinary concentrations in glyphosate users were higher in the post-activity urine samples for both the PIPAH (UK) (1.7 μg/L) and

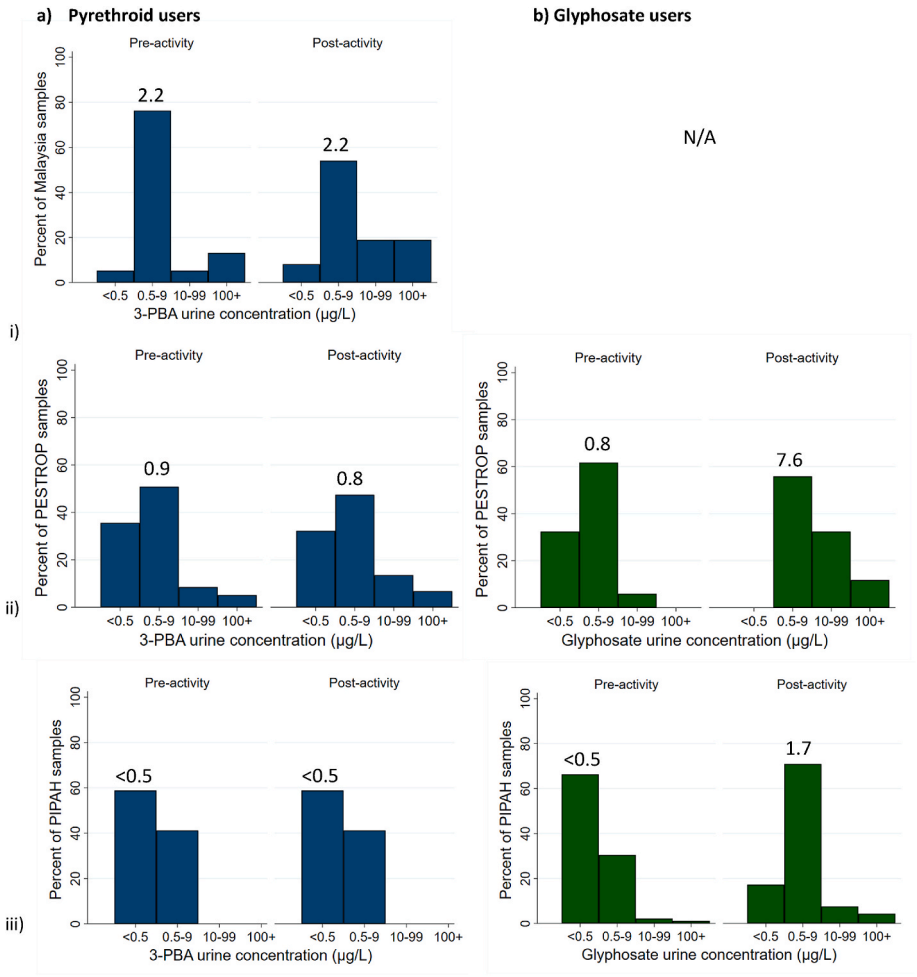

Fig. 1. Histograms of pre- and post-activity urinary biomarker concentrations for participants who used a) pyrethroids and b) glyphosate in i) Malaysian Farmers (Malaysia) (no glyphosate users) ii) PESTROP (Uganda), and iii) PIPAH (UK). The '<0.5' category represents < LoQ. Median pre and post-activity biomarker concentrations in µg/L are indicated above the applicable bin.

PESTROP (Uganda) (7.6 µg/L) studies. All post-activity values for glyphosate were above the LoQ in the PESTROP (Uganda) study (Fig. 1).

For the PESTROP (Uganda) study, the binary use (i.e., mixing/applying) and duration of activity were highly correlated (*rho* = 0.99) (Fig. S2.1); use was included based on a lower AIC value (i.e., 869.4 vs 892.6). The mixing/application of glyphosate on the day of sample collection was associated with nearly 12-fold higher concentrations: 11.7 (95% CI: 5.47–24.9). Lack of literacy was linked to three-fold higher urinary concentrations (3.57 [95% CI: 1.11–11.4]) (Fig. 3i). A sensitivity analysis found a non-significant increase in biomarker levels when glyphosate was also used in the previous week: 2.20 (95% CI: 0.86–5.64). There was no clear association with the quantity of product mixed/applied or individual hygiene practices (data not shown).

In the PIPAH (UK) study, several parameters were associated with higher concentrations: other/no formal education compared to secondary education (2.66 [95% CI: 1.16–6.14]), duration (hours) of mixing/spraying/finishing (1.09 per hour [95% CI: 1.02–1.16]), and (borderline) neither use of gloves/facemask nor a cab compared to a cab (3.02 [95% CI: 0.97–9.47]) (Fig. 3ii). A sensitivity analysis with individual hygiene practices in separate models identified three-fold lower concentrations only with changing masks regularly (0.31 [95% CI: 0.11–0.84]). There was a non-significant increase in biomarker levels when glyphosate was also mixed/sprayed on the day prior to sampling (2.04 [95% CI: 0.82–5.09]). See Table S2.5 for coefficient values across the three studies.

There was no association (*rho* = −0.09 to 0.06) between exposure algorithm scores and urinary glyphosate concentrations in the PIPAH (UK) and PESTROP (Uganda) studies (Figs. S4.2-4.4).

4. Discussion

Our study analysed urinary biomarkers of pesticide exposure to pyrethroids and glyphosate in occupational studies in three continents. Urinary biomarker concentrations were higher in applicators in the Malaysian Farmers (Malaysia) and PESTROP (Uganda) studies than those in the PIPAH (UK) study. This difference was more pronounced for glyphosate (used only in the PESTROP [Uganda] and PIPAH [UK] studies) than for 3-PBA. Formulation/spraying of the AI on the day of urine sampling, duration of formulation/spraying, less PPE protection, and lower education were associated with higher urinary biomarker concentrations, but no one factor was consistently associated across biomarkers and studies. This apparent lack of consistency may be due to complicating factors, such as the relevance of different exposure routes (e.g., delayed dermal uptake) or differences in metabolism across AIs. There were also some nuances in contextual data that are challenging to codify (e.g., proper use/reuse of PPE, application practices, farming systems).

4.1. Mixing/application of AI & duration of exposure

The use of glyphosate in the PESTROP (Uganda) study was the only instance where (binary) mixing/application was associated with

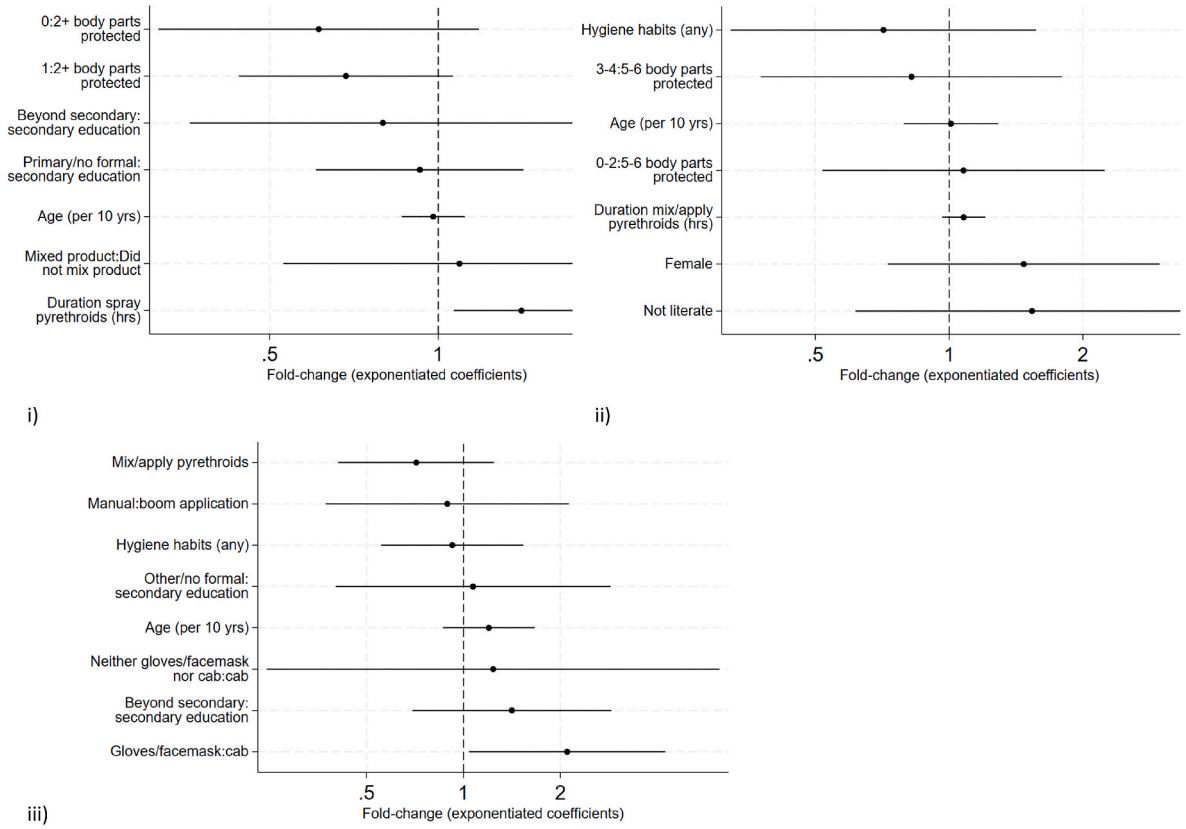

Fig. 2. Tobit regression coefficient plots for urinary 3-PBA concentrations (pyrethroid exposure) across i) Malaysian Farmers (Malaysia), ii) PESTROP (Uganda), and iii) PIPAH (UK) studies. Coefficients are mutually adjusted for all variables shown, as well as sample time (pre/post-activity) and urinary creatinine.

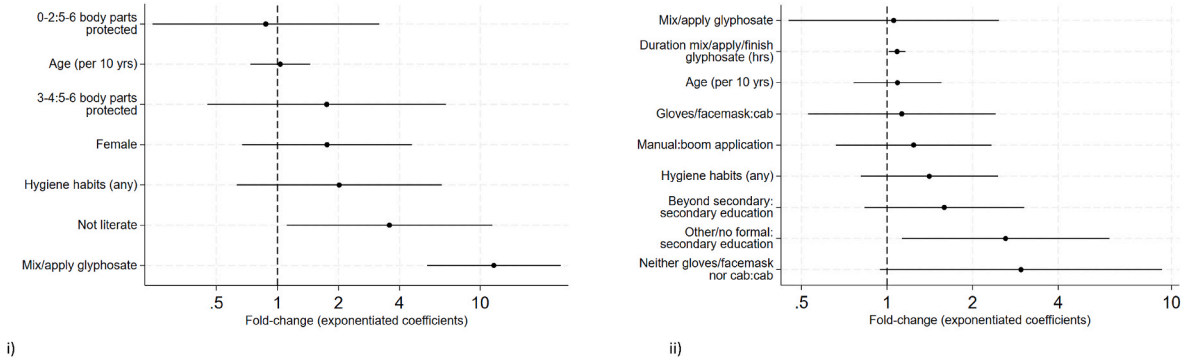

Fig. 3. Tobit regression coefficient plots for urinary glyphosate concentrations across i) PESTROP (Uganda) and ii) PIPAH (UK) studies. Coefficients are mutually adjusted for all variables shown, as well as for sample time (pre/post-activity) and urinary creatinine.

increased urine concentrations. There may be many reasons why mixing/application of an AI is not clearly linked to urinary metabolite levels. These include the efficacy of personal protection used, the timing and contribution of different exposure routes (e.g., ingestion, inhalation, dermal uptake), re-entry exposure on non-spraying days, and possible absorption or reabsorption from previously contaminated hands or gloves (Connolly et al., 2019a; Kohsuwan et al., 2022). It was difficult to separate the effect of an activity with a specific AI from its duration on the day of sampling. There was also potential misclassification in duration, as in the PIPAH (UK) study, there were n = 1 and n = 6 cases of pyrethroid and glyphosate use, respectively, with reported durations of 0 h.

Longer duration of activity was found to be associated with higher urinary concentrations in multiple IMPRESS studies and with the use of both AIs. This finding coincides with another study in Egypt that found total hours applying pesticides and total hours in the field to be most strongly associated with urinary biomarkers of pesticides (albeit, AIs not included in our study [e.g., chlorpyrifos]) (Callahan et al., 2017). Where data were available in the present study, there were non-significant or borderline associations between higher urinary concentrations and glyphosate mixing/application on one day prior to urine sample collection (PIPAH, UK) or for pyrethroid/glyphosate mixing/application on the 7 days (PESTROP, Uganda) before collection. A study of amenity horticulturists in Ireland also found higher concentrations in those who also had sprayed glyphosate on the day before (Connolly et al., 2018). Positive associations with use in the prior year may not have been identified, possibly due to that being too long of an interval between exposure and sampling to permit detection or to the greater chance of bias with longer periods of recall (Mueller et al., 2022b).

4.2. Timing of sampling

Urinary excretion half-lives have been reported to range from 5.7 (Ratelle et al., 2015) to 8.7 h (Ferland et al., 2015) for 3-PBA and 5.5 (Connolly et al., 2019b) to 9.0 h (Zoller et al., 2020) for glyphosate. Such half-lives indicate a limited potential for accumulation during repeated use (for example, a half-life of 10 h indicates that about 70% of the exposure measured in a sample reflects the previous 24-h' exposure [Droz et al., 1991]). However, it is also known that the route of exposure can have a significant impact on the rate of uptake (and therefore the "observed" excretion rate). Inhalation and ingestion exposures are generally rapidly absorbed. Peak excretion occurs shortly after exposure, whereas skin exposure results in delayed uptake (due to time taken to penetrate the skin layers to reach the blood supply) and also continued uptake after the cessation of exposure due to the 'reservoir effect'. Approximately three quarters of pyrethroid (46/59; 78%) and glyphosate (25/34; 74%) users in the PESTROP (Uganda) study (i.e., where these data were available) provided urine samples at least 4 h following exposure and therefore likely reflect exposure from all routes. Samples that were provided sooner will generally reflect inhalation or ingestion exposures, which are usually regarded as minor routes in pesticide exposure assessment. These samples may therefore not have fully captured metabolised biomarkers of exposure, thus weakening the ability to detect associations with exposure modifying factors.

4.3. PPE

Only in the PIPAH (UK) study was less PPE protection associated with higher urinary concentrations of 3-PBA and glyphosate. That study was the only setting where the reference PPE category was the use of tractor cabs to mix/apply AIs. Pesticide applicators in tropical, LMIC settings tend to wear less PPE due to a combination of factors, including heat, poor availability, insufficient training, and lower general awareness of potential health risks (Andrade-Rivas and Rother, 2015). Wearing clean clothes during application was previously related to lower exposure to chlorpyrifos in applicators in Egypt (Callahan et al., 2017). Sprayers who wore long compared to short-sleeved shirts on vegetable farms in Thailand had marginally lower dermal exposure to glyphosate (Bootsikeaw et al., 2021). PPE training was not associated with 3-PBA concentrations in farmworkers in Mexico (López-Gálvez et al., 2018). Only instances of changing gloves (3-PBA) or masks (glyphosate) were found to be associated with lower urinary concentrations in the PIPAH (UK) study. Acquavella et al. (2004) previously observed that urinary concentrations were appreciably lower for farmers who wore rubber gloves when mixing and loading glyphosate formulations. There was no association in our analysis with the completion of any hygiene habits or semi-quantitative dermal exposure estimates (i.e., DREAM). Same day sampling may be too short a period to identify urinary biomarkers based on dermal exposure, which typically involves slower uptake than oral exposure routes (Buchholz et al., 2021). However, a previous study on glyphosate showed that the observed excretion rate was consistent with that from an oral volunteer study (Connolly et al., 2019a) despite an assumed exposure from all routes (with dermal exposure dominating, Connolly et al., 2019b) in workers using manual knapsacks.

4.4. Education

Lower education level and illiteracy were associated with higher urinary concentrations of glyphosate, but not with biomarkers of pyrethroids. Formal education and training have been found to coincide with more awareness of pesticide risks (Saeed et al., 2017). A survey of farmworkers in Kuwait found over two thirds did not read or follow instructions; educated farmers were more likely to use PPE (Jallow et al., 2017). Education and literacy may represent more awareness and understanding of risks, access to PPE, and understanding of proper use of PPE, all of which could lead to lower pesticide exposures. Indeed, there is considerable evidence to suggest that demographic factors (i.e., education/literacy levels) are among the significant determinants associated with PPE use and pesticide safety practices (Sapbamrer and Thammachai, 2020). There may not have been sufficient exposure variation in 3-PBA concentrations to detect associations with education using the models in our study.

4.5. Strengths and limitations

This study analysed two biomarkers from pesticide applicators in three different settings. Exposure indicators were assigned via objective means, and there was sufficient variation in urinary biomarker concentrations from which to detect statistical associations with exposure modifying factors. The key novel contribution of this study is the use of harmonised urine sample collection procedures across unique geographical settings. The use of a consistent laboratory analysis protocol (i.e., all samples were analysed at the same facility in the UK) is also a strength. Collection of biological samples and analysis of exposure can be costly and time-consuming, so the insights from the present study are valuable. Several study limitations constrain the interpretation of findings. For two of the studies (PIPAH, UK & Malaysian Farmers, Malaysia), urinary samples were provided during only one day. A longer period of sample collection may have produced stronger findings, particularly for pyrethroid use. For example, a study that examined urinary concentrations of 3-PBA for three consecutive days following exposure found that maximum levels were achieved 18–32 h after exposure onset (Ratelle et al., 2016). The mostly weak correlations identified in the analysis of urinary biomarker concentrations and exposure intensity scores may be due in part to using data for only one day. Although AIs entail unique half-lives, we adopted a pragmatic approach by using a standardised method for sample collection across studies. Hence, the interval between exposure (i.e., activity) completion and sample collection was not consistent among participants. There will therefore be variability amongst participants as to where in the uptake-excretion curve a particular sample was collected (e.g., if a worker sprayed in the early morning, their post-shift sample likely reflects mostly dermal uptake, whereas if they sprayed in the late afternoon, their post-shift sample likely reflects mostly inhalation and ingestion uptake as any skin exposure would still be being absorbed). We had limited and non-standardised information on some potentially important exposure modifiers (e.g., area being sprayed, quantities used), which rendered it not possible to quantify reliably for inclusion in analysis. The PPE protection categories were not directly comparable between the studies due to the different items used. Several of the PPE items in the PESTROP (Uganda) study were articles of clothing and not PPE per se. This may explain why lower concentrations with higher protection (via tractor cabs) were only suggested in PIPAH (UK) participants. In general, poor quality data would attenuate associations. The analysis was also limited by the number of participants using each AI, which may have reduced power and generalisability of results. Further to this point, there was a risk of model overfitting given the number of participants. Nevertheless, more certainty is provided by parameter coefficients with similar results across studies (e.g., duration of exposure). The more modest changes in post-activity 3-PBA concentrations compared to those of glyphosate could be due to some differential AI usage leading to smaller changes in the doses observed across the sampling period in our study; this lack of variation also would have led to reduced study power.

4.6. Implications for exposure assessment

Our study assessed the use of urinary biomarkers to measure exposure to different pesticides and investigated the role of exposure modifying factors. Based on our analysis, there was evidence from individual studies that higher urinary concentrations were associated with formulation/spraying of the AI on the day of urine sampling, longer

duration of formulation/spraying, lower PPE protection, and less education/literacy.

Our study highlights several important considerations for the use of biomarkers for pesticide exposure and also more broadly for pesticide exposure questionnaires.

First, the inclusion of biomarkers with concentrations that are < LoQ require techniques to quantify these data for statistical analysis (e.g., Tobit regression, multiple imputation [Lubin et al., 2004]).

Second, the timing of collection of samples should correspond to biological half-life and exposure routes. Biomarkers with slower excretion, for example, chlorpyrifos (Atabila et al., 2018), would require delayed sampling with respect to exposure since detection of metabolites may not be as evident immediately following application. Also, repeated, frequent mixing/spraying can lead to plateauing of metabolite excretion negating distinction, for example, between pre- and post-application on a given day. In such cases, it would not be possible to analyse a given exposure day and questionnaire data may need to reflect longer timeframes; pre -or post-season urine samples may be required as controls. Since most exposures are mixed routes and skin exposures are absorbed far less effectively than inhalation or ingestion exposures (e.g. Griffin et al., 1999), sample collection is often a pragmatic compromise.

Third, related to the previous point, the frequency of use is important to take into account in pesticide exposure questionnaires, particularly when using biomarkers with longer half-lives. Exposure from prior days with formulation/spraying in the previous day or week may affect urinary biomarker concentrations and will impact the association of biomarker levels with exposure affecting factors (use, PPE, hygiene, etc.) unless these factors are constant across working days.

Fourth, as well as frequency of mixing/spraying, the quantity mixed/applied, including amount and area sprayed, given in standardised and harmonised units, would be useful to study in future research. Other practices and observations also may be valuable to capture in future studies, such as the reuse of PPE items. As noted above, it was not possible to parameterise these data in the present analysis.

Fifth, to detect health effects from exposure to specific AIs in epidemiological studies, it would be necessary to include individuals with a range of practices to achieve sufficient exposure contrast. Furthermore, harmonisation of contextual data, where possible and appropriate, across multiple studies would facilitate data pooling and larger sample sizes for analysis.

Sixth, other pathways can contribute to the exposure signal, for example, through household use, diet, or spraying from nearby agricultural fields (Madrigal et al., 2022), though these pathways would likely be more important for residential compared to occupational exposures.

Our analysis indicates that assessing acute exposure to specific AIs via biomonitoring could be most valuable in settings with less frequent applications, but where there is the potential for higher doses, using AIs with relatively short biological half-lives. Our results suggest it would be important to ascertain for study participants the duration and frequency of AI use (e.g., mixing and application), amount of PPE protection, and education level. Repeated sampling also on non-application days will provide additional insight.

5. Conclusion

We used urinary biomarkers to assess the importance of different exposure modifying factors for pyrethroids and glyphosate in three occupational studies. Formulation/spraying of AIs, duration of formulation/spraying, PPE protection, and education were all associated with biomarker concentrations, but no factor was consistently associated with exposure across biomarkers and studies.

Ethical approvals

PIPAH: Ethical approval for the study was obtained from the University of Sheffield's Research Ethics Committee (REC) (Reference Number HSL29).

PESTROP: Ethical approval was obtained from the Higher Degrees Research and Ethics Committee at Makerere University in Uganda (reference no. 719).

Malaysian Farmers study: Ethical approval for the study was obtained from the University of Manchester RECs (2017-0439-3979) and a Malaysian Medical REC (NMR-17-424-34635[IIR])

CRediT authorship contribution statement

William Mueller: Methodology, Formal analysis, Writing – original draft. **Kate Jones:** Methodology, Data curation, Writing – review & editing. **Samuel Fuhrimann:** Methodology, Investigation, Writing – review & editing. **Zulkhairul Naim Bin Sidek Ahmad:** Investigation. **Craig Sams:** Investigation. **Anne-Helen Harding:** Methodology, Writing – review & editing. **Andy Povey:** Methodology, Writing – review & editing. **Aggrey Atuhaire:** Investigation. **Ioannis Basinas:** Methodology, Writing – review & editing. **Martie van Tongeren:** Methodology, Writing – review & editing. **Hans Kromhout:** Methodology, Writing – review & editing. **Karen S. Galea:** Conceptualization, Writing – review & editing, Supervision.

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

The authors do not have permission to share data.

Acknowledgments

The project team would like to thank all the participants who consented to participate in the study. They would also like to thank the project advisory board members (Scientist Emeritus Dr Aaron Blair, Professor Len Levy, Dr Mark Montforts, and Professor Silvia Fustinoni) who provided advice on this study. Dr Lützen Portengen is thanked for his suggestions on the statistical analysis and Dr Mark Cherrie is thanked for his helpful review of a draft of this manuscript.

CropLife Europe funds the IMPRESS study, of which this manuscript reports results thereof. The contents, including any opinions and/or conclusions expressed of this manuscript, are those of the authors alone.

The PIPAH study is funded by the HSE in Great Britain. The PESTROP study was supported by the Swiss Network for International Studies. Samuel Fuhrimann was also supported by fellowship of the Swiss National Science Foundation, Switzerland (SNSF; grant number: P400PM_180757 and P4P4PM_199228). The Malaysian Farmers study was funded by the Ministry of Higher Education, Malaysia.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117651.

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