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Wong, Hie Ling and Brown, Colin David orcid.org/0000-0001-7291-0407 (2021) Assessment of occupational exposure to pesticides applied in rice fields in developing countries: a critical review. International Journal of Environmental Science and Technology. pp. 499-520. ISSN 1735-1472

https://doi.org/10.1007/s13762-020-02834-6

Assessment of occupational exposure to pesticides applied in rice fields in developing countries: a critical review

Short title: Review of occupational exposure to pesticides in rice

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Acknowledgements The authors gratefully acknowledge the support of this review by the University Malaysia Kelantan and the University of York.

Author contributions All authors contributed to the study design and methods. The first draft of the manuscript was written by Hie Ling Wong and Colin Brown critically revised the previous versions of the manuscript. All authors read and approved the final manuscript.

Abstract

Rice is a globally-significant staple cereal for which cultivation is concentrated in developing countries and, to a large extent, in smallholder farms. There is significant potential for operator exposure to pesticides during such rice production, but research to date is fragmented. This review evaluates methods and outcomes of studies to quantify pesticide exposure amongst rice growers in developing countries. Knapsack sprayers are used very frequently in rice cultivation, but existing exposure estimation methods lack the functionality to generate robust estimates of exposure. Direct measurement methods have been applied in a range of developing countries to measure dermal contact and/or respiratory inhalation during pesticide handling activities, and these have sometimes been coupled with biological monitoring for exposure. Only a few studies have collected contextual information in parallel with exposure assessment, using interviews or questionnaires to capture information on agricultural practices and personal protective measures. There is general agreement that dermal exposure is likely to be larger than inhalation exposure, with dermal contact exacerbated by risk factors including crop structure, maintenance status of equipment, and use of any personal protective equipment. There is frequent use within the reviewed studies of pesticide active substances that have been restricted in other parts of the world. Overall, there is an urgent need for more systematic studies to address gaps in knowledge and improve exposure estimates for use in health analysis and risk assessment.

Keywords: biological monitoring; dermal; exposure estimate; farmer; inhalation; paddy; risk assessment

Introduction

Rice (*Oryza* sativa) is a globally-significant staple cereal (Wang and Deng 2018), with developing countries accounting for more than 96% of total production between 2014 and 2016 (equivalent to 477.7 million tonnes; FAO 2018a). There are typically two to three harvests per year (Toan et al. 2013), with irrigated cropping systems covering about half of the world's rice harvested areas (48%), followed by rainfed lowland systems (32%), upland systems (13%), and flood-prone systems (7%) (Capri and Karpouzas 2008). The global rice area increased from 700 million hectares in 2009 to 770 million hectares in 2017 (FAO 2018b), with 89% of the total area in Southeast Asia (How et al. 2015). Nevertheless, the global rate of increase in rice yields at 1.0% per year is much less than the 2.4% per year required to meet an anticipated need to double the yield by 2050 (Ray et al. 2013); much of the increase to meet this gap is expected to come from smallholder rice farmers in developing countries (Yamano et al. 2016).

Modern agricultural practices typically involve extensive use of pesticides to ensure food security (Sruthi et al. 2017), and application to rice is the third largest use of pesticides globally (Anyusheva et al. 2016). Rice farmers often rely heavily on the use of pesticides to control a range of common pests (either prophylactically or in response to pest outbreak), to ensure good product appearance, high rice grain yields and thus high income, and to save costs associated with labour and time (Fabro and Varca 2012; Sapbamrer and Nata 2014; Abdollahzadeh et al. 2015; Mohamed et al. 2016; Wang et al. 2018). Typically, the most abundantly applied pesticides in rice fields are insecticides (39 – 85%), followed by herbicides (16 – 63%), fungicides (7 – 31%) and other active ingredients like acaricides (7 – 14%) (Berg 2001; Sapbamrer and Nata 2014; Sattler et al. 2018). Often, developing countries have less onerous pesticide registration procedures than developed countries, and this can mean that there are a larger number of pesticides authorised for use; as an example, in 2011 there were 87 active substances authorised for use on rice in India compared to 16 and 15 authorised for rice in Italy and France, respectively (European Commission 2011). This is because rice intensification programmes in many Asian countries typically involve excessive use of pesticides (Heong et al. 2002). Several authors have anticipated a further increase in the use of pesticides on rice, with increased potential for adverse effects on the environment and human health (Snelder et al. 2008; Qiao et al. 2012).

Pesticides have the potential to cause a range of human health effects that will depend on their toxicity, route, frequency and duration of exposure, and the susceptibility of exposed individuals (WHO 2018). Exposure of rice farmers to pesticides has previously been associated with various health effects ranging from acute poisoning through to chronic diseases including skin and eye irritation, headaches, dizziness, coughing, nausea, blurred vision, fatigue, respiratory disorders, abnormal semen, and chronic kidney disease (Tuc et al 2007; Kedia and Palis 2008; Qiao et al. 2012; Jayasumana et al. 2015; Da Silva et al. 2016; Sankoh et al. 2016; Elahi et al. 2019). Each year tens of thousands of farmers are affected by their exposure to pesticides, with the majority of those affected living in developing countries (Wilson and Tisdell 2001). Despite this known impact from pesticides, exposure assessment remains poorly developed and has been identified as a major limitation for both epidemiological investigations and post-authorisation monitoring of pesticides (Kalliora et al. 2018). A systematic review on emerging health risks associated with agricultural intensification in South East Asia (73 peer-reviewed articles published between 2000 and 2015) confirmed that shortcomings in exposure assessment result in significant difficulties in establishing causal relationships between the occurrence of a health outcome and the timing of pesticide exposure (before, during, or after pesticide activities; Lam et al. 2017).

Quantitative exposure assessment is central to determining the risk to farmers' health from the use of pesticides (Kim et al. 2012), and regulatory procedures in developed countries prescribe that no product authorisation will be granted unless adequate data or use of predictive models are presented to demonstrate no unacceptable risks (Regulation EC 1107/2009; Cao et al. 2018). In many developing countries like those in Southeast Asia, there are no national systems to monitor pesticide risk on a routine basis and, where data are collected, they are rarely made publicly available (Schreinemachers et al. 2015). Thus there can be significant gaps in knowledge relating to exposure measurements in developing countries (Pan and Siriwong 2010), and established exposure databases and models from developed countries and international organisations are often used as surrogates in the evaluation of pesticides (Atabila et al. 2017; Jansen 2017).

To date, a tiered approach to exposure assessment remains appropriate for regulatory assessment purposes and for post-registration surveillance of pesticides in use (EFSA 2014). According to the OECD Guidance Document on conducting studies of occupational exposure to pesticides during agricultural application (OECD 1997), the first tier compares generic exposure data derived from published databases with the no observed effect levels (NOELs) to determine the margin of safety (e.g. exposure modelling); the second tier refines the absorbed dose from the dermal route based on dermal absorption data (biological monitoring or biomonitoring); and the third tier involves field study under different use patterns when no acceptable generic exposure data and/or inadequate margins of safety are available (field or direct measurement). While direct field measurement can quantify the potential dose of pesticides in contact with skin or inhaled, biological monitoring can be used to measure the internal dose of the chemical (or its metabolites) absorbed by the human body via any possible route that may cause biological effects (Maroni et al. 2000; US EPA 2018). ECHA (2016) recommends the use of all available tools including measured data, biological monitoring, and/or exposure models to describe the chemical exposure, noting that a combination of measured exposure data and modelling approaches may provide the most appropriate assessment.

Overall, rice paddies are a major crop grown in developing countries where pesticide use is less strictly regulated or monitored, and this may lead to greater potential for health impacts than in developed countries. Whilst health effects are generally found to be a function of the total mass and number of pesticides handled (Dasgupta et al. 2007a), farmers' actual exposure to pesticides can be influenced by a wide range of factors which also include properties of the pesticide and product formulation, application practices, environmental conditions and working behaviour related to the use of personal protective equipment (PPE; Wong et al. 2018). While measuring exposure under the actual conditions of use is very important to underpin accurate pesticide risk assessment as part of regulatory procedures (Gangemi et al. 2016; Lee et al. 2018), the irrigated and submerged cultivation systems that are common in rice can lead to pesticide exposure pathways and scenarios that are different from most studied crop types.

This review investigates the methods that have been applied in assessing rice farmers' exposure to pesticides in developing countries. To do this, major scenarios and drivers of pesticide exposure in rice fields are identified and the use of direct exposure measurement methods (e.g. whole-body dosimetry and personal air sampling methods), integrated methods based on biological monitoring, and the use of predictive exposure models to estimate exposure are assessed. Methods used for risk characterisation among rice farmers exposed to pesticides are also assessed. Review findings are used to identify gaps in knowledge for the current risk assessment in relation to farmers' exposure to pesticides in rice fields and implications for the regulatory assessment schemes in developing countries.

Materials and methods

This review included original peer-reviewed articles written in English and published by November 2019, for farmers' non-dietary routes of exposure to pesticides applied to rice in developing countries. Two multidisciplinary environmental science citation databases were chosen as complementary to one another, namely the Web of Science (Clarivate Analytics) and the Google Scholar databases. The initial search was designed to identify all literature with potential relevance for the review based on the following search string: (rice OR paddy) AND (pesticide OR herbicide OR fungicide OR insecticide OR rodenticide OR molluscicide) AND (farmer OR operator OR applicator OR sprayer OR worker) AND (exposure OR monitoring OR measurement OR biological monitoring OR modelling OR simulation). This wide search was followed by article screening and selection processes, first on the title, then on the abstract, and finally on full-text reading.

Non-human and non-exposure assessment studies were excluded from this review; this included articles reporting pesticide fate and dissipation behaviour in paddy fields and in rice plants, behavioural aspects of pesticide use and the implementation of integrated and sustainable pest management systems, ecological and dietary risk assessment, and epidemiology studies.

Results and discussion

Table 1 summarises 22 articles on pesticide exposure assessment for rice farmers in developing countries. Of the 22 studies, 16 were carried out in Asia and the earliest study found in the literature was published in 2007. The selected articles report exposure assessment studies ranging in duration from one day up to a few months and with sample sizes ranging from 16 to 223 farmers. Application using knapsack or backpack sprayers was the most commonly considered (12 of the 22 studies), and 11 studies assessed pesticide exposure during applications, three studies included mixing/loading tasks, and two studies assessed exposure as the difference between measurements made pre- and post-application.

Figure 1 shows the major methods used in the 22 reviewed articles in assessing rice farmers' exposure to pesticides. Biological monitoring (collection and analysis of biological samples such as blood or urine) was most common (10 studies), followed by direct measurements (for example, measuring residues landing on the skin or taken in via respiration; 6 studies) and predictive modelling (3 studies). There were also four studies that used different combinations of assessment methods, namely biological monitoring and probabilistic techniques (2 studies), exposure modelling and personal air sampling (1 study), and biological monitoring and whole-body dosimetry (1 study). Meanwhile, 13 of the 22 studies also used interview or questionnaire surveys for the assessment of occupational exposure in rice fields (Table 1).

Table 2 shows that chlorpyrifos was the most frequently assessed pesticide active substance (11 studies), whilst most other chemicals were only assessed in a single study; for example, 13 active substances were only assessed in a study conducted by Hamsan et al. (2017). Insecticides were the most frequently studied type of pesticide (15 compounds), followed by fungicides and herbicides (7 and 5 compounds, respectively). Of the 25 active substances assessed, 14 have been banned for use in the European Union (PPDB 2019), whilst 15 have been withdrawn in at least one country according to Pesticide Action Network (PAN) International (2019) (http://pan-international.org/pan-international-consolidated-list-of-banned-pesticides/). Of the 13 active substances not approved for use in the European Union according to the EU Pesticides Database (2019; https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN), five substances had already been removed from the EU market for up to 9 years at the time the respective studies were conducted (fenthion, diazinon, carbofuran, paraquat, and trichlorphon; Table 2).

Scenarios and drivers of pesticide exposure in rice fields

Pesticide risk assessment is based on knowledge about the drivers of pesticide exposure and their interactions during typical pesticide handling and application activities (Rubino et al. 2012). Of the 22 selected articles, 13 used interviews or questionnaire surveys to collect contextual information alongside other assessment methods, including the characteristics of farmers, type of sprayers and PPE used, and self-reported health symptoms.

Generally, practice for applying pesticides in rice fields may vary in relation to demographic profiles, rice varieties, the reasons for cropping (e.g. personal consumption, livestock feed or commercial cultivation), the hazard labelling of pesticide products, and geographical locations, with the occurrence of pests and diseases often determining the timing of applications (Dasgupta et al. 2007a; Matsukawa et al. 2016). Interviews or questionnaire surveys are commonly used to collect information on a variety of exposure parameters for detailed risk assessment (ECHA 2015), where surveyed data typically vary in accordance with the specified exposure scenarios and study requirements. Typically, the establishment of causal inferences for pesticide-related health problems based on the results of surveys requires the monitoring of health effects, particularly for longer-term pesticide poisonings (Sankoh et al. 2016; Hongsibsong et al. 2017).

Under field conditions, total amount or concentration of pesticides applied has been consistently identified as the primary influence on occupational exposure among applicators (Colosio et al. 2012; Phung et al. 2012a; Atabila et al. 2019). There are also positive and significant associations between adsorbed daily doses during application and both the duration of spraying and the number of spray tanks filled (Spearman ρ correlation coefficient (r): 0.53 – 0.59; p-value < 0.05; Atabila et al. 2018b). Application parameters including duration of pesticide spraying (0.5 – 1 hour per day), type of sprayer (backpack sprayer > hand sprayer), type of pesticide, and time of spraying period (early morning) were significantly associated with the levels of blood cholinesterase in a group of 33 rice farmers studied in Thailand (p-value < 0.033; Sombatsawat et al. 2014). The height of rice crops at spraying may also influence pesticide distribution on different body parts; for instance, taller crops caused larger exposures to the upper legs due to greater contact with pesticide-contaminated leaves (crop heights of 80, 50, 30 and 12 cm resulted in 28, 21, 14 and 0.4% of total dermal exposure, respectively; Atabila et al. 2017). Similarly, their shorter body height caused female farmers to lift their sprayers to higher positions closer to their chests resulting in larger exposures via the chest compared to male farmers (mean concentrations of 145 and 32 mg kg^{-1}, respectively; Lappharat et al. 2014). Other exposure factors include the type of formulation (e.g. absorption of granular formulations by the skin is less than that of liquid formulations; Gammon et al. 2011; Berenstein et al. 2014), foliar density and frequency of contact with crops (Choi et al. 2013), condition of the machinery (e.g. 31 of 104 respondents reported leaking sprayers in a study by Snelder et al. 2008), and the use of personal protective measures.

Of the 22 reviewed articles, nine were conducted among smallholder rice farmers (Table 1). Small-scale farming is usually the main source of income and livelihood in developing countries, where pesticides are often used as a substitute for labour and ploughing services (Rahman and Chima 2018). Farm size *per se* is not significantly associated with exposure level (Atabila et al. 2017), but the common use of backpack/knapsack sprayers (mist guns, and manual and electric (power) sprayers) is an important feature of small-scale farming systems. Typically, the use of backpack/knapsack sprayers can lead to higher levels of pesticide exposure when compared to the use of mechanical application methods such as trucks or aerial sprays in developed countries (Panuwet et al. 2008; Phung et al. 2012b). This is because rice farmers often walk through the fields swinging the spray wand in a sweeping motion during application activities, thus they can be intensely exposed to the spray plume (Bellinder et al. 2002; Li et al. 2019). There is also concern that small-scale farmers in developing countries may have high pesticide exposure due to unsafe working practices, lack of PPE, and weaker legislative protection (Da Silva et al. 2016; Phung et al. 2019). Despite these concerns, chemical risk assessment is seldom performed for small-scale and family-based enterprises, which have been overlooked by national systems even in developed countries (Rubino et al. 2012).

Table 1 shows that eight of the 22 reviewed articles assessed occupational dermal exposure during pesticide application in rice fields, three assessed pesticide exposures due to mixing/loading activities, whilst 11 did not separate the exposure assessment by individual pesticide handling activities. During applications, larger exposure to target compounds was measured on legs compared to arms and hands (93 – 4998, 2 – 148, and 1 – 64 mg per application, respectively), mainly due to the respective surface areas exposed (18%, 7% and 2% of 1.7 m^2 total body surface, respectively) (Snelder et al. 2008). Overall, the median exposures of four operators using pressurised knapsack/backpack sprayers were highest for lower anatomical regions (40% of total dermal exposure (TDE); 17, 16 and 7% for lower legs, upper legs and feet), followed by hands (39% of TDE) and upper anatomical regions (18% of TDE; 8, 7, 4, 2 and 1% for back abdomen, front abdomen, lower arms, head and upper arms, respectively); the relatively greater exposure to the hands might be due to spillage that was observed during mixing/loading of pesticides (Atabila et al. 2017). Thus, the use of proper PPE is essential to reduce occupational exposure to pesticides; for instance, gloves and thick long trousers are recommended to reduce dermal exposures via hands and legs, respectively (Zhao et al. 2016; Atabila et al. 2017).

There were only two reviewed studies that assessed the exposure of rice farmers to pesticides via inhalation, even though inhaled pesticides can be very hazardous because very small pesticide droplets or aerosols can be absorbed readily by the body (Sombatsawat et al. 2014). Of the two reviewed inhalation studies, the measured pesticide concentrations in air samples during application and/or mixing/loading were relatively small due to collection taking place in the early morning in the presence of calm or light wind. For instance, Baharuddin et al. (2011) reported pesticide airborne concentrations of 0.03 – 0.06 ppm using a personal air sampling pump among paddy farmers who used knapsack sprayers in the presence of light winds (mean value of 0.6 $\pm$ 0.4 m s^{-1} between 7.00 and 11.00 am). It is recommended to apply pesticides during periods with wind speeds between 0.5 and 1.8 m s^{-1} to ensure the lowest potential for pesticide drift (Snelder et al. 2008), noting that wind speed at the height of the nozzle can also be influenced by local factors such as the presence of trees (Defra 2006). On the other hand, Wong et al. (2018) reported that formulation type influenced pesticide exposure to a greater extent during mixing/loading than during application due to inhalation exposures (i.e. wettable powder > liquid > wettable granule formulation). To date, there has been no attempt to measure the level of inhalation exposure in rice fields based on the use of different pesticide formulations.

Sapbamrer et al. (2017) used urine tests to identify impacts on farmers' health that were associated with different pesticide-associated activities; findings included associations between mixing pesticides and appearance of white/red pimples (OR: 6.2) and harvesting crops and increased anxiety (OR: 6.0). Nevertheless, there has been no attempt to quantify the level of dermal exposure due to other pesticide activities in rice fields, including for example, re-entering a treated field or cleaning a sprayer (EFSA 2014). Under actual working conditions, rice farmers' total non-dietary exposure to pesticides may be significantly larger than the sum arising from mixing/loading and application activities.

Field measurement

Figure 1 shows that eight studies used direct methods to measure rice farmers' exposure to target pesticide compounds, comprising three whole-body dosimetry studies, one patch study, one hand-wipe study and one study with water-sensitive paper for dermal exposure assessment, and two personal air sampling studies for inhalation exposures. Typically, whole-body dosimetry is considered as the most accurate technique in direct measurements because it removes the need for extrapolation of exposure data from one anatomical area to another; that extrapolation is a major limitation of the patch method that may lead to incorrect exposure estimates (Atabila et al. 2017; Atabila et al. 2018a).

Of the eight studies with direct measurement methods, six translated the measured active substance concentrations into (average) absorbed daily doses via skin dermal (ADD_D, mg kg^{-1} day^{-1}) or respiratory inhalation (ADD_I, mg kg^{-1} day^{-1}) as:

$$ADD_{(D\ or\ I)} = \frac{TE_{(D\ or\ I)} \times Abs_{(D\ or\ I)}}{BW} \quad (1)$$

$$Average\ ADD_{(D\ or\ I)} = \frac{TE_{(D\ or\ I)} \times Abs_{(D\ or\ I)} \times EF \times ED}{BW \times AT} \quad (2)$$

where $TE_{D\ or\ I}$ is the total exposure measured via the dermal or inhalation route (mg day^{-1}), $Abs_{D\ or\ I}$ is the absorption value for the respective route of exposure, EF is the exposure frequency (fraction of total time when exposure occurs), ED is the exposure duration (year), BW is the body weight (kg), and AT is the averaging time (year) equivalent to ED for non-carcinogenic effects. Overall, the estimated dermal daily exposures (5.0 x 10^{-3} to 3.4 x 10^{-1} mg kg^{-1} day^{-1}) were at least three to four orders of magnitude larger than the estimated inhalation exposures (2.8 x 10^{-6} to 1.6 x 10^{-5} mg kg^{-1} day^{-1}). That is, inhalation exposures are typically less than 0.1% of dermal exposure during both mixing/loading and application activities with knapsack sprayers (Choi et al. 2013). Studies on toxicities arising from dermal or inhalation exposure are generally lacking for most pesticides, with toxicology focusing predominantly on oral dosing. Hence, the respective exposure levels are typically adjusted using absorption factors. Dermal absorption via the skin surface is known to be a function of the percentage of active substance in the product; for example, the European Union risk assessment scheme assumes absorption factors of 25 and 75% for pesticide products that contain >5 and ≤5% of the active substance(s), respectively (EFSA 2012; So et al. 2014). Respiratory inhalation can be particularly dangerous due to the likelihood of a higher percentage absorbed dose, so risk assessment schemes often adopt a worst-case assumption of 100% absorption of all inhaled chemicals by the body (Kegley and Conlisk 2010; Lee et al. 2018). In assessing the level of risk, guideline values expressed as no observed adverse effect levels (NOAELs) are typically derived from route-extrapolated oral toxicity studies.

Predictive modelling

Only three of the 22 studies used predictive exposure models to estimate daily occupational exposure to pesticides in rice fields. The studies comprised the combined use of the Pesticide Handlers' Exposure Database (PHED) and the Agricultural Handlers' Exposure Database (AHED) for applications of granular and liquid pesticides using aerial/ground-boom sprayers (total dermal exposures ranged from 4.0 x 10^{-2} to 3 x 10^{-1} mg kg^{-1} day^{-1}; Gammon et al. 2011); the semi-quantitative Dermal Exposure Assessment Method (DREAM) to estimate the emission, deposition and transfer of pesticides of different physical states (solids, liquids and vapours) on different body parts using a knapsack sprayer (mean of total inhalation and dermal exposures were 0.03 – 0.06 ppm and 21.8 – 80.9 ppm, respectively; Baharuddin et al. 2011); and application of the World Health Organisation Predicted Exposure Assessment Model (WHO-PEAM) for occupational exposure to liquid insecticides using backpack sprayers (means of inhalation during spraying and dermal exposure during mixing/loading larger than dermal exposure during spraying; 1.13 x 10^{-2}, 1.0 x 10^{-2}, and 8.4 x 10^{-4} mg kg^{-1} day^{-1}, respectively; Phung et al. 2019).

The DREAM and WHO-PEAM models could potentially have applications in estimating non-dietary exposure to pesticides during the use of knapsack/backpack sprayers in developing countries, but both models have limitations that need to be considered. The semi-quantitative DREAM programme was developed using an integrated approach whereby a structured questionnaire was used to assign quantitative values to model variables; dermal exposure estimates are given in terms of a Dermal Unit (DU) ranging from low (0 – 9.99 DU) to extremely high (> 1000 DU) categories of exposure, but these cannot be compared with the guideline values for risk characterisation (Baharuddin et al. 2011). Prediction from the WHO-PEAM was shown to match measured daily doses for liquid pesticides (Phung et al. 2019), but the model does not account for the influence of formulation type on exposure during handling procedures; for example, dusty wettable powder formulations have been shown to contaminate hands more easily than liquids (Zhao et al. 2016). Development of a comprehensive model that can describe the full range of operating conditions in rice fields should be a priority to supplement the limited field measurements.

Biological monitoring

In biological monitoring, biomarkers of exposure are typically used to evaluate the actual absorption of chemicals by measuring the concentration of a chemical or its metabolites in body fluids (OECD 1997). The measured concentration of the chemical in the body can be expressed as the internal exposure dose, which can be used to improve the setting of threshold values of biomarker metabolites and thus the limits of exposure to single pesticides (Colosio et al. 2012). Figure 1 shows the use of biological monitoring in 14 studies comprising six blood tests, five urine tests, one combined use of a urine test and whole-body dosimetry, one combined use of a urine test and predictive modelling, and one combined use of urine, blood and serum tests. Of the six blood studies reviewed, the health impacts to rice farmers from exposure to different groups of pesticides (e.g. organophosphates, carbamates, and organochlorines) were determined based on the percentage of DNA damage, comet tail length, and level of acetylcholinesterase (AChE); this includes two studies that evaluated health risks due to the use of pesticide mixtures. However, a blood test performed at a specific moment does not yield specific information about previous exposures (Varona-Uribe et al. 2016), and the measurement units do not allow risk characterisation based on guideline values. In comparison, the five urine studies assessed rice farmers' exposure to chlorpyrifos based on its major urinary metabolite 3,5,6-trichloro-2-pyridinol (TCP), where measured urinary TCP concentrations are translated to absorbed daily dose (ADD_{TCP}, mg kg^{-1} day^{-1}) as:

$$ADD_{TCP} = \frac{C_{TCP} \times C_n \times CF \times R_{mw}}{BW} \quad (3)$$

where C is the concentration of urinary TCP excreted per day (μg g^{-1} creatinine), C_n is the expected mass of creatinine excreted per day (g day^{-1}), CF is a correction factor of 100/70 for urinary TCP, R_{mw} is the ratio of the molecular weights of chlorpyrifos and TCP, and BW is body weight (kg). Based on measured urinary TCP concentrations, the predicted baseline and post-application exposures to chlorpyrifos were 3.0 x 10^{-5} – 2.0 x 10^{-3} mg kg^{-1} day^{-1} and 3.5 x 10^{-4} – 9.4 x 10^{-2} mg kg^{-1} day^{-1}, respectively. The estimated baseline exposure can be used to correct the occupational exposure for the background exposure (Atabila et al. 2018b), thus allowing risk assessment due to a typical pesticide handling activity.

Two of the three biological monitoring studies with concurrent use of other measurement methods indicate close agreement between measurements of urinary TCP and results of the whole-body dosimetry method (mean values of post-application exposure were 1.5 x 10^{-2} and 1.6 x 10^{-2} mg kg^{-1} day^{-1}, respectively; Atabila et al. 2019), and that of the WHO-PEAM predictive model (the sum of baseline and post-application exposures were 2.0 x 10^{-2} and 2.2 x 10^{-2} mg kg^{-1} day^{-1} based on the urinary TCP and the model, respectively; Phung et al. 2019).

Risk characterisation

In this review, seven out of eight studies that calculated hazard quotients (HQs) predicted acute and/or chronic HQs greater than 1 while one of the two margin-of-exposure (MOE) studies predicted MOE less than 100; both sets of outcomes indicate the potential for risks to health among rice farmers from the use of pesticides. Of the ten risk characterisation studies, HQ and MOE are calculated by comparing the adsorbed daily dose (ADD, mg kg^{-1} day^{-1}) with the guideline value (e.g. reference dose (RfD) or point of departure ($PODI$); mg kg^{-1} day^{-1}) for single active substances as:

$$HQ = \frac{ADD}{RfD} \quad (4)$$

$$MOE = \frac{PODI}{ADD} \quad (5)$$

Typically, the RfD and $PODI$ are estimated based on a no observed (adverse) effect level (NO(A)EL) derived from animal studies and adjusted using safety or uncertainty factors (generally take as 10 for inter-species extrapolation and 10 for variations in intra-species sensitivity; Snelder et al. 2008). The deterministic HQ (or MOE) is used to evaluate a non-carcinogenic toxicant based on the most representative single-point exposure estimate such as the median-exposed group (US EPA 1992). The HQ method cannot account explicitly for the variability in sensitivity and other factors across a study population, but this can be partly addressed by different percentiles of exposure (Atabila et al. 2018a). In contrast, the probabilistic approach can take into account the variability and uncertainty of exposure and effects estimates based on the dose-response and exposure distributions. For instance, 33% of rice farmers in the study of Phung et al. (2013) had post-application exposures to chlorpyrifos that exceeded the respective guideline value based on a cumulative frequency distribution generated with Monte Carlo simulation, whilst 29% of the population of farmers was affected based on the cumulative frequency distribution for measured data. The probabilistic approach is typically used as an *ad hoc* method for higher tier exposure assessment when standardised deterministic methods give insufficient reassurance of safety (EFSA 2014).

General discussion

In this review, studies estimated a range of non-dietary exposures of rice farmers to pesticides during mixing/loading and/or application between 8.4×10^{-4} and 3.4×10^{-1} mg kg^{-1} day^{-1}, with estimated dermal exposures at least 3 to 4 magnitudes of orders greater than those from inhalation exposure. Based on small numbers (≤ 4) of Korean rice farmers, Kim et al. (2012) reported small inhalation exposures that constituted 0.001 – 0.2% of the dermal exposure, while Zhao et al. (2016) reported larger pesticide exposures at the thigh compared to the lower leg during applications due to higher crop heights (0.4% and 0.1% of total exposure, respectively). The two studies indicate close agreement with the major findings of this review, but the high variability in measured exposure data indicate a need for more repetitions in field measurements (Kim et al. 2012). According to the OECD guidance series on testing and assessment No. 9 (OECD 1997), a minimum of ten subjects is needed in the measurement of occupational exposure to and/or absorbed dose of pesticides in the field studies. Overall, more qualified exposure research that meets the quality criteria is required to improve the existing database (Groβkopf et al. 2013).

Human health risk assessment can be based both on actual exposure data collected by direct measurement and exposure distributions predicted by exposure models for various exposure scenarios (Spinazze et al. 2017); both will have inherent limitations and uncertainties including inaccuracies in field measurements or estimation of input parameters, and deficiencies in model structure (La et al. 2015). Typically, definition of exposure scenarios and associated prediction of exposure in rice fields can simplify the in-field assessment (Colosio et al. 2012). However, predictive modelling is often preferred due to complexities in measuring dose via different routes and limitations in biological monitoring together with the wide range in climatic and working conditions that need to be considered (Colosio et al. 2012). Meanwhile, biological monitoring can be integrated with field measurements and predictive modelling to derive a provisional biological exposure limit for individual active substances. Overall, mathematical models and computational tools that can describe the complex interactions between agronomic and environmental conditions and pesticide exposure can supplement limited field measurements in a cost-effective way (Salcedo et al. 2017).

This review also indicates the use of pesticide active substances in developing countries that have been banned elsewhere (Table 2). The regulatory authorities have been urged to increase the monitoring of prohibited pesticides (Varona-Uribe et al. 2016), with immediate phasing out of very hazardous pesticides through national policies and enforcement in order to restrict public access to these chemicals (Konradsen et al. 2003). Over time, production of new and potent formulations is increasing due to emergence of pest resistance and sanitary controls (Mostafalou and Abdollahi 2013; Jabran and Chauhan 2015; Machado and Martins 2018). However, new pesticides produced in developing countries generally have poor risk information due to the lack of a consolidated system for pesticide management (Panuwet et al. 2012; Jansen 2017). Typically, pesticide registration in developing countries requires the registrants to provide data on active substances and formulated products (e.g. chemical and toxicological properties, efficacy and residue testing under field conditions, and their ecosystem impacts), with little or no oversight of the sale, use, or disposal of marketed pesticides (Kaewboonchoo et al. 2015). As a whole, the list of pesticides approved for use needs to be reviewed on a regular basis to ensure proper distinction between banned, restricted and general use pesticides (Snelder et al. 2008; Elahi et al. 2019).

Conclusion

Rice is a major crop grown in developing countries, where the common use of knapsack/backpack sprayers and associated application practices are major drivers of rice farmers' exposure to the pesticides that they handle. Whilst multiple methods have been applied to quantify exposure of rice farmers to pesticides, the review indicates the advantage of using combinations of direct field measurements to assess external exposure concentrations under actual working conditions, biomonitoring (primarily urine tests) to estimate internal dose, and/or predictive models to interpret and extrapolate monitoring data. There was agreement across the reviewed studies that dermal exposures were generally larger than inhalation exposures, and that hands and lower anatomical body regions were the most contaminated areas. This evidence base can be communicated to encourage the uptake of PPE to protect those parts of the body. The review also indicates the need to monitor and regulate the use of pesticides in developing countries that have been restricted or deregistered elsewhere. Predictive models could have an important role in this, but further research will be required to underpin development of available tools to make them specific to conditions of rice cultivation in developing countries. More work is particularly required to quantify potential exposure scenarios in submerged cropping systems, including application by walking along the rice plots or walking in contaminated rice paddies, the influence of formulation type on pesticide exposure during mixing and loading the knapsack/backpack sprayer, and exposure during re-entry into treated fields for crop inspection. The findings of this review can be used to improve current risk assessment and regulatory procedures for pesticides in developing countries.

Declarations:

Funding: This research was undertaken as part of the core academic activities of the authors, and without external funding.

Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Ethics approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate: Not applicable

Consent for publication: The authors have approved the manuscript for submission.

Availability of data and material (data transparency): Not applicable

Code availability: Not applicable

Authors' contributions: All authors contributed to the study design and methods. The first draft of the manuscript was written by Hie Ling Wong and Colin Brown critically revised the previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements The authors gratefully acknowledge the support of this review by the University Malaysia Kelantan and the University of York.

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Table 1 Summary of 22 occupational exposure assessment studies based on direct measurements and/or concurrent use of biological monitoring, exposure models, or probabilistic techniques for rice farmers in developing countries

Reference	Pesticide assessed	Study area	Study period/year	Study population	Study method(s)	Field task(s) & type of sprayer	Exposure estimation and (expected) outcomes
Dasgupta et al. (2007b)	Organophosphate and carbamate	Vietnam	Summer-autumn-winter growing periods in 2004	190 rice farmers	Structured questionnaire; acetylcholinesterase enzyme (AChE) blood test	Not mentioned	35% of farmers had AChE reduction of at least 25% of AChE in red cells and in plasma (acute poisoning) and of this, 21% of farmers had a reduction >67% (chronic poisoning), 5% had a reduction >33% (high acute poisoning) and 9% had a reduction > 25% (low acute poisoning). The medical test results indicated that farmers' self-reported symptoms had very weak associations with actual poisoning (p-values: 0.05 – 0.17).
Snelder et al. (2008)	20 different products comprising insecticides, herbicides and molluscicides	Philippines[a]	2002	104 rice and corn farmers (22 rice farmers sprayed with water using knapsack sprayer)	Questionnaire; spray simulation experiments (spraydrift deposition) and dermal exposure measurement (water-sensitive papers); margin-of-exposure (MOE)	Pesticide application & knapsack equipment	Average dermal exposure to pesticides determined from 17 spray simulation experiments for different body parts, and extrapolated to yearly exposure among rice farmers; leg had higher exposure (approx. 5.5×10^{-5} mL cm^{-2} y^{-1}) than (left/right) hand and arm (< 1.0×10^{-5} mL cm^{-2} y^{-1}). Based on relative body proportions, pesticide deposition on legs was 31 times higher than on arms. All estimated MOE were less than 100, indicating a serious threat to human health.
Pan and Siriwong (2010)	Chlorpyrifos and profenofos	Thailand	Not mentioned	29 rice farmers	Cross-sectional study; interview; hand-wipe samples, hazard quotient	Pesticide application & backpack and mist gun	Median concentrations of chlorpyrifos and profenofos contaminated on hands were 1.955 mg kg^{-1} (0.29 – 105.62 mg kg^{-1}) and 2.62 mg kg^{-1} (0.51 – 22.86 mg kg^{-1}), respectively. One farmer for chlorpyrifos and 14 farmers for profenofos had dermal (hand) exposures greater than the US EPA reference doses (HQ > 1), indicating long term exposure may result in chronic adverse health effects.
Baharuddin et al. (2011)	2,4-D and paraquat	Malaysia	2008	140 paddy farmers and 80 office workers (non- exposed group)	Cross-sectional study; questionnaire; personal air sampling pump; Dermal Exposure Assessment Method (DREAM)	Pesticide application & knapsack sprayers (manual, motorised and pressurised)	Estimated dermal exposures for manually operated sprayers were slightly higher than motorised sprayers (2,4-D exposures with proper PPE were 37.76 ± 22.89 and 21.83 ± 9.33 ppm, respectively; paraquat exposures with proper PPE were 36.37 ± 22.78 and 25.24 ± 12.98 ppm, respectively). Estimated inhalation exposures for motorised sprayers were slightly higher than manual sprayer (2,4-D exposures were 0.027 ± 0.019 and 0.038 ± 0.0028 ppm, respectively; paraquat exposures were 0.054 ± 0.037 and 0.056 ± 0.021 ppm, respectively).

Reference	Pesticide assessed	Study area	Study period/year	Study population	Study method(s)	Field task(s) & type of sprayer	Exposure estimation and (expected) outcomes
Gammon et al. (2011)	Carbofuran	Ohio	2009	Three acute and one 21-day dermal absorption studies	Toxicity and dermal absorption studies; Pesticide Handlers' Exposure Database and Agricultural Handlers' Exposure Database (PHED/AHED) computer models; margin-of-exposure (MOE)	Open cab solid broadcast spreader application; push-type granular spreader mixing/loading and application	Estimated dermal exposures using a single layer with no gloves was highest for 'push-type' granular spreader (open pour; 342.50 μg kg day^{-1}), followed by solid broadcast spreader, open cab (46.77 μg kg day^{-1}) and solid broadcast spreader, open cab (39.68 μg kg day^{-1}). All MOEs calculated from dermal exposure were >100, indicating no unacceptable risks to the workers.
Phung et al. (2012a)	Chlorpyrifos	Vietnam[a]	Summer-autumn rice season in June 2010	18 rice farmers (13 males and 5 females)	Interview; 24-hour urine sampling and health data; hazard quotient; probabilistic approach	Not mentioned	Baseline exposure levels (0.03 – 1.98 μg kg^{-1} day^{-1}) were below the chronic guidelines, but post-application exposure levels (0.35 – 94 μg kg^{-1} day^{-1}) had exceeded most of the acute guidelines at the 95th percentile level (HQs: 10 – 20).
Phung et al. (2012b)	Chlorpyrifos	Vietnam[a]	2009	18 rice farmers	Urine test; hazard quotient	After application & backpack sprayer	Mean urinary TCP level was highest at 24 h after pesticide application (47.5 ± 12 μg TCP g^{-1} creatinine) and returned to the baseline value at 144 h (the 6th day) after application. Post-application absorbed daily dose (ADD) varied from 0.4 to 94.2 μg kg^{-1} day^{-1} with mean of 19.4 μ g^{-1} kg^{-1} day^{-1}, that is, approximately 80-fold higher than the mean baseline exposure (0.24 μg kg^{-1} day^{-1}). The mean HQs ranged from 2.1 to 6.9 based on the US and Australian acute reference doses, but still lower than the FAO/WHO reference dose.
Qiao et al. (2012)	Not mentioned	China	1997 – 1998 production season	100 households	Cross-sectional data; farm household survey and sit-down interview; physical and blood examination	Not mentioned	Results of blood tests indicated abnormalities of the functions of neurological system, liver and kidney among the farmers. That is, 5% of the farmers had choline esterase (CHE) values lower than the normal range while 22% had Alanine transaminase (ALT) values higher larger than the normal range. Farmers who spray more pesticides were more likely to have both visible (headache, nausea and skin problems) and invisible (neurological, liver and kidney systems) health impacts.

Reference	Pesticide assessed	Study area	Study period/year	Study population	Study method(s)	Field task(s) & type of sprayer	Exposure estimation and (expected) outcomes
Phung et al. (2013)	Chlorpyrifos	Vietnam	Summer-autumn rice season in 2010	18 rice farmers (Phung et al. 2012a; 2012b)	Urine test; hazard quotient; Monte Carlo simulation (MCS); overall risk probability (ORP)	Not mentioned	The mean of baseline exposure-absorbed daily dose (EADD) was 0.24 μg kg^{-1} day^{-1} (0.03 to 1.98 μg kg^{-1} day^{-1}), with 0.13 and 0.55 μg kg^{-1} day^{-1} at the 50^{th} and 95^{th} percentiles, respectively. The mean of post-application EADD was 19.4 μg kg^{-1} day^{-1}, with estimated 97.7 μg kg^{-1} day^{-1} at 95^{th} percentile. The mean of lifetime average daily exposure dose (ELADD) was 0.7 μg kg^{-1} day^{-1} (0.05 – 4.2 μg kg^{-1} day^{-1}), with 0.31 and 2.14 μg kg^{-1} day^{-1} at the 50^{th} and 95^{th} percentiles, respectively. The HQs for post application and lifetime exposures ranged were 0.98 – 32.5 and 0.2 – 7.1, respectively.
Vivien et al. (2013)	Organophosphate	Malaysia	Not mentioned	160 rice farmers (exposed group) and 160 adults from the fishing village (un-exposed group)	Cross-sectional; genotoxic assays – micronuclei assay (chromosome breakage) and comet assay (DNA damage)	Not mentioned	The mean of blood cholinesterase level showed a significant difference between exposed and unexposed group (p-value: 0.001), with at least 2 – 2.5 folds increases in micronuclei frequency (means of 14.5 and 5.5 per 1000 cells, respectively) and comet tail length (means of 24.4 and 12.85 μm, respectively). That is, chronic exposure to OP showed an inhibition to blood cholinesterase level.
Lappharat et al. (2014)	Chlorpyrifos	Thailand	Oct 2012 – Jan 2013	35 rice farmers	Cross-sectional study; in-person interview; patch technique; hazard quotient	Pesticide application & backpack sprayer	Average daily chlorpyrifos concentration measured in gauze patches was higher in males than females with 526.34 ± 478.84 and 500.75 ± 595.15 mg kg^{-1}, respectively. At the mean level, the calculated average daily dose was highest in lower leg (M: 526.10 x 10^{-4} mg kg^{-1} day^{-1}; F: 391.31 x 10^{-4} mg kg^{-1} day^{-1}, followed by upper leg (M: 277.78 x 10^{-4} mg kg^{-1} day^{-1}; F: 229.95 x 10^{-4} mg kg^{-1} day^{-1}) and arm (M: 113.87 x 10^{-4} mg kg^{-1} day^{-1}; F: 140.45 x 10^{-4} mg kg^{-1} day^{-1}) and other body parts. However, females had relatively higher exposure for chest on clothes (343.66 x 10^{-4} mg kg^{-1} day^{-1}) compared to males (64.94 x 10^{-4} mg kg^{-1} day^{-1}). At the 95^{th} percentile, the largest arithmetic average concentration was lower leg (869.69 mg kg^{-1}), intermediate for chest on clothes, upper leg and arm (552.34, 406.83 and 379.53 mg kg^{-1}, respectively), and followed by back, head and chest under clothes (139.86, 38.43 and 8.53 mg kg^{-1}, respectively). HQs at the mean and 95^{th} percentile levels were 0.2 – 79.3 and

Reference	Pesticide assessed	Study area	Study period/year	Study population	Study method(s)	Field task(s) & type of sprayer	Exposure estimation and (expected) outcomes
							0.6 – 369.9 respectively, indicating potential for adverse health effects due to continuous dermal exposure.
Sapbamrer and Nata (2014)	Not mentioned	Thailand	Aug – Oct 2012	182 rice farmers (exposed subjects) and 122 non-farmers (controlled group)	Cross-sectional study; interview; whole blood acetylcholinesterase (AChE) activity	Not mentioned	Rice farmers had significant lower median of AChE activity than the controls (9,594 vs. 10,530 U/L, respectively; p-value: 0.005) and a significantly higher prevalence of difficulty in breathing and chest pain (Odds ratio (OR): 2.8 and 2.5 and p-values: < 0.01 and < 0.05, respectively).
Sombatsawat et al. (2014)	Organophospate and carbamates	Thailand	3-times blood collection (24-hour after application, 15 and 30 days after)	33 rice farmers	Cross-sectional study; questionnaire and face-to-face interview; blood tests	Not mentioned	73% of total farmers had abnormal acetyl cholinesterase (AChE) levels for the first blood collection (24 hours after application), that accounts for 49 and 42% of total farmers after 15 and 30 days, respectively. The activity of AChE level showed significant difference between within 24 hours after and 15 days after application (p: 0.003, F: 10.24) and 30 days after the application and previous (p: 0.002; F: 12.00). Likewise, the plasma cholinesterase (PChE) levels showed significant different between within 24 h after and 15 days after application (p: 0.0023; F: 5.71) and 30 days after the application and previous (p: 0.007; F: 8.24). Blurred vision was significantly related with the AChE and PChE levels for the first collection after 24 hours of application in eye symptoms (p-values of 0.039 and 0.024, respectively). The abnormal AChE and PChE levels returned to normal levels with self-recovery by time.
How et al. (2015)	Mixtures of organophosphates (chlorpyrifos, diazinon, dimethoate, fenthion, malathion, quinalphos, trichlorphon)	Malaysia	Sept – Oct 2012 (vegetative stage)	160 male farmers and 160 adults as control group	Cross-sectional study; face-to-face interview; comet assay for DNA test	Not mentioned	Farmers who chronically exposed to a mixture of OPs had an average 2-fold significant increase (p-value < 0.05) of DNA damage (comet tail length) compared to control group (24.35 vs. 12.8 μm, respectively). Both farmer and control groups bear certain extent of genotoxic burden, including individual factor (age, sex, body mass index and tobacco use), occupational factors (period of pesticide exposure and PPE use) and residential factors (location and duration of residency).
Varona-Uribe et al. (2016)	31 pesticides (15 organochlorines, 10 organophosphorus,	Colombia	Not mentioned	223 rice field workers	Cross-sectional study; blood, serum and urine test	Not mentioned	Pesticide exposures varied greatly among rice field workers. At the mean level, concentrations of pesticides in blood, serum, or urine were larger for organophosphorus (0.56 – 21.05) and

Reference	Pesticide assessed	Study area	Study period/year	Study population	Study method(s)	Field task(s) & type of sprayer	Exposure estimation and (expected) outcomes
	5 carbamates, ethylenethiourea)						organochlorines (0.42 – 46.36) compared to carbamates (0.03 – 0.04) and dithiocarbamates (0.002), with unit of concentrations not defined. Two selected groups of mixtures were associated with a higher percentage of DNA damage and comet tail length, respectively; α-benzene hexachloride, hexachlorobenzene, and β-benzene hexachloride (β: 1.21; 95% CI: 0.33 – 2.10) and pirimiphos-methyl, malathion, bromophosmethyl, and bromophos-ethyl (β: 11.97; 95% CI: 2.34 – 21.60).
Atabila et al. (2017)	Chlorpyrifos	Ghana[a]	Dec 2015 – Jan 2016	24 rice applicators	Whole-body dosimetry technique	Pesticide application & hand-pressurised knapsack sprayer	During a spray event, the total dermal exposure (TDE) during a spray event at the median and 95th percentile level was 24 and 48 mg, respectively, with the corresponding percentage of the amount applied was 0.03 and 0.06%, respectively. Hands were the most contaminated anatomical regions for both proportion of TDE (39%) and skin loading (13 μg cm^{-2}), while lower anatomical region was more contaminated compared to upper anatomical region (82 and 18% of TDE, respectively). The levels of exposure were found to be significantly influenced by the quantity of application and the heights of the crops (p values < 0.05).
Hamsan et al. (2017)	azoxystrobin, buprofezin, chlorantraniliprole, difenoconazole, fipronil, imidacloprid, isoprothiolane, pretilachlor, propiconazole, pymetrozine, tebuconazole, tricyclazole, trifloxystrobin	Malaysia	Dec 2015 – Feb 2016	83 farmers	Cross-sectional study; interview; personal air sampling; hazard quotient	Pesticide application & backpack sprayer	The maximum concentrations of target compounds in air samples ranged from 47.8 ng m^{-3} (azoxystrobin) to 462.5 ng m^{-2} (fipronil), with the highest mean concentration for pretilachlor and the least for imidacloprid (107.2 and 19.0 ng m^{-3}, respectively). Meanwhile, the highest frequency of detection in personal air samples was tricyclazole (67 of 83 total samples) and the least for azoxystrobin (8). Estimated HQs were < 1 indicated no significant chronic non-carcinogenic health risks due to inhalation exposure. The HI value was < 1 indicated inhalation risk of combined exposures to pesticides was not significant.

Reference	Pesticide assessed	Study area	Study period/year	Study population	Study method(s)	Field task(s) & type of sprayer	Exposure estimation and (expected) outcomes
Sapbamrer et al. (2017)	Not mentioned	Thailand[a]	Sept – Oct 2014	68 rice farmers and 16 farmers cultivating rice and other crops	Cross-sectional study; interview; urine test	Mixing/loading, spraying, scattered seed, harvested crops, packed products & motorised and manual knapsack sprayers	Mean concentration of urinary DAPs level was 10.93 ± 19.64 μg g^{-1} creatinine (1.48 – 163.90 μg g^{-1} creatinine). The concentrations of urinary DAPs were not associated with health symptoms. It is possible that the level of exposure might be not high enough to cause poisoning and health symptoms, or low-level DAPs had limitations for assessing adverse health outcomes. Farm tasks were associated with the prevalence of skin irritation and muscle system.
Atabila et al. (2018a)	Chlorpyrifos	Ghana[a]	Not mentioned	24 rice applicators	Whole-body dosimetry technique; hazard quotient	Pesticide application & hand-pressurised backpack sprayer	Mean concentration of total dermal exposure was 25,800 μg day^{-1} (9,700 – 48,900 μg day^{-1}). Acute dose among the median-exposed and 5%-highly exposed groups were 15 and 27 μg kg^{-1} day^{-1}, respectively (HQ values ranged from 1.5 to 5 and 2.7 to 9, respectively). Chronic dose among the median-exposed and 5%-highly exposed groups were 0.3 and 0.6 μg kg^{-1} day^{-1} (HQ values ranged from 0.03 to 1 and 1.2 to 2, respectively).
Atabila et al. (2018b)	Chlorpyrifos	Ghana[a]	5 – 31 Dec 2015	21 rice applicators (< 2 ha small-scale farming)	Urine sampling (24 h); hazard quotient	Pre- and post-application & hand-pressurised knapsack sprayer	The median absorbed dose for post-application increased 30-fold (6 μg kg^{-1} day^{-1}) compared to prior to application (0.2 μg kg^{-1} day^{-1}). HQs > 1 based on the acute and chronic guideline values of the US EPA, suggesting risk of acute and chronic health effects.
Atabila et al. (2019)	Chlorpyrifos	Ghana[a]	Not mentioned	16 rice farmers (small scale < 2 ha)	Whole body dermal dosimetry; urinary TCP method	Pesticide application & hand-pressurised knapsack sprayer	The whole-body dermal dosimetry method (5 – 29 μg kg^{-1} day^{-1}) showed less variation compared to the urinary TCP method (1 – 71 μg kg^{-1} day^{-1}), but both had close agreement at the mean level (16 and 15 μg kg^{-1} day^{-1}, respectively). Thus, the whole-body dosimetry method is valid for providing estimates where the urinary TCP method cannot be applied.
Phung et al. (2019)	Chlorpyrifos	Vietnam[a]	2009	18 rice farmers	Questionnaire; 24-h urine sampling; Exposure estimation using the WHO-PEAM model	Mixing/loading and spraying & backpack sprayer	Using biological urinary TCP, the mean of baseline absorbed daily dose (ADD) was 0.24 μg kg^{-1} day^{-1} (0.03 – 1.98 μg kg^{-1} day^{-1}). The post-application ADD was approximately 80 times higher with mean of 19.4 μg kg^{-1} day^{-1} (0.35 – 94 μg kg^{-1} day^{-1}). Using WHO-PEAM, the mean of predicted dermal dose (PDD) during mixing/loading was 10 μg kg^{-1} day^{-1} (5.4 – 15 μg kg^{-1} day-

Reference	Pesticide assessed	Study area	Study period/year	Study population	Study method(s)	Field task(s) & type of sprayer	Exposure estimation and (expected) outcomes
							[1]). During application, washing and maintenance, the mean of predicted inhalation daily dose was 11.3 μg kg^{-1} day^{-1} (2.3 – 32.5 μg kg^{-1} day^{-1}), that for the mean of predicted dermal daily dose was 0.84 μg kg^{-1} day^{-1} (0.65 – 1.05 μg kg^{-1} day^{-1}). Exposure estimates from the whole-body dosimetry method showed less variation than those from the urinary test (5 – 29 and 1 – 71 μg kg^{-1} day^{-1}, respectively), but both were in close agreement at the mean level (16 and 15 μg kg^{-1} day^{-1}, respectively). A refined WHO-PEAM model can be used readily as a field method without biological monitoring.

[a]Studies conducted for small-scale rice farmers.

Table 2 List of the 25 pesticide active substances assessed in at least one of the 22 reviewed articles and their respective date of assessment, pesticide type and current status based on the international Pesticide Properties Database (PPDB 2019), the EU Pesticide Database (2019) and the Pesticide Action Network (PAN) International (2019)

Active substance	Reviewed studies		PPDB (2019)		EU Pesticide Database (2019)	PAN International (2019)
	No. of studies	Date of assessment	Pesticide type	Status of use in Europe	Date of published review report on the withdrawal	Total bans (number of countries)
2,4-D	1	2008	Herbicide	Approved	-	3
Azoxystrobin	1	2015 - 2016	Fungicide	Approved	-	-
Buprofezin	1	2015 – 2016	Insecticide, acaricide	Approved	-	-
Carbofuran	1	2009	Insecticide, acaricide	Not approved	Sept 2007	63
Chlorantraniliprole	1	2015 – 2016	Insecticide	Approved	-	-
Chlopyrifos	11	2010 – 2019	Insecticide	Approved	-	4
Chromafenozide	1	2011	Insecticide	Approved	-	-
Diazinon	1	2012	Insecticide, acaricide	Not approved	Sept 2006	32
Difenoconazole	1	2015 – 2016	Fungicide	Approved	-	1
Dimethoate	1	2012	Insecticide, acaricide	Not approved	May 2019	4
Fenthion	1	2012	Insecticide	Not approved	July 2003	31
Fipronil	1	2015 – 2016	Insecticide	Not approved	Review report not available	37
Imidacloprid	1	2015 – 2016	Insecticide	Approved	-	-
Isoprothiolane	1	2015 – 2016	Fungicide	Not approved	Review report no available	-
Malathion	2	2012; Article published in 2016	Insecticide, acaricide	Approved	-	2
Paraquat	1	2008	Herbicide	Not approved	July 2007	46
Pretilachlor	1	2015 – 2016	Herbicide	Not approved	Review report not available	-
Profenofos	1	Article published in 2010	Insecticide, acaricide	Not approved	Review report not available	29
Propiconazole	1	2015 – 2016	Fungicide	Not approved	March 2019	28
Pymetrozine	1	2015 – 2016	Insecticide	Not approved	June 2018	30
Quinalphos	1	2012	Insecticide, acaricide	Not approved	Review report not available	30
Tebuconazole	1	2015 – 2016	Fungicide	Approved	-	1
Trichlorphon	1	2012	Insecticide	Not approved	September 2006	52
Tricyclazole	1	2015 – 2016	Fungicide	Not approved	July 2016	-
Trifloxystrobin	1	2015 – 2016	Fungicide	Approved	-	-

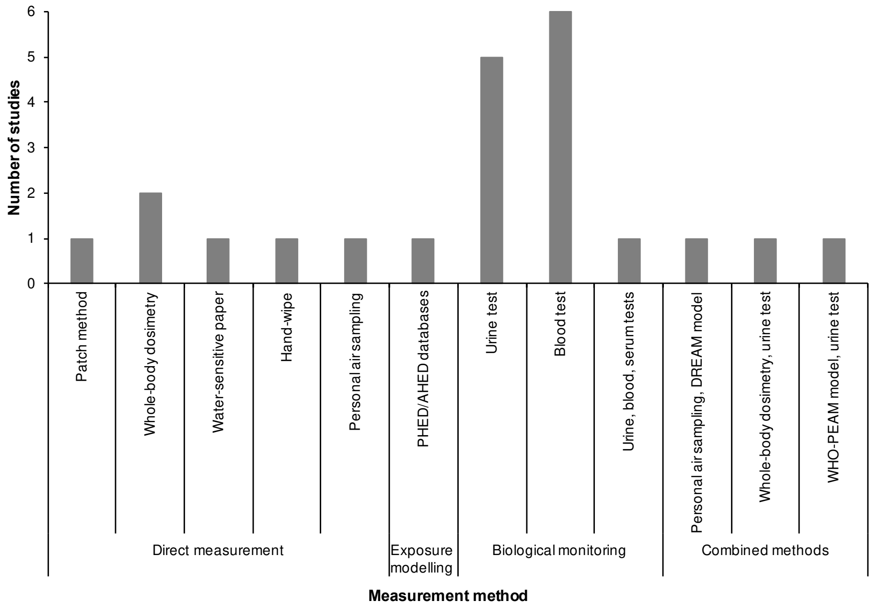

Fig. 1 Classification of the 22 reviewed articles based on the methods that have been applied in assessing rice farmers' exposure to pesticides in developing countries