COZEN O'CONNOR

July 14, 2023

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VIA E-MAIL ONLY

Editorial Board
BMC Public Health, Springer Nature
The Campus, 4 Crinan Street
London, N1 9XW
United Kingdom

Re: Threatened Retraction of "The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review", BMC Public Health (2020)

Dear Messrs./Mesdames:

Please be advised that I represent the authors of "The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review", BMC Public Health (2020) (the "Pesticide Poisoning Article" attached hereto as **Exhibit A**), Wolfgang Boedeker, Ph.D., Meriel Watts, Ph.D., Peter Clausing, Ph.D., and Emily Marquez, Ph.D. (collectively, "Authors"). I have been advised that on or about Monday, July 17, 2023, you intend to issue a Retraction of the Authors' Pesticide Poisoning Article. Committee on Publication Ethics (COPE) Guidelines indicate that Retraction of Authors' Pesticide Poisoning Article is inappropriate. A Retraction would damage Authors' professional reputations and hinder their ability to publish elsewhere. While the Authors' stand behind the integrity and validity of their work and research, they would be open to compromise and would be willing to agree to the posting of an Expression of Concern on your website, coupled with a modification to your standard license agreement allowing them to seek publication in a second peer-reviewed journal. The Authors feel strongly that the importance of the topic of their work requires more scientific debate, not the complete elimination of their findings from scientific discourse. Even their critics would appear to agree.[1]

On its face, the basis for your Retraction is related to methodological concerns that cannot be proven to undermine the Authors' scientific conclusions. Concerns over the methodology the Authors used to interpret data sets and extrapolate missing data in order to, ultimately, lead to conclusions regarding unintentional, acute pesticide poisonings on a global scale ("Global UAPP") are concerns left to the scientific process and scientific debate so that consensus can be reached on an updated Global UAPP figure.[2] This figure is critically important for public health and global policy and has not been updated in over 30 years. The Authors' attempt to do so here should be

[1] S. Eliza Dunn, Jennifer E. Reed, Christoph Neumann, "Letter to the editor regarding the article 'The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review." (BMC Public Health 2021) ("We read with interest the article entitled 'The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review'. We wholeheartedly agree that it is important to evaluate the extent of this issue.").

[2] Oreskes, Naomi, "Why Trust Science?", p. 52, Princeton Univ. Press (2019) (quoting Longino, Helen E., "Science as a Social Knowledge: Values and Objectivity in Scientific Inquiry" p. 216, Princeton Univ. Press (1990)).

encouraged to ultimately lead to consensus on this important issue. Not only is the Retraction unwarranted, it will do nothing to further the science.

Your proposed Retraction states:

> The Editor has retracted this article because concerns were raised about the use of 'ever' prevalence of pesticide poisoning to represent annual frequency in the extrapolations. Expert assessment has confirmed the validity of this concern and also concluded that the assumption of annual exposure for countries where the time frame is not reported is unreliable. The Editor therefore no longer has confidence in the results and conclusions presented.

The above can be summarized as a concern regarding extrapolation where a limited data set was available to provide annual, country-specific figures. The Authors made clear in their submissions that they used 'ever' prevalence data and data with qualitative, but not quantitative, timeframes. Limitations were taken into account and made public for review. Ultimately, their Pesticide Poisoning Article met peer review, which should not be disregarded absent "clear evidence that the findings are unreliable, either as a result of major error (eg, miscalculation or experimental error), or as a result of fabrication (eg, of data) or falsification (eg, image manipulation)." *COPE Guidelines: Retraction Guideline*s, Version 2 at p. 2 (Nov. 2019).[3] There is no evidence, much less "clear evidence", that Authors' findings are unreliable.[4] Indeed, the fact that you still have not posted the proposed Retraction indicates the lack of evidence. Concern over the Pesticide Poisoning Article was first raised by a reader in 2021. *See supra* n. 1, attached hereto as **Exhibit B**. COPE Guidelines indicate Retraction is to be "published promptly." *COPE Guidelines* at p. 2. That years have passed since a concern was first raised (without a single, additional public criticism) makes it obvious that the scientific debate is ongoing and there is no consensus on the issue, much less anything "clear" to challenge Authors' conclusions.

The only public concern[5] with the Pesticide Poisoning Article has been responded to by the Authors, leaving the issue of the use of 'ever' prevalence data and data with qualitative, but not quantitative, timeframes open for debate.[6] For example, whether Authors' extrapolation of annual figures based on consistent, qualitative information (as opposed to quantitative timeframe information) is reliable is clearly a matter of differing opinion. It is not unreasonable to conclude that the words "more often", "day-to-day", "during or after application", "on occasion", *etc.* represent (at a minimum) an annual figure. Wolfgang Boedeker, Meriel Watts, Peter Clausing, and Emily Marquez, "Rebuttal by the authors of a planned retraction by the journal's editor,"

[3] *Available at* https://publicationethics.org/sites/default/files/retraction-guidelines-cope.pdf (last visited July 14, 2023).

[4] No concerns have been raised over the Authors' integrity in their scientific work (fabrication, falsification, plagiarism, *etc*.).

[5] I have been advised that an unidentified person has raised a concern regarding the Pesticide Poisoning Article and the Authors were not given the opportunity to respond in an open forum. If the Editorial Board wishes to confirm this information, provide the name of the individual to illuminate his/her qualifications, and provide this unidentified person's concerns in an open forum, Authors will likewise respond in an open forum to further the discourse.

[6] Wolfgang Boedeker, Meriel Watts, Peter Clausing, and Emily Marquez, "Response to: 'letter to the editor regarding the article 'The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review.'" (BMC Public Health 2021), attached hereto as **Exhibit C**.

attached hereto as **Exhibit D**. There is nothing "clear" about this issue. Put simply, there is no basis for completely invalidating Authors' work through Retraction. Just because a reader believes that evaluating the global, acute effects of pesticides should be done by using a different metric, does not mean that the one used is completely invalid.

Ultimately, Authors' Pesticide Poisoning Article has done what all good science should do—spark scientific debate. However, the Authors have been transparent and forthcoming about the limitations of the data available to them and also understand the consequences to their reputation and ability to republish if a Retraction is issued. For that reason, Authors would be willing to compromise on a statement of Expression of Concern. According to the COPE Retraction Guidelines, "if conclusive evidence about the reliability of a publication cannot be obtained. . . an editor could consider publishing an Expression of Concern." *COPE Guidelines*, at p. 6. An Expression of Concern, coupled with the ability to republish to further discourse on this important topic, would mitigate harm to Authors' professional reputation. It would also fall within the ambit of COPE Guidelines.

The Editorial Board is not the arbitrator of truth, but a means of ensuring scientific process(es) are adhered to and scientific discourse is furthered. Adhering to COPE Guidelines not only ensures the quality of the discourse, it also ensures that the most important thing to a scientist (his/her reputation) is not damaged by the heat of scientific debate.

Please contact me at your earliest opportunity if you would be open to further discussions with the Authors regarding a reasonable compromise of the above issues.

Sincerely,

COZEN O'CONNOR

By: Amorie Hummel
AH

Enclosures

Cc: Wolfgang Boedeker, Ph.D. (*via email only*)
Meriel Watts, Ph.D. (*via email only*)
Peter Clausing, Ph.D. (*via email only*)
Emily Marquez, Ph.D. (*via email only*)
Iratxe Puebla, COPE Facility and Integrity Officer (*via email only*)

EXHIBIT A

Boedeker et al. BMC Public Health (2020) 20:1875
https://doi.org/10.1186/s12889-020-09939-0

BMC Public Health

RESEARCH ARTICLE Open Access

The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review

Wolfgang Boedeker[1*], Meriel Watts[2], Peter Clausing[1] and Emily Marquez[3]

Abstract

Background: Human poisoning by pesticides has long been seen as a severe public health problem. As early as 1990, a task force of the World Health Organization (WHO) estimated that about one million unintentional pesticide poisonings occur annually, leading to approximately 20,000 deaths. Thirty years on there is no up-to-date picture of global pesticide poisoning despite an increase in global pesticide use. Our aim was to systematically review the prevalence of unintentional, acute pesticide poisoning (UAPP), and to estimate the annual global number of UAPP.

Methods: We carried out a systematic review of the scientific literature published between 2006 and 2018, supplemented by mortality data from WHO. We extracted data from 157 publications and the WHO cause-of-death database, then performed country-wise synopses, and arrived at annual numbers of national UAPP. World-wide UAPP was estimated based on national figures and population data for regions defined by the Food and Agriculture Organization (FAO).

Results: In total 141 countries were covered, including 58 by the 157 articles and an additional 83 by data from the WHO Mortality Database. Approximately 740,000 annual cases of UAPP were reported by the extracted publications resulting from 7446 fatalities and 733,921 non-fatal cases. On this basis, we estimate that about 385 million cases of UAPP occur annually world-wide including around 11,000 fatalities. Based on a worldwide farming population of approximately 860 million this means that about 44% of farmers are poisoned by pesticides every year. The greatest estimated number of UAPP cases is in southern Asia, followed by south-eastern Asia and east Africa with regards to non-fatal UAPP.

Conclusions: Our study updates outdated figures on world-wide UAPP. Along with other estimates, robust evidence is presented that acute pesticide poisoning is an ongoing major global public health challenge. There is a need to recognize the high burden of non-fatal UAPP, particularly on farmers and farmworkers, and that the current focus solely on fatalities hampers international efforts in risk assessment and prevention of poisoning. Implementation of the international recommendations to phase out highly hazardous pesticides by the FAO Council could significantly reduce the burden of UAPP.

Keywords: Pesticide, Insecticide, Herbicide, Poisoning, Mortality, Morbidity, Incidents, Occupational, Farmer, Farmworker, Agriculture

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Background

Human poisoning by pesticides has long been seen as a severe public health problem [1–4]. As early as 1990, a task force of the World Health Organization (WHO) estimated that about one million unintentional pesticides poisonings with severe manifestations occur annually, leading to approximately 20,000 deaths [5]. Additionally, two million cases were expected to result from intentional self-harm. It was recognized that people in the developing world were particularly affected by the impact of pesticide poisoning and the number of cases was probably much higher as many cases remain unreported. Jeyaratnam further estimated 25 million cases of occupational acute pesticide poisonings per year, the bulk of which were not recorded, as most of the affected did not seek medical attention [6]. During the last two decades, international bodies have taken up the issue and adopted a number of resolutions and programs to address the detrimental effects of pesticide use [7–11]. Despite these efforts, global pesticide use has continued to grow steadily to 4.1 million tonnes per year in 2017, an increase of nearly 81% from 1990 [12].

Whilst numerous small surveys of pesticide poisoning have been published in the thirty years since the WHO publication there are no updated estimates for global pesticide poisoning. Peer reviewed authoritative studies still rely on the pervasive but outdated WHO estimates, which were derived using data from the 1980s [13]. With respect to self-harm, a recent systematic review of data from 2006 to 2015 concluded that pesticides account for 14–20% of global suicides leading to 110,000–168,000 fatalities yearly over the period 2010–2014 [14], a marked reduction from the 258,234 estimated for 2002 [15], the fall being attributed to regulation of some toxic pesticides and a rural-urban population shift [14]. An estimated 14 million people have died from suicide using pesticides since the advent of the Green Revolution in the 1960s [16].

However, no updated estimates of unintentional pesticide poisoning (accidental or occupational) have been carried out so far. In general, even recent publications often fail to differentiate between intentional and unintentional poisonings [17, 18], or between pesticide and other chemical poisonings [19], or are silent on unintentional pesticide poisonings and instead refer exclusively to suicides [20].

Recently, there has been a tendency for policy instruments to focus only on deaths and hence ignore the much larger number of people who suffer acute non-fatal pesticide poisoning. Regrettably, the Sustainable Development Goals (SDG) also focus only on deaths when it comes to poisonings [21]. One recent review, in summarizing the effects of pesticides on human health, completely omitted mentioning acute effects at all [22]. However, this lack of attention to acute pesticide poisoning, and especially to acute non-fatal occupational poisoning, may have hampered the development of measures to prevent such poisoning at both national and international levels. Additionally, it ignores the role such poisonings may play in understanding long-term health effects. Acute pesticide poisonings can be indicative of exposures that may lead to chronic outcomes, and are deserving of attention for this reason alone. As well, other losses are incurred as a result of acute pesticide poisoning -- the loss of quality of life, loss of well-being, and loss of ability to work. For these reasons, we aimed to carry out a systematic review of the global distribution of unintentional acute pesticide poisoning (UAPP) and to develop a current estimate of annual worldwide UAPP. We focused on occupational exposure, as this issue seems to be least well understood but is likely to be the most common source of exposure that results in unintentional acute intoxication.

Methods

To achieve our goal of a current estimate of annual world-wide UAPP, we carried out a systematic review of the scientific literature and additionally used publicly available mortality data from the WHO. This systematic review is based on a protocol (supplement S1) according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [23] and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (see supplement S6). Mortality data are provided by the World Health Organisation (WHO) Cause of Death Query online (CoDQL), part of the WHO Mortality Database [24]. Data were first extracted from included publications and sources, then we made country-wise synopses and estimated the annual numbers of national UAPP. Finally, the total of annual world-wide UAPP was estimated based on national figures and population data for FAO-defined regions and sub-regions.

Literature review

Search procedure for publications

The primary sources for this review were the electronic databases PUBMED, EMBASE and Web of Science. We aimed at broad search categories while also aiming for a manageable number of hits. An orientating PUBMED search was refined by varying the search terms, term truncation and limiting to specific fields. The results were compared and checked against articles known to be relevant for the review. Search terms from missed articles were added, but skipped when results were shifted to more clinical, treatment, or general toxicological issues.

We searched publications using the term "pesticide" or its synonyms or subgroups (e.g. insecticide). We allowed for any reference to human poisoning or health effects by surveys or taken from registers in terms of incidence, prevalence or specified by morbidity and mortality. We did not impose any restrictions on study designs or case identification. The final search strategy was set up for PUBMED (Table 1) and adapted to the other search engines. Search results, including abstracts, were stored using the literature data management software Zotero [25] which allows handling of references, abstracts, and full-texts including checking for duplicates.

All authors checked their own collections for eligible papers to supplement the automatic search. Further, articles were identified in the course of the selection and extraction step of the review by inspecting bibliographic reference lists of included papers and citation tracking.

Eligibility criteria, study selection, and data collection

We included publications reporting on UAPP covering accidental, homicidal and malicious poisoning. We aimed at the number of UAPP per well-defined populations and time-spans. Studies dealing exclusively with suicidal pesticide poisonings and intentional self-harm were excluded. So were studies on long-term effects such as cancer, if they did not include UAPP. The profiles of pesticide use pattern, exposure factors, and crop growing differ in various parts of the world and change over time. In order to best capture the current situation, on the basis that pesticide management is likely to have changed considerably since 1990, we chose to exclude data prior to 2006. A later cut-off date was likely to have resulted in too few studies to provide sufficient information for the analysis. However, in the automatic search we also included articles with a publication date from 2000 on for a separate analysis of trends (not presented here). The assessment of the eligibility of studies was based on exclusion and inclusion criteria given in Table 2.

All references resulting from the automatic search were screened by title and abstract for eligibility of studies. Papers that appeared to meet the eligibility criteria by their abstract, or did not offer sufficient information to make a determination, were obtained in full text. Eligibility of full-text articles was then assessed independently by two reviewers each. If there was disagreement, consent was sought by discussion with the entire team of authors.

Data from eligible publications were extracted according to the following principles:

1. Data aggregation
   - across pesticides: If UAPP figures were given only for several specific pesticides (e.g. insecticides, fungicides) or for active ingredients we extracted the overall number of cases (e.g. insecticides + fungicides);
   - across types of poisoning: if UAPP figures were provided specifically for several types of poisoning (e.g. accidental, homicidal) we summed up and extracted the overall number of cases;
   - across years: If UAPP were provided for multiple years we calculated the average of cases over the latest years (maximum of 5); we annualized UAPP when reported for a shorter period;
   - across symptoms: If UAPP figures were given for specific symptoms but without "overall" figures, we selected the symptom with the highest prevalence and used those case numbers.
2. We excluded studies that exclusively provided data prior to the year 2006. If an article provided data both prior to and after 2006 only data from 2006 and later were extracted. If yearly data were

Table 1 Terms and results of final PubMed search

Step	Search Terms	Hits
#7	• #6 AND Humans[Filter]	1028
#6,	• #5 AND ("2000"[Date - Publication]: "2018"[Date - Publication])	1408
#5	• #4 AND (survey[tw] OR register[tw] OR inciden*[tw] OR prevalen*[tw] OR mortality[tw] OR morbidity[tw])	2088
#4	• #3 AND (poison*[tw] OR "health effects"[tw])	10, 677
#3	• #1 OR #2	124, 856
#2	• insecticides[tw] OR insecticide[tw] OR fungicides[tw] OR fungicide[tw] OR herbicides[tw] OR herbicide[tw] OR rodenticides[tw] OR rodenticide[tw]	89, 801
#1	• Pesticide[tw] OR pesticides[tw] OR "crop protection chemicals"[tw] OR agrochemicals[tw] OR agrochemical[tw]	54, 771

searched 2018-11-26, tw = textwords

Table 2 Exclusion and inclusion criteria for assessment of eligibility

Criteria for	
Inclusion	• papers giving the number of UAPP per well-defined population and time span • published 2006–2018
Exclusion	• papers not explicitly stating results on UAPP • papers exclusively reporting on suicidal poisoning/ intentional self-harm • studies on long-term effects such as cancer that did not include UAPP • studies on poisoning treatments or clinical outcomes • modelling or simulation or biochemical studies • ill-defined survey populations or hospital data with unclear catchment area • language other than English, German, Spanish • data prior to 2006

not given, a group decision for eligibility was sought.

3. If a publication reported on more than one study or gave data for several use-types (e.g. rural, urban) we extracted one record for each type;
4. If a publication gave the number of UAPP of the survey sample but also provided a national estimation we extracted the national UAPP figure.

A MS-Excel sheet was drafted for the extraction of data and subjected to a series of pilot test extractions by all four reviewers. Causes of disagreements between reviewers' test extractions were discussed and led to revised versions of the extraction sheet (see supplement S2 for the final version). Data extraction was done independently by two reviewers per paper. If there was disagreement, consent was sought by the entire team of authors. Data analysis was carried out with SAS statistical software, Version 9.4 (SAS Institute, Inc., NC, USA).

Risk-of-bias assessment

Our review aimed to estimate the global distribution of UAPP. Our concerns about study bias therefore were focused on the prerequisites of a valid extrapolation from a study population to the national level and from the national level to the international region. A risk-of-bias assessment can help to select studies in the data synthesis step, especially when more than one study is available for the same categories of reporting. Our risk-of-bias assessment was directed to systematic differences of the study population and the target population as well as to systematic differences in the determination of poisoning. These bias types were assessed by extracting information on the sampling procedure, the identification and evaluation of poisoning (supplement S2).

WHO mortality database

In addition to the data provided by the publications, we extracted mortality data for UAPP based on national statistics from the WHO Cause of Death Query online (CoDQL) [24]. The data comprise deaths registered in national civil registration systems with underlying cause of death as coded by the relevant national authority. Underlying cause of death is defined by CoDQL as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" [24]. The CoDQL allows for extracting cause of death data by country, year, sex and age.

Most countries report cause of death data using the International Classification of Diseases revision 10 (ICD10). WHO allows reporting either by a 3-digit or by a 4-digit code. On a 3-digit level the ICD10 code "X48" refers to "Accidental poisoning by and exposure to pesticides," with a fourth digit that indicates the site where the incident occurred. ICD10 code "X487" stands for farms and ranches but includes only buildings and land under cultivation whereas "farmhouses and home premises of farm" are excluded from this coding [26]. The coding of the location of poisonings is dependent on context information of the specific poisoning incidents; however, these data are often not available to the coding institution. In this case, countries reporting at the 4-digit level make use of "x489 unspecified place".

Data for all countries reporting by ICD10 were extracted from CoDQL for the most recent 5 years after 2005, where available. We averaged the crude numbers of UAPP per country over the included years. In addition to all fatalities children up to 15 years of age and poisonings at farms were considered separately. Countries report only for ICD codes with incidents, so a missing code was considered as zero incidents for our purposes. So, if a country reported by ICD10 3 or 4-digit codes (see supplement S3b for details), but provided no codes × 48, we set × 48 = 0. Additionally, for those reporting by 4-digit codes but providing no code × 487, UAPP with farms as the place of occurrence were considered to be zero (× 487 = 0).

Data coded by ICD revision 9 were excluded from analysis because there are no extensional codes to identify accidental pesticide poisoning. The same applies to countries reporting by a WHO prepared aggregated code-list.

Synopses and estimation of national UAPP

If no national figures on UAPP were given by the data sources extracted, we extrapolated from study populations by applying the ratio of UAPP (the number of cases per population size) to the respective national population. If these ratios were available from more than one study we used the average. We guided the extrapolation as close as possible to the study population, so, for example, abstaining from extrapolating to the entire population when the study base was farmers.

When data from more than one source were available per country we preferred:

1. national figures,
2. the more general approach,
   - on pesticides (e.g. reporting on pesticides in general in contrast to insecticides only)
   - on health outcomes (e.g. all UAPP symptoms in contrast to ocular effects of UAPP)
   - on populations (e.g. all farmers in contrast to female farmers only),
3. more recent data, or

4. studies with less risk-of-bias (e.g. with representative samples and verified diagnoses) given the same study characteristics.

We reported fatal and non-fatal cases of UAPP on three types of populations: general (the "all" population category from supplement S2), farming/occupational (includes "farmers & workers", "farmers only" and "workers only") and children (< 15 years). Data on the respective national populations were searched for via the internet if not provided by the extracted publications. We looked for population data most closely matching the studied population and study period. Alternatively, we used data from the World Bank [27]. World Bank provides figures on the overall population and children, as well as the size of total employment and the percentage of employment in agriculture. We calculated the size of the "farming/occupational" population by multiplying the share of agriculture by the total employment.

Estimation of international UAPP

A list of countries and their allocations to regions and sub-regions was taken from the Food and Agricultural Organization of the United Nations (FAO). FAO splits Oceania into 4 sub-regions. As we found data only for one country from Melanesia, and none from Micronesia and Polynesia, we combined these with Australia and New Zealand into one sub-region. Furthermore, we combined southern and middle Africa, as both sub-regions were poorly covered by national estimates. A table of countries with extraction data shown by region and sub-region can be found in supplement S4.

We based the estimation of annual worldwide UAPP on the national estimates. The country specific case numbers were summed per sub-regions and the respective sums multiplied by the share of these country populations to the overall population in the sub-regions for a reference year 2016. In detail:

For each sub-region (j = 1,...,m) and country (i = 1,…,n_j) with national UAPP cases_i we

1) summed the country specific cases for region j

$$cases_j = \sum_{i=1}^{nj} cases_i$$

2) calculated weights w_j of the population size of respective countries to the overall population in region j (POP_j)

$$w_j = \frac{\sum_{i=1}^{n_j} pop_i}{POPj}$$

3) estimated cases per region by division of weights j

$$\text{cases}_{\text{est j}} = w_j^{-1}\,\text{cases}_j$$

We applied this procedure separately for fatal and non-fatal UAPP. For fatal UAPP, we restricted the extrapolation to the general population since occupational fatal UAPP cannot correctly be assessed by ICD codes. For non-fatal UAPP, we based the extrapolations on the farming/occupational population because this population was well covered by studies.

Results

Selection procedure

Results of the selection procedure are given in Fig. 1. We screened 1683 references by abstract, of which 985 were excluded. Of these, 74 articles could not be obtained because they were published in journals not listed in PubMed, or in journals not accessible by German libraries, or were written in the Chinese language (list of excluded papers available from the authors). Following the screening of abstracts and the hand-search, 824 articles were subjected to full-text assessments.

Finally, we included 157 articles in our data synthesis [28–184]. Since some articles reported on several countries or populations, 175 records were extracted for national synopses. We retrieved WHO mortality data from the CoDQL on 115 countries for the general population and the subsets of children and farming each (see supplement S3a, b). In total, the data covered 141 countries. The paper of Lekei et al. [101] is a re-analysis of earlier studies [100] and therefore the data were not extracted, but were considered in the country synopsis.

Study characteristics of extracted publications

Extracted data from all included publications (175 records) are given in annex Table A1. UAPP figures on a national level were provided by 25% of the records, mostly originating from mortality registers, poison-call-centres, or hospital discharge statistics. The majority of publications provided figures for regional study populations. There were 14% of records with data on a group of pesticides (e.g. organophosphate insecticides) or active ingredients (e.g. aluminium phosphide) only, whereas in the majority of papers, pesticides in general were covered. Most studies had a focus on occupational poisoning, with farmers and (mainly agricultural) workers addressed in 110 of all 175 records. Fifty-six records referred to a general population (that is, without any subgroup stratification) and 9 papers highlighted poisoning in children. The outcome type was non-fatal UAPP in 77% of records whereas 18% provide both mortality and morbidity data.

Because the surveys had different objectives they used varied designs, most of them (60%) with random sampling to achieve some representativeness for the study population (see examples in Table 3).

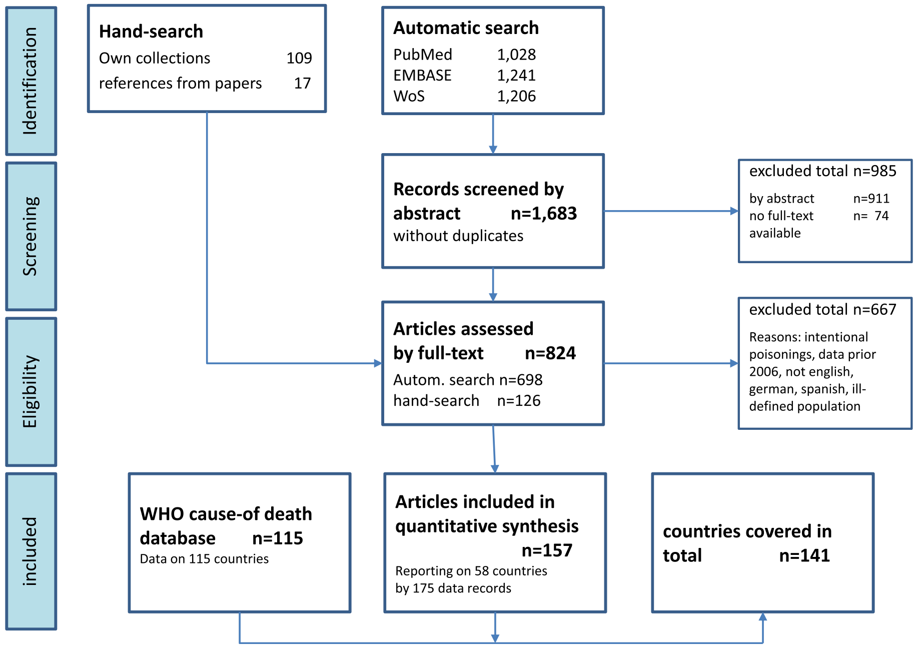

Fig. 1 Flowchart for results of the selection procedure of studies and data

Case identification of UAPP was done in 39% of the studies by study scientists or by ICD codes from registers. However, in most studies (57%) poisoning was self-reported to field researchers mainly based on a provided list of symptoms of pesticide intoxication. Whereas many studies seem to make use of a WHO standard definition (e.g. [86, 128]), others stretch the identification period, e.g. to a month [149]. Biomarkers like cholinesterase were used for case identification in 11% of studies, whereas only 3 studies aimed at an identification of active ingredients in biological samples.

UAPP reported in extracted publications

Approximately 740,000 annual cases of UAPP are reported resulting from 7446 fatalities and 733,921 non-fatal cases (Table 4). Data differed with respect to the populations. Only four records provided data on fatal UAPP for children and no study was identified that reported on fatal UAPP in farmers or workers only populations.

The distribution of UAPP is strongly affected by maximum numbers. High numbers are reported from some registers, e.g. the annual 77,690 non-fatal UAPP given by the United States National Poison Data System [117] or the number of fatalities from accidental pesticide poisonings in India (6488 average 2014–2015) according to the National Accidental Deaths and Suicides Report of the government [123]. The maximum number of non-fatal cases was 209,512 in South Korea, reported by Lee et al. 2012 [96] and derived as the nationwide results of a representative survey of male farmers.

Our review had a good coverage of non-fatal UAPP for the farming/occupational population, mostly reported by surveys on specific study populations in specific agricultural regions (Table 5), but there were no surveys or limited data for several countries. The average number of participants (=sample size) of these 99 studies was 347, with a mean of 136 non-fatal cases reported. The ratio of non-fatal UAPP (cases/sample size) is 51% on average. When based on a representative sampling the sample sizes and the mean of non-fatal cases were larger, but the ratio of UAPP was smaller compared to simple or not detailed sampling strategies. When the identification of UAPP was done by study scientists the median ratio of UAPP was about 10% lower than in surveys with self-reported poisoning.

Based on the data extracted, we can report only for the general population a total of 7466 fatalities. A small number of studies provided data on fatal cases for sub-populations, with four studies reporting a total of three deaths in children and two studies reporting a total of 60 deaths in farmers and workers. However, the single largest report which covered 87% of fatalities (from the Government of India) did not differentiate the figure of 6488 fatalities into the sub-populations of children, farmers and workers. Therefore, it seems highly likely that the figures for fatalities in the sub-populations are underreported.

Table 3 Examples for sampling strategies used in studies

Without random sampling: "Present study was conducted in the southern Punjab i.e. Multan and Bahawalpur Divisions, the major cotton growing areas of Pakistan. The field study was limited to a manageable geographical area where female cotton pickers are living and have a great potential to be exposed to pesticides. The villages selected on the willingness of the female workers that participate in the study … After preliminary survey two female groups (13–35 years of age) were selected as cotton pickers and non-pickers (30–37 female in each group) from the selected area." [162]
"Participants were recruited with the assistance of community leaders, churches, and local groups in the study area. Letters were sent to each of these entities which contained a clear explanation of reasons for the study, study objectives, inclusion criteria, consent to participate, and voluntary participation. These leaders and groups made announcements to the general public or community gatherings for a month. Those farmers who expressed interest in participation were invited to meet at the community leaders' residence, group meeting locations, or church premises. At these meetings, the principal investigator reviewed the study and explained the content. If the farmer wished to participate, the consent form was signed, and the questionnaire was given to complete." [163]
With random sampling: "From a universe of approximately 3500 subjects, a random sample of about 1100 workers directly exposed to pesticides was performed, considering as such those subjects who mix/load and/or apply pesticides.… As mentioned, applicators are professional workers authorized by the Agriculture, Livestock and Food Ministry to perform their tasks. They usually work in several extensive crops in the same area of the province, as independent professionals (the owners of the machinery) or as employees of an agrarian company." [46]
"The 2005 and 2006 surveys were conducted by a market research company and included 6359 users in 24 countries … Approximately, 250 users were sampled from each country. In each country, a local market research team identified regions where the use of pesticides was moderate to intensive… The selection of respondents was on the basis of quota sampling and targeted users on smallholdings of below average size and contract spray operators in countries where there were significant numbers of such users. The local market research teams designed their target smallholder farmers in terms of farm size and typical crops grown. Screening questions were used to ensure that the sample satisfied the quota requirements." [169]
"The target population of this survey included male farmers residing in rural areas in South Korea. The sampling frame for this survey was constructed by use of 2010 Korean Agricultural Household Registry data. Primary sampling units were formed out of the local administrative districts. We stratified primary sampling units into three strata based on three variables, which were the number of farm households, the farm household population by age group (< 15, 15–65, > 65) and the proportion of households residing in apartments. The selection of a 3% limit of error in the estimate yielded a needed sample size of roughly 2000. A total of 197 primary sampling units were selected by probability proportional to size sampling method. In the final sampling stage, the sample size in a primary sampling unit was 10. Trained interviewers visited each selected household and explained about the study." [96]

UAPP reported in WHO mortality database

Mortality data could be extracted for 115 countries reporting by ICD10 using three or four-digit codes. Seventy-nine of these provide data on UAPP (supplement S3a). Twelve countries reported UAPP on a three-digit level only (× 48) so no information on the place of incidents was available, meaning no farmer/farmworker populations could be identified. Thirty-six countries that did report data gave no entries for × 48, so zero UAPP is assumed (supplement S3b). Almost all countries contributed data for the 5 years before 2016. However, due to a late switch to ICD10 coding, data from Greece and Tunisia was available for 2 years and for Jamaica for 3 years only prior to 2016.

Overall, 835 yearly fatalities due to UAPP were notified, 139 of these occurring in children and 21 in the farming environment (Table 6). The distribution is rather uneven with a country maximum seen in Guatemala, resulting from 687 fatal cases in 2011–2015. The highest number of yearly fatalities in children was reported by Egypt based on 177 fatalities over the same time period. For farms, data were available from 91 countries, 73 of them reporting zero UAPP. However, this may follow from missing information on the place of occurrence of UAPP so that farm accidents were not coded. Among the ten countries with the highest number of annual fatal UAPP on the basis of WHO Cause-of-death data, five were from south and central America.

National estimates of UAPP

In order to derive national estimates of UAPP all extracted papers and WHO mortality data were revisited for each country. For those 58 countries covered by publications, these country synopses specify which data were used for national estimates and highlight specific limitations of the data used and estimations (supplement S5).

UAPP data were rarely reported by more than one paper per country for the general and child populations. An exception is the USA with yearly reports of poison control centres and other institutions, so that fatal poisoning was covered by seven papers for the general population, and two papers each for farming/occupational and children. For non-fatal poisoning in a general population again the USA was well covered by an overall maximum of 11 papers. The databases were different for non-fatal poisoning in the farming/occupational population, with more than 50% of the countries covered by more than one paper, most of them by two or three publications.

In general, the studies in our review vary widely with respect to the study populations, assessment of poisoning, years, and between countries. For the national estimates we therefore refrained from any weighting or standardisation of outcomes. Sometimes, a national estimate could be derived for a specific user group only. For example, for Pakistan we derived 81,750 non-fatal UAPP in 2010. However, this was based on studies of female cotton pickers only [39, 162] and we refrained from extrapolating this figure, which was based on a subpopulation of agricultural workers, to the total population. For Zambia, no national estimate was derived although one paper was extracted [179], as this study reported data from two hospitals with no clear catchment area stated

Table 4 Reported annual UAPP by population types

Population type[a]	Studies / records	Fatal cases				Studies / records	Non-fatal cases			
	N	Mean	Median	sum	Min;Max	N	Mean	Median	sum	Min; Max
general	28	266	3	7446	0; 6488	45	11,090	236	499,095	2; 77,690
children	4	1	1	3	0; 1	9	959	55	8637	12; 8005
farmers & workers	2	30	30	60	4; 56	36	191	129	6892	21; 935
farmers only	0					56	3872	87	216,813	18; 209,512
workers only	0					17	146	81	2485	19; 783
Total	34	221	1	7508	0; 6488	163	4503	98	733,921	2; 209,512

[a]according to types given in publications, "general" includes "children" and occupational groups when studies did not differentiate the sub-populations

and therefore was considered not reliable for a national estimate.

All country specific synopses were collated, including those countries for which no data were available from extracted publications but for which there were WHO mortality data (Annex A2). This annex reports for each country on the above mentioned three population categories. The numbers of fatal and/or non-fatal UAPP are given, along with the years and size of the respective population. Across all countries, a population of approximately 5 billion is covered with approximately 775 million children and approximately 750 million farming/occupational population. For all countries for which we had data, we arrived at approximately 309 million cases of UAPP annually. This overall figure resulted from very different national estimates. For example, for the farming/occupational population the highest estimated number of non-fatal UAPP was 145 million for India, resulting from a prevalence ratio of 62% and a reference population of 234 million. This prevalence was the mean of 6 publications. In contrast, the minimum number of 270 non-fatal cases was for Australia, with an estimated farming population of 349,697. This national estimation was derived from one paper of poison control centres in the state of Victoria only. For children, we derived non-fatal UAPP with a mean ratio of 19 per 100,000 children from nine countries: USA, Canada, China, South Africa, UK, South Korea, Tanzania, Malaysia, Moldovia.

Worldwide estimates of UAPP

The World Bank provides population data on 220 countries with a total population of approximately 7.5 billion for the reference year 2016. In this review, 69% of this population is represented by national estimates of UAPP. However, the coverage differs with respect to fatal and non-fatal UAPP.

For fatal UAPP, 117 countries of our review with national estimates represented a population of around 5 billion (Table 7). The national estimates summed to an overall fatal UAPP of 7609, which by our extrapolation procedure resulted in about 11,000 fatalities worldwide

Table 5 Reported annual non-fatal UAPP among farming/occupational populations from regional surveys by study characteristics

		All	Sampling[a]		Diagnoses[b]	
			representative	simple or not stated	by study scientists	self-reported
Studies/ records	N	99	60	39	8	91
Sample size	Mean	347	419	237	290	352
	Median	250	254	121	213	250
	Min	23	45	23	68	23
	Max	1958	1958	1040	542	1958
Non-fatal cases	Mean	136	148	118	109	139
	Median	90	114	74	81	95
	Min	18	18	19	26	18
	Max	783	783	450	276	783
Ratio = non-fatal cases / sample size	Mean	0.51	0.47	0.57	0.47	0.52
	Median	0.47	0.40	0.57	0.39	0.47
	Min	0.08	0.08	0.14	0.16	0.08
	Max	1.00	1.00	1.00	1.00	1.00

[a, b] see extraction sheet, supplement S2

Table 6 Annual fatalities from UAPP reported by countries according to WHO Mortality Database

	Countries	Yearly fatalities			
Population	N	Mean	Median	Sum	Max
General	115	7.3	0.5	835	137
Children	115	1.2	0	139	35
Farmer	91	0.2	0	21	8

annually. The vast amount of these fatalities are expected to occur in southern Asia, which is covered in this review by three countries (India, Iran, Maldives) with 70% of the population in this region. Western Africa is poorly covered in this estimation, as there is a national estimation for only one country (Cabo Verde), representing about 0.15% of the regional population.

With respect to non-fatal UAPP (Table 8), national estimates are available for 44 countries reporting on 81% of the respective worldwide farming/occupational population. The sum of national estimates of approximately 309 million is extrapolated by our procedure to around 386 million non-fatal UAPP worldwide annually. The lowest share of countries in this review to the overall population of the sub-region is seen for Central America (2%), which is represented by Costa Rica only. For eastern Asia, a weight greater than one was calculated because the average population of the study years of the extracted papers was greater than the population of the respective FAO region in the reference year 2016. For some regions, our extrapolation was based on only one country. For example, for middle and southern Africa, figures were based on Cameroon, but its national estimate of non-fatal UAPP was derived from 5 surveys of rather good quality. No national estimates on non-fatal UAPP were available for central Asia and Eastern Europe.

Discussion

The aim of this paper was to systematically review the literature on the prevalence of UAPP and to estimate the annual global distribution. In total, we estimate that about 385 million cases of UAPP occur annually worldwide including about 11,000 fatalities. This estimation depends on the quality and validity of data as well as the estimation procedure.

Effects of single estimation steps

Our extrapolations follow a step-wise approach. The effects of the different estimation steps are highlighted in Table 9. For fatal UAPP, almost no difference is seen

Table 7 Estimated worldwide annual fatal UAPP by region

Region	Subregion	Population in subregion	Population in review[a]	Weight[b]	Number of countries[a]	Sum of fatalities in review	Estimated fatalities in subregion
AFRICA	East	405,425,679	42,752,218	0.10545	3	8.5	81
	Middle-Southern	217,729,520	53,771,984	0.24697	1	16.6	67
	Northern	228,846,848	133,894,911	0.58509	3	90.3	154
	Western	362,197,544	539,560	0.00149	1	0	0
AMERICA	Caribbean	43,278,165	31,557,456	0.72918	19	6.1	8
	Central	174,988,756	167,463,654	0.957	8	283.4	296
	North	359,792,066	353,535,331	0.98261	3	5.4	6
	South	420,434,194	395,970,288	0.94181	12	215.2	229
ASIA	Central	70,118,950	61,486,031	0.87688	4	3.5	4
	Eastern	1,616,177,218	1,532,006,035	0.94792	5	320.2	338
	South-Eastern	641,760,625	195,058,336	0.30394	5	48.4	159
	Southern	1,846,671,142	1,284,597,898	0.69563	3	6539.30	9401
	Western Asia	262,879,373	160,485,199	0.61049	12	23.6	39
EUROPE	Eastern	293,011,923	94,597,984	0.32285	7	24.2	75
	Northern	96,464,409	94,640,537	0.98109	8	1.2	1
	Southern	160,067,370	154,290,938	0.96391	13	13.7	14
	Western	195,338,358	191,762,460	0.98169	7	6.6	7
OCEANIA	AUS, NZ, Mel-Mic-Polynesia	40,153,128	28,353,352	0.70613	3	2.4	3
All	**all**	**7,435,335,268**	**4,976,764,172**		**117**	**7609**	**10,881**

[a]countries with data on fatal UAPP
[b]w_j = population in review divided by region's population, details see text Estimation of international UAPP

Table 8 Estimated worldwide annual non-fatal UAPP among the farming/occupational population by region

Region	Subregion	Population in subregion	Population in review[a]	Weight[b]	Number of countries[a]	Sum of non-fatal cases in review	Estimated non-fatal cases in subregion
AFRICA	East	110,892,829	72,889,835	0.66	6	33,480,337	50,936,173
	Middle-Southern	43,418,696	5,519,071	0.13	1	2,696,550	21,213,838
	Northern	18,237,245	4,189,286	0.23	1	2,216,132	9,647,501
	Western	52,622,701	28,778,253	0.55	6	18,502,947	33,833,710
AMERICA	Caribbean	3,602,799	1,271,668	0.35	1	203,466	576,445
	Central	11,986,716	259,564	0.02	1	83,060	3,835,727
	North	2,931,504	2,294,329	0.78	1	1078	1377
	South	24,345,793	18,917,959	0.78	6	6,165,372	7,934,306
ASIA	Central	6,983,220	0	0.00	0	.	.
	Eastern	152,053,052	189,363,417	1.25	2	20,793,763	16,696,758
	South-Eastern	105,088,068	94,439,399	0.90	6	49,645,682	55,243,562
	Southern	292,859,652	282,851,206	0.97	5	174,141,658	180,303,510
	Western Asia	14,083,454	889,267	0.06	3	231,353	3,663,972
EUROPE	Eastern	12,990,116	0	0.00	0	.	.
	Northern	919,915	397,175	0.43	1	91,350	211,580
	Southern	4,008,995	1,324,195	0.33	2	418,900	1,268,217
	Western	1,920,615	797,471	0.42	1	57,863	139,357
OCEANIA	AUS, NZ, Mel-Mic-Polynesia	1,620,369	349,697	0.22	1	270	1251
All		**860,565,737**	**704,531,792**		**44**	**308,729,782**	**385,507,286**

[a]countries with data on non-fatal UAPP
[b]w_j = population in review divided by region's population, details see text Estimation of international UAPP

between the reported numbers from eligible publications and the national estimations, as the data were already on a national level and WHO Mortality Database added very little. The world-wide extrapolation added some 3000 cases over all regions. In contrast, for non-fatal UAPP, a steep increase occurs by extrapolating from numbers in extracted publications to the national level. That is because non-fatal UAPP was mostly recorded by surveys on study populations and the national estimates resulted from applying the poisoning ratios to larger national at-risk populations. So, the estimation of non-fatal country-wise UAPP is a crucial step in our review and depends upon the reliability of assessed incidence of UAPP. We found a median ratio of 47% of respondents suffering from UAPP from all included surveys (Table 5), with a span between zero and 100% showing high variability across studies, countries, and populations studied. This variability was lower when countries were compared using studies with the same study design. This matches the results of an international survey in 11 countries and different populations in the year 2006 [169]. The ratio of UAPP was lowest for Spain (30%) and highest for Morocco (85%), pointing to a possible influence of the study designs.

Table 9 Fatal and non-fatal annual UAPP according to different estimation steps

Sum of cases	Fatal	Non-fatal	All
Extracted publications	7508	733,921	741,429
National estimates[a]	7609	308,729,782	308,737,391
Worldwide estimates[a]	10,881	385,507,286	385,518,167

[a]Based on general population for fatal and on farming/occupational population for non-fatal UAPP

Relation to other estimates of UAPP

Our estimation considerably exceeds the pervasive 1990 WHO figure of about 1 million annual cases of UAPP. This figure, however, was understood to refer to poisonings with severe manifestations only and relied mostly on hospital data. WHO concluded that the numbers of "poisonings may be matched by a greater number of unreported, but mild, intoxications and acute conditions such as dermatitis" [5]. In revisiting the WHO assessments Jeyaratnam provided an estimate for those unreported, mild intoxications as 25 million cases in developing countries [6]. His estimate was an extrapolation from surveys of self-reported symptoms undertaken in just two countries in Asia, in which 6.7% of agricultural workers in Malaysia were poisoned per year and 2.7% in Sri Lanka. We were unable to arrive at an occupational estimate for either of these countries because of a lack of recent data, but our estimate for developing countries is higher, with an overall global farming/occupational estimate for a yearly UAPP incidence of 44% (Table 10). Our estimates ranged from a low of 0.05% in the USA to a high of 84% in Burkina Faso. Consistently high rates of UAPP were found in South Asia and South East Asia, mostly in the 54–65% range. High rates were also found in Africa, ranging from 21% in Cote d'Ivoire to 84% in Burkina Faso.

Apart from the USA, the only other country to register below 1% was Australia. However, for both of these countries, the data came from registers and did not include farmer/worker surveys. The respective underestimation of non-fatal UAPP is visible from the low number of cases for North America. Only 1078 cases were reported for the occupational population in this region (Table 8) whereas in the USA alone, more than 70,000 cases of non-fatal UAPP occurred annually among the general population (Table A2). Unfortunately, the register-based data do not allow for differentiation between subpopulations, and the share of the farming/occupational population in the UAPP total is therefore not available.

In conclusion, our world-wide estimates of UAPP follow from a better coverage of countries and data sources compared to earlier studies. An increase of pesticide poisoning might have resulted from the increase in global pesticide use between 1990 and 2017. Whereas the world-wide tonnage increase in pesticide use was about 80%, this includes a 484% increase in South America and a 97% increase in Asia, compared to a decrease in Europe of 3% [12]. So, many more farmers and workers are likely to be exposed to pesticides now globally, or more exposed through more frequent use. Our estimates are based on the size of the agriculture population provided by the World Bank, which is calculated by a given share of the total employment. It has to be pointed out that these estimates are probably too low because "employment" is for some countries too narrow a definition, as it might not include informal employment and people engaged in subsistence farming.

Challenges for estimations of UAPP

Comparability of case identification and at-risk times

There is no generally agreed understanding of what constitutes acute pesticide poisoning. Studies often refer to a classification tool provided by the Intergovernmental Forum on Chemical Safety (IFCS), which was hosted by the WHO [185]. An acute pesticide poisoning by the IFCS definition is any illness or health effect resulting from suspected or confirmed exposure to a pesticide within 48 h. Clinical presentations and symptoms of poisoning were tabulated by this tool. The chosen latency period from exposure to onset of symptoms is decisive for case identification and comes as a trade-off, especially as unspecific symptoms like headache or nausea are also recognized as exposure effects. A too-short period might exclude symptoms with longer latency, while a too-long period could lead to the recognition of poisoning by symptoms that might have resulted from other causes.

Besides the case definition, the studied at-risk-time when exposure might have taken place is also crucial for identification of acute poisoning.

Figures of UAPP in this review originated from registers (e.g. mortality or hospital discharge) or from surveys. Registers usually provide data by ICD codes based on medical records of all defined cases and time span, whereas the surveys identify UAPP by questionnaires applied cross-sectionally to a selected population. Usually, persons are the observation units in surveys and person characteristics are related to the poisonings, whereas cases are reported from registers and monitoring of poisoning is the aim. As a person can suffer from repeated poisonings in a given time span, the incidence of cases usually exceeds the incidence of poisoned persons.

Studies included in this review varied with respect to case definition and at-risk time. Several referred to the IFCS definition with differing at-risk-times e.g. a week [31], or even lifetime "… whether any of 12 listed symptoms had ever been experienced within 48 h of using such pesticides …" [157]. Other studies used their own definitions focused on symptoms, which can show up immediately after spraying [58], within 24 h [53], or have delayed latency for up to a month [149]. Furthermore, some studies refrained from mentioning any latency time and left it to the respondents to link symptoms to exposure, such as "during application last year" [35], or "had ever experienced incidents related to agrochemicals" [169]. Such differences among surveys might lead to different results. For example, Choudhary et al. [53] studied poisoning symptoms with respect to different exposure times. Prevalence of skin related problems was highest in the 18 months exposure group (50%), in contrast to those exposed for 12 months (13%) or for 6 months of exposure (8%). However, no information was given on how often or to what extent pesticides were used in those periods. Kofod et al. [186] question the validity of self-reported symptoms as a proxy for acute organophosphate poisonings. The authors found a high prevalence of nonspecific symptoms, taken from a standardized list of clinical presentations, in the intervention group (chlorpyrifos application) as well as in the placebo group (neem application). The study also found no difference in biomarker plasma cholinesterase (PchE) activity between the groups and after intervention. A surprisingly high percentage of the farmers reported

Table 10 Incidence of yearly non-fatal UAPP among the farming/occupational population by regions and countries

Region	Sub-region	Country	UAPP (%)
AFRICA	East	Ethiopia	21.01
		Kenya	35.17
		Malawi	78.00
		Tanzania	76.35
		Uganda	66.00
		Zimbabwe	45.10
		Mean	*53.60*
	Middle-Southern	Cameroon	48.86
	Northern	Morocco	52.90
	Western	Burkina Faso	83.83
		Cote d'Ivoire	20.00
		Gambia	51.52
		Ghana	39.04
		Nigeria	69.10
		Senegal	30.52
		Mean	*49.00*
AMERICA	Caribbean	Jamaica	16.00
		Mean	*16.00*
	Central	Costa Rica	32.00
		Mean	*32.00*
	North	USA	0.05
	South	Argentina	47.40
		Bolivia	34.80
		Brazil	19.80
		Chile	17.63
		Colombia	66.38
		Venezuela	60.99
		Mean	*41.17*
ASIA	Eastern	China	10.88
		South Korea	23.00
		Mean	*16.94*
	South-Eastern	Cambodia	62.00
		Indonesia	53.83
		Laos	39.00
		Philippines	57.99
		Thailand	36.03
		Vietnam	57.35
		Mean	*51.03*
	Southern	Bangladesh	55.64
		India	62.00
		Iran	59.35
		Nepal	65.00
		Pakistan	81.75
		Mean	*64.75*
	Western Asia	Georgia	20.00
		Kuwait	82.00
		Palestine	34.50
		Mean	*45.50*
EUROPE	Northern	UK	23.00
	Southern	Portugal	34.00
		Spain	30.00
		Mean	*32.00*
	Western	France	7.26
OCEANIA	AUS, NZ, Mel-Mic-Polynesia	Australia	0.08
All	*All*	*Mean*	*43.6*

symptoms for a seven-day period which was thought to be a "washout" period without any pesticide exposure."

In summary, it is difficult to assess the influence of different study characteristics on our estimations because most studies gave no clear case definitions and timeframes. In general, we aimed at annual figures and averaged figures when data for more than 1 year was provided by registers. However, we made use of survey results as annual prevalence, even when the at-risk time was considered longer. Furthermore, for our analysis we did not account for different latency periods in case definitions, nor for some surveys requiring two symptoms as a determination of poisoning while most only required one. We acknowledge that extrapolations might lead to an overestimation of country-wide UAPP by surveys directed to regions with high pesticide usage or high-risk populations, and by studies using non-specific symptoms as case indicators.

Underreporting by register and hospital discharge data

Data from registers like the WHO Mortality Database or hospital discharge statistics rely on the utilisation of health services and effectiveness of reporting systems. Both are limited in many countries. Utilisation is hampered as individuals suffering from acute pesticide poisoning may not seek medical care for various reasons, such as access to transportation or lack of medical facilities, lack of financial capacity, inability to take time off from work or fear of losing paid work, language and cultural barriers, or lack of health insurance [187]. The country specific reporting systems might give further causes for underreporting [188] including:

- lack of a universal, mandatory legal duty to report incidents,
- lack of a central reporting point for all incidents,
- similarity of symptoms associated with pesticide poisonings to other causes,
- misdiagnosis by physicians because of a lack of familiarity with pesticide effects,
- inadequate investigation of incidents to identify the pesticide that caused the effects,
- difficulty in identifying and tracking chronic effects,
- reluctance or inability of physicians to report incidents,
- limited geographic coverage of individual poisoning databases.

Studies have examined the number of counted deaths or poisonings against what is likely an underlying and greater number of poisonings. A survey conducted in a potato-producing province in Ecuador reported a pyramid of estimated pesticide health impacts with 4 deaths per year translated to 10 hospitalisations per year, with 40 poisonings that reached medical care per year, 400 possible poisonings with no clinical care, and 4000 cases of prevalent subclinical neurotoxicity with important performance deficits [189]. A recent study calculated a factor of up to 71 to correct for underestimation of occupational pesticide poisoning in routine community based surveillance [101].

Finally, we expect a considerable underreporting of fatal occupational UAPP because the respective ICD10 codes were not used or WHO cause of death data were not available. For example, a Government of India document [123] reported about 6500 fatalities, many of them probably resulting from occupational exposure, but India did not transfer these data to the WHO Mortality database nor did the government identify the number of occupational poisonings in its report.

Public health framework

Realizing that the conditions of use in developing countries are such that toxic pesticides cannot be used safely, the FAO/WHO International Code of Conduct on Pesticide Management [190] states that “Pesticides whose handling and application require the use of personal protective equipment that is uncomfortable, expensive or not readily available should be avoided, especially in the case of small-scale users and farm workers in hot climates”. In 2006, the FAO Council recommended that consideration be given to the progressive ban of highly hazardous pesticides [8], a call that was supported by the 2015 International Conference on Chemicals Management (ICCM4) [10], and by a FAO/WHO Guideline to the International Code of Conduct on Pesticide Management [190]. The lack of action on FAO’s 2006 recommendation and the ongoing problems with pesticides led the UN Special Rapporteur on the Right to Food to recommend to the UN Human Rights Council in 2017 that there needs to be a comprehensive binding treaty to regulate pesticides throughout their life cycle [11]. Implementing these recommendations, especially encouraging all stakeholders to implement agroecologically based alternatives to highly hazardous pesticides, also recommended by ICCM4, would drastically reduce the unacceptably high level of UAPP. Several studies have indicated that phasing out highly hazardous pesticides does not need to result in reduced agricultural productivity [191, 192].

Limitations

In addition to the above mentioned challenges for estimating world-wide UAPP, our study has some limitations. First, the search strategy might have been too restrictive in order to identify all relevant publications. We therefore carried out some sensitivity tests, e.g. by deleting items or by extending to more specific terms like e.g. “organophos*” or to active ingredients in pesticides, but these appeared to barely change our results. Further, we might have missed relevant contributions in the grey literature and surely from national or regional poison control centres.

Second, our world-wide estimate of UAPP is partly based on a weak database. Some countries were covered by only one publication or by data on small samples sizes of specific study populations. For example, Venezuela was covered by one study with 50 workers fumigating against dengue fever- related mosquitoes using organophosphate pesticides. We therefore subjected those countries with limited data (Albania, Australia, Bahrain, Cote d’Ivoire, Malawi, South Africa, Venezuela) to a sensitivity analysis by exclusion from the world-wide extrapolation. However, this reduced the global estimate by just 1 %. Furthermore, for Greece and Tunisia, mortality data from the WHO Mortality database was available only for 2 and 3 years respectively. However, we do not expect this to bias the 5-years average annual UAPP in comparison to the many countries reporting on more years.

We have grouped countries in regions and sub-regions according to FAO’s determination, with the understanding that consistency in types of agriculture, pesticides used and conditions of use that influence exposure is likely to be greater across sub-regions than regions. Overall, studies reported too heterogeneously for global extrapolations to be based on pesticide use pattern.

Finally, although deaths from pesticides in food are known to still occur [193], we did not try to estimate them, nor was there anything in the publications we reviewed that could lead to such an estimate.

Conclusions

Our systematic review, which was carried out according to the international scientific PRISMA standards, updates outdated WHO figures on world-wide unintentional acute pesticide poisoning and complements a recent review on suicidal pesticide poisoning. Taken together, robust evidence is provided that acute pesticide poisoning is an ongoing major global public health challenge. This is despite the efforts over recent years to establish programs to improve the safety of pesticide use.

Our results point to a heavy burden of non-fatal UAPP, particularly for farmers and farmworkers, with about 385 million cases of UAPP and 11,000 deaths per year. This brings into focus the current bias towards focusing only on fatalities and the need to more seriously address the problem of non-fatal UAPP in both the international policy arena and in national pesticide, agriculture, environmental, and health policies.

Estimations of world-wide UAPP depend on the quality and comprehensiveness of the databases. Currently, neither registers nor surveys are sufficient to base estimations on solid, high quality data covering all countries and pesticide use patterns. International support to implement national documentation and monitoring systems is necessary in order to improve the coverage of the WHO Mortality Database. Furthermore, registers for hospital discharges or poison control centres typically seem not to be consolidated on a national level and do not inform national mortality registers. Many countries lack surveys of UAPP amongst farmers and workers. Additionally, surveys on UAPP lack a standardized case-definition of acute poisoning and should clearly report the chosen population and at-risk times. Future study directions on UAPPs would include prospective cohort studies for chronic outcomes to better understand long term effects of acute poisoning. Efforts to estimate global fatalities amongst farmers and workers, and children, were hampered by the lack of differentiation of fatalities in hospital and government reports. In the future, government and hospital reports should differentiate between farmers, workers, and children in reporting mechanisms in order to allow a better understanding of the extent of the problem in these population categories. Finally, improvements of the data base would allow for a regular and reliable monitoring of UAPP and support the evaluation of preventive public health policies. However, in our view, our review of the existing documentation of unintentional pesticide poisoning is sufficient to identify a problem that warrants immediate action.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-020-09939-0.

Additional file 1: Table A1. Extracted articles by study characteristics.

Additional file 2: Table A2. Summary of national estimates.

Additional file 3: S1. Protocol for a systematic review on the global distribution of acute unintentional pesticide poisoning.

Additional file 4: S2. MS-Excel sheet for data extraction.

Additional file 5: S3a. Countries with fatalities of UAPP retrieved from WHO Cause of Death Query online. **S3b.** Countries reporting no fatalities of UAPP retrieved from WHO Cause of Death Query online.

Additional file 6: S4. Table Countries with extraction data by region and sub-region.

Additional file 7: S5. National syntheses of UAPP by country.

Additional file 8: S6. PRISMA checklist.

Abbreviations

CoDQL: Cause of Death Query online; FAO: Food and Agricultural Organization of the United Nations; ICD: International Classification of Diseases; IFCS: Intergovernmental Forum on Chemical Safety; PAN: Pesticide Action Network; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; SDG: Sustainable Development Goals; UAPP: Unintentional acute pesticide poisoning; UN: United Nations; WHO: World Health Organization

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Authors' contributions

WB designed the systematic review, did the data management and analyses and drafted the manuscript; MW initiated and co-ordinated the group; MW and EM contributed parts of the manuscript; EM, MW, PC, WB participated to the same extend in the assessment and extraction of publications as well as in revising, commenting, and editing the manuscript. All authors read and approved the final documents.

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CORRESPONDENCE

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Letter to the editor regarding the article "The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review"

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Abstract

We read with interest the article entitled "The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review". We wholeheartedly agree that it is important to evaluate the extent of this issue. We would like to understand the numbers provided in this article, which appear to overestimate the global burden of pesticide poisonings. We also feel that addressing the benefits of these chemistries is important for a complete evaluation.

Keywords: Pesticide poisoning, Pesticides, Crop protection, Public health, Chemistry, Toxicology

Main text

Dear Editor,

We read with interest the article entitled "The global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review" [1]. We wholeheartedly agree that it is important to evaluate the extent of this issue. We would like to understand the numbers provided in this article, which appear to overestimate the global burden of pesticide poisonings. We also feel that addressing the benefits of these chemistries is important for a complete evaluation.

Pesticides are critical for public health. They ensure food security and protect people from insect-borne illness, toxic weeds and carcinogenic mycotoxins which contaminate crops after fungal infections. The World Health Organization (WHO) estimates the global annual burden of malaria and dengue alone to be over 315 million cases [2]. Additionally, the WHO estimates that 690 million people were severely malnourished in 2019 [3]. Pesticides are vital tools for the control of these diseases. Additionally, pesticides are important for farmers to support the social, environmental and economic sustainability needs of society.

In this study, the authors extracted from 157 publications 740,000 annual cases of unintentional acute pesticide poisoning (UAPP) resulting in 7446 fatalities from which they estimated global burden. We are uncertain as to how they arrived at these figures though a substantial proportion of the numbers appear to have been extracted from inflated US data [4–10]. When no data were available for a particular country, the authors extrapolated using UAPP frequencies from other geographies, sometimes relying on sparse, possibly unrepresentative, data. For example, fatal UAPP cases in Western Africa were estimated from data representative of only 0.15% of its population. Similarly, data representing only 2% of the regional population informed the reported non-fatal cases in Central America [1]. The US data seem to have come from American

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Association of Poison Control Centres (AAPCC) reporting from 2012 to 2017. Although they never establish a case definition of UAPP, it appears the authors have conflated exposure, or coming in contact with a substance, with poisoning, which involves developing adverse symptoms upon exposure. Using the *exposure data* reported by the AAPCC they claim that there are between 72,000–77,000 *poisoning cases* per year. A review of the actual AAPCC exposure data shows degrees of poisoning, ranging from none, to minor, moderate, major and death. From 2012 to 2017 the average annual number of patients exhibiting any poisoning symptom was 15,576 [4–10] -- far fewer than the numbers suggested by Boedeker et al. [1]. Additionally, these numbers combine intentional and unintentional poisonings [4–10], whereas the intent of the paper was to evaluate acute unintentional poisoning. Based on these and the extrapolated data previously mentioned, the authors estimate that 385 million cases of UAPP occur annually world-wide, which we contend overestimates the global burden of UAPP.

Several issues should be addressed in order to establish a more accurate estimation of UAPP. First, the definition of UAPP is inconsistent among included studies. Second, the authors conflate incidence and prevalence values which results in overestimation of annual UAPP cases; cases which occurred prior to the year of interest would be inadvertently included, inflating the final estimate of annual frequency. Third, the authors rely predominantly on self-reported data, which might introduce recall bias to the data. Fourth, as illustrated above, the authors extrapolate potentially unrepresentative estimates to reach national and global counts. This extrapolation has not been validated, nor is it reproducible given the data presented.

This study identifies gaps in knowledge regarding UAPP frequency among geographic regions, and identifies opportunities for the improvement of future studies. However, as discussed above, the study does not establish reproducible numbers nor a validated method for extrapolating the current data. Therefore, the results reported by Boedeker et al. [1] are not strong enough to support policy decisions but have served to point to significant gaps in knowledge. Given this, we would be open to collaborating with the authors on exploring a more robust method for assessment in order to support efforts to reduce the global burden of UAPP.

There is active research to develop viable, less hazardous alternatives to existing pesticides, and ongoing activities to reduce the risk of pesticides in use. Over the past two decades several low-toxicity chemistries have been introduced to the market for crop protection and vector control [11]. Moreover, all new products undergo risk assessments by regulatory agencies before introduction. These assessments include evaluating the conditions of use in low-income markets that comply with the International Code of Conduct on Pesticide Management. A constructive and informed discussion on the role of crop protection and the use of pesticides in sustainable food production is productive and pesticide safety should be addressed in partnership with governments, farmers, NGOs and other stakeholders.

Abbreviations

AAPCC: American Association of Poison Control Centres; NGOs: Non-Governmental Organizations; UAPP: Unintentional Acute Pesticide Poisoning; WHO: World Health Organization

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Authors' contributions

SED evaluated the poison center data and wrote the public health aspects of the letter. JR evaluated the epidemiology and reported her evaluation in the letter. CN wrote the conclusion of the letter. All authors have read and approved the manuscript.

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Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

SED and JR both are employees of Bayer Crop Science, CN is an employee of CropLife International.

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Publisher's Note

EXHIBIT C

BMC Public Health

CORRESPONDENCE Open Access

Response to: "letter to the editor regarding the article "the global distribution of acute unintentional pesticide poisoning: estimations based on a systematic review"" by Dunn et al. 2021 in BMC public health

Wolfgang Boedeker[1*], Meriel Watts[2], Peter Clausing[1] and Emily Marquez[3]

Abstract

In a correspondence to BMC Public Health, Dunn et al. (Dunn SE, Reed J and Neumann C. BMC Public Health (n.d)) respond to our review on the occurrence of unintentional, acute pesticide poisoning (UAPP). Based on a systematic review and further data sources we estimated that about 385 million cases of UAPP occur annually world-wide including around 11,000 fatalities (Boedeker W. et al. BMC Public Health:1875, 2020).

Keywords: Pesticide, Insecticide, Herbicide, Poisoning, Mortality, Morbidity, Occupational, Farmer, Farmworker, Agriculture

Main text

Dunn et al. [1] question the results of our study [2] and elaborate on two examples for a suggested general overestimation. We reply to these examples first and follow with response to the more general comments of the critics.

Dunn et al. state: "We are uncertain as to how they arrived at these figures though a substantial proportion of the numbers appear to have been extracted from inflated US data". This is not correct. Our estimation of UAPP made no use of this data source because we restricted non-fatal UAPP to the occupational/farming population, which is not specified in the reports of the US Poison Control Centers. However, if we were interested in the general population in this respect, we would use the US Poison Control Center reports as a welcomed and valid input. This is because Dunn et al. err in two more aspects. First, the reports do specify intentional as well as unintentional UAPP (see Table 22A Mowry et al. [3]). Second, a restriction to incidents with documented symptom severity– as thought necessary by the critics – would lead to underreporting, as the follow-up of the medical outcomes could be done by the Poison Control Centre in less than 50% of the cases.

Dunn et al. use the data coverage of Western Africa as an example of an inflated extrapolation. They suggest that overestimation of fatal UAPP follows from having data from just 0.15% of its population. Unfortunately, they choose not to mention that our estimate of fatal UAPP in Western Africa is zero. Data were available for Cabo Verde only, which reported no fatalities of UAPP to WHO (see Suppl S3b of our paper). Furthermore, Dunn et al. do not seem to have understood our estimation method. In contrast to their apprehension "When no data were available for a particular country, the authors extrapolated using UAPP frequencies from other

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geographies", we did not extrapolate national figures from data of other countries. If there were no data available for a country, no national figures were derived. We detailed our estimation method explicitly. Along with the data presented in our paper and the supplements, the estimates can easily be reproduced using a pocket calculator.

When it comes to further points raised by Dunn et al., we refer to our article where we have elaborated at length on the issues of case definition, validity of data sources, representativity, and their possible influence on our estimations. We also acknowledged reasons for over- and underreporting and tried to assess bias by sensitivity analyses. Finally, we think that our figures have been derived by valid methods and procedures and fill a research gap that has been left open for 30 years. The estimates are the best we could arrive at on the basis of available data but should still not be reported with too many decimals.

Our article is on the estimation of the annual worldwide UAPP, with a focus on the farming population. Still, Dunn et al. feel that addressing the benefits of pesticides "is important for a complete evaluation", a weird public health perspective often taken by the pesticide industry to obscure issues. We fail to see how millions of UAPP could be balanced by millions of malaria cases or malnourished people. However, even in these areas, there is scientific consensus that pesticides are not just a simple cure but part of the problem. For example, the prevention of malaria relies on a complex understanding of the vector ecology, local needs, and environmental conditions but replacement of this approach leads to a simplified dependency on insecticides and severe new problems, e.g. by insecticide-resistant vectors [4].

Also, it is common knowledge by now, that the cause of malnutrition and hunger is not a lack of pesticides but of availability and not production of food. Dunn et al. might get the idea from the Special Rapporteur of the UN General Assembly who critiqued "… the expansion of an international economic regime that promotes the unequal distribution of resources, the exploitation of agricultural workers, a rise in monocultural production and a lessening of diversity in food systems in times of climate emergency. … Investment should be diversified and reconciled with more responsible and sustainable food system methodologies, such as agroecology, as well as traditional knowledge. That requires a well-conceived shift away from industrial agriculture, which constitutes the main driver of the climate emergency, coupled with the promotion of transformative, resilient and sustainable practices. Agroecology avoids the use of dangerous biochemicals and pesticides; supports the local food movement; protects smallholder farmers, including women, and small fisheries; respects human rights; enhances food democracy, traditional knowledge and culture; maintains environmental sustainability; and helps to facilitate a healthy diet" [5].

Lastly, we welcome the ongoing evaluation of new and existing pesticides against the FAO/WHO Code on Conduct on Pesticide Management, especially Article 3.6 which states that "Pesticides whose handling and application require the use of personal protective equipment that is uncomfortable, expensive or not readily available should be avoided, especially in the case of small-scale users and farm workers in hot climates" [6]. Implementation of this article would likely result in a dramatic reduction in UAPP.

Abbreviations
FAO: Food and Agricultural Organization of the United Nations; PAN: Pesticide Action Network; UAPP: unintentional acute pesticide poisoning; UN: United Nations; WHO: World Health Organization

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Authors' contributions
WB drafted this response. EM, MW, PC participated in editing and revising the manuscript. All authors read and approved the final document.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The review has been commissioned by the Pesticide Action Network (PAN). PAN is a network of over 600 participating nongovernmental organizations, institutions and individuals in over 90 countries working to replace the use of hazardous pesticides with ecologically sound and socially just alternatives. PAN North America and PAN Asia Pacific support this review financially by assigning staff members (EM) and consultants (MW). PC and WB are former members of the board of the Pesticide Action Network (PAN Germany) without remuneration.

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EXHIBIT D

“The global distribution of unintentional acute pesticide poisoning: estimations based on a systematic review” – article published in BMC Public Health 2020 (https://doi.org/10.1186/s12889-020-09939-0)

Rebuttal by the authors of a planned retraction by the journal’s editor

1 Background

We, the authors of the above-mentioned article, were informed by BMC Public Health on 29.04.2023 that they plan to retract the paper. The decision was reportedly taken based on one Editorial Board member's assessment. The reason for this was given as the dissatisfaction of a reader with the answer we gave on 05.01.2023 to his critique on the use of a French study in our review.

Following a request by the authors for additional information we were informed that the Editorial Board member and the reader had concerns not just about the data of France but also with respect to some other countries. Following a further request by the authors the names of these countries were provided. No analysis by the Editorial Board member or reader was provided for these additional countries.

The concerns assume that generally an overestimation of poisonings cases occurs by using a reported “history of pesticide poisoning” or poisoning in an unspecified time frame for annual estimations. This assumption is wrong. Acute poisonings are by definition bound to a reasonably short time span (e.g. 24 h) after exposure. Acute poisonings can occur repeatedly when exposure occurs repeatedly, so many times in a year. Pesticides can be applied on a weekly basis by the same persons, for a number of crops. For example, Tomenson & Matthews (2009) – an industry-led international survey on pesticide poisoning – reported for Cameroon that within 12 months there were 1418 incidents by 154 users, so 9.2 cases per person per year. In general, there is little interest in studying lifetime incidence in surveys of acute intoxications and it is reasonable to assume that respondent’s report of acute poisonings refer to the repeating periods of pesticide application.

We discussed at length in our article the heterogenicity of the included studies as well as the consequences of low data-coverage of countries and provided results from sensitivity analysis. This was obviously to the complete satisfaction of the peer-reviewers of the paper.

In what follows, we first give detailed answers to the critique on using data on France and the other countries for which the Editorial Board member and reader had concerns. We show that this critique is unfounded and false and-- if true-- the effect on our results would be negligible. We then turn to the procedure by which the journal managed the critique and point to the scientifically unsound exclusion of authors and expertise in this process. Finally, we rebut the plan for retraction also due to the fact that two of the three parts of our article consist of a state-of-the-art systematic review and the analysis of a routine database, neither of which are addressed by the critique at all.

2 The critique in detail

We provide a detailed inspection of the critique on the inclusion of studies from France and several other countries, and our comments on them.

2.1.1 The "French reader" critique

Critique taken from the reader's email to BMC Public Health as reported on 03.01.2023 to the authors	**Reply by authors**
"I was rather surprised by the very large number found, and decided to have a specific look at the estimate for my own country, France. Indeed, the paper states an estimate of 7 fatal poisoning every year. See Table 7 on… and 139,357 non fatal poisoning"	The figures are wrongly cited. The figures mentioned are not for France but for Western Europe.
"These numbers are way larger than current estimates generally agreed in France."	Where does this come from? Which estimates? Are there any documents supporting this claim? Neither the information nor the source of the information have been provided so the claim cannot be examined or included.
"The paper states 'A history of pesticide poisoning was reported by 845 individuals (6.1%) among the 13,900 who completed the information (89.7%). ' Thus, a few percent of the respondent have declared to have suffered AUPP once in their lifetime. It appears that the authors of the paper have used this percentage as if it was representative of a yearly frequency, thus increasing the frequency of poisoning (and therefore the number of yearly UAPP) by a factor of 30-40."	This is a wrong assumption, since a "history of pesticide poisoning" logically does not mean "once in a lifetime". A history of pesticide poisoning also includes a person with acute poisoning in every year-- or even several times per year. All such incidents would be counted just as one poisoned person, if a poisoning history was reported. In fact, the exact question of the study referred to, by Baldi et al., was "Have you ever been intoxicated by a pesticide?" with answer categories: "Never - Once - Several times. If yes, in which year(s)" 3 answers were possible. The said study reports the prevalence of poisoning with no indication that only the "once"-category was analysed. The enrollment phase was 2005-2007. The "factor of 30-40" mentioned by the critic is without references and therefore without validity.

Even if this criticism was justified, deletion of the French data in total would change our global estimations by 0.04 %! The critique is not just wrong but overall negligible to the estimate.

2.1.2 Critique on other countries

After repeated inquiry, we received information on further countries of concern to the Editorial Board Member by email from the team Manager, BMC Series from 27.04.23: "The other countries on where concerns have been raised by the reader and Editorial Board Member include the UK and Cameroon where 'ever' prevalence has been used as an annual estimate. Furthermore, the concerns also flag that you have assumed annual exposure where the timeframe is not reported in other countries (e.g. Nigeria, Tanzania, Zimbabwe)."

We provide a detailed exploration of the studies with respect to the above-mentioned countries and highlight sections relevant for the time-frame of exposure.

(i) Countries with alleged "Ever" prevalence of poisonings

Cameroon:

For Cameroon our national estimations could be based on 5 surveys, including one strictly reporting an annual prevalence. We used the overall mean prevalence of 49 %, which is lower than that of the pesticide-industry study by Tomenson and Matthews (2009) reporting annual prevalence for Cameroon.

Achancho et al. 2019: 21% "… it was found that 21% of them said that they experience headache, after spraying".

Assokeng et al. 2017: 39 % "As far as discomforts of gardeners are concerned, various health problems were observed during handling: headache, transpiration, cold, burns and eye aches."

Pouokam et al. 2017: 40.3 % "Concerning themselves, 158 farmers interviewed declared to have experienced at least one case of pesticide accident during manipulation."

Tandi et al. 2014: 84.9% "Most farmers (85.0%) reported at least one symptom of acute pesticide poisoning following spraying."

Tomenson & Matthews 2009: 59% "… shows the percentages of users experiencing incidents in the last 12 months."

UK

For UK, our national estimations could be based on only 1 survey. Deleting UK data would reduce our global estimate by 211,580 non-fatal cases, which translates as 0.05 % of the estimate; and this in itself would provide an error as acute unintentional pesticide poisoning does occur in UK, as documented in this study and others that did not meet the systematic review criteria.

Solomon : "whether any of 12 listed symptoms had ever been experienced within 48 h of using such pesticides "

(ii) Countries with alleged not reported time frame

Nigeria:

For Nigeria (Africa Western) results could be based on 3 surveys. We used the overall mean prevalence of 60.9 %, which is lower than that of studies strictly reporting cases occurring during use of pesticides. In the following studies, the various surveys asked farmers what symptoms they experienced after using pesticides, and surveys were reported as being taken in a specific year, or reported the month and year.

Bassi et al 2016: 42% "Thus, clients present with multiple finding or symptoms. In this study most farmers experienced chest pain/tightness, cough, headache, dizziness, reddening of the eyes; sneezing and rheum more often".

Oluwole & Cheke 2009: 91.3% "For the human health effects, only acute symptoms that appeared within 48 hours of pesticide sprays were considered… Each interview took about 15–25 minutes to complete and all were conducted during March 2008." And: "By asking the farmers if they experienced any health weakness (discomfort) in their day-to-day handling of chemical pesticides. A majority (91.3 per cent) responded that they or someone in their family had suffered from pesticide-related health symptoms during or after application of pesticides."

Ugwu et al 2015: "One hundred and one (101) farmers corresponding to 74% of the sample reported having experienced at least one of the symptoms on occasion of pesticide handling." Data reported in this study was collected in 2014- see Table 4.

Tanzania

For Tanzania (Africa East) results could be based on 4 surveys including one reporting annual prevalence and one reporting 3-month prevalence. We used the overall mean prevalence of 76.4 % which is comparable to studies strictly reporting an annual prevalence or shorter.

Da Silva et al. 2016: 61 % "Pesticide users were asked if they had experienced the symptoms during or soon after direct contact with pesticides. To be counted as a pesticide-related symptom, the exposure had to be direct contact, and the symptoms had to occur on the same day or the next day. We also asked for the frequency of experienced acute health symptoms."

Lekei et al 2014: 93 % "Approximately 93% of respondents reported previous poisoning by pesticides in their lifetimes (past year inclusive) with frequency ranging from 1 to a maximum of 7 times; 76.4% of the poisoned respondents reported two or more poisonings and 63.5% reported 3 or more poisonings at some point in the past. The 112 farmers with past APP reported approximately 432 past poisonings in total."

Manyilizu et al: 76.6% "Every disease symptom out of 12 (symptoms) had occurred to an average of 51% (66/128) farm workers in the past three months."

Tomenson & Matthews 2009: 74.8 %. "… shows the percentages of users experiencing incidents in the last 12 months." Good example for multiple intoxications. 154 users experienced poisonings and reported 1418 incidents, so 9.2 per user and year."

Zimbabwe

For Zimbabwe (Africa East) results could be based on 1 survey. This adds approximately 2 million non-fatal poisonings to the Africa East estimation of 51 million.

Magauzi et al. 2011: 45.1 % "We assessed the health effects of agrochemicals in farm workers in commercial farms of Kwekwe District (Zimbabwe), in 2006… Forty-five percent of the participants stated that they had suffered some multiple symptoms at one point in time that they knew or suspected to have been caused by pesticide exposure".

3 Comment on scientifically unsound action and process of BMC Public Health

There was no information provided to the authors about any kind of investigation into our paper, nor about an additional critique, prior to being informed about the planned retraction. We, the authors, were piece-wise informed about the reasons, only after repeatedly asking for them. In view of conflicting statements by BMC Public Heath, we still do not know whether the "Research Integrity Group" of the journal was involved. We are informed that only one Editorial Board Member had concern about some of the data used, and that this evaluation is the basis of the retraction. We learned by email on 26.04.2023 "... that the details of the investigation remain confidential."

Editors in general have several ways of handling articles in dispute:

- inviting the critic to a correspondence making the dispute open to the scientific community,
- starting a new review process to make sure that expert's knowledge is involved,
- considering need for a correction of a paper.

None of these options have been used by BMC Public Health. The Editor seems to prefer to plan a retraction based on a critic who obviously is a well-known pesticides aficionado in France and who by his own account from a comment since deleted on twitter is acting "on a subject that is not in my strict field of competence."

> Twitter
> https://twitter.com › fmbreon › status
>
> Francois-Marie Bréon on Twitter: "Mais à la base, il y avait ...
>
> 3 days ago — (supprimé depuis) **qui** affirmait qu'il y avait plusieurs centaines ... sur un **sujet qui ne relève pas** de **mon domaine** de **compétence strict**.

Dr. Bréon's area of expertise appears to be as a scientist specializing in climate change and measuring CO_2 emissions, and he has not written a scientific publication on pesticides or pesticide poisonings that we could find; instead he has engaged in public commentary on pesticides on twitter. The Editor assumes that this reader's critique has escaped the attention of several reviewers during the review process. The Editor further mentioned a letter to the editor, Dunn et al 2021, published by 3 employees of the global pesticide industry. The authors replied to this letter in the journal.

We know of the desire of the pesticide industry to downplay the incidence of acute unintentional pesticide poisoning, but that is not an acceptable reason for a reputable journal to retract a paper. We found only one study carried out by the pesticide industry on acute unintentional pesticide poisoning – that of Tomenson & Mathews (2009) which we used in our estimate. The annual prevalence reported in their paper was in line with or above that reported in other studies.

4 Rebuttal in general

The editor of BMC Public Health is obviously not aware of the overall structure of our article. The paper consists of 3 parts:

1. a systematic review of the literature, carried out and reported by PRISMA standards,
2. an analysis of data from WHO cause-of-death database for fatal poisonings,
3. a synopsis of surveys on non-fatal poisonings.

We know of no critique concerning the first two parts, still a retraction of the paper would affect these parts and suppress important results based on scientifically sound methods. We furthermore have shown that the mentioned critique to part 3 is unfounded. In the best case, this discussion should be open to the scientific community—an important exchange which would be suppressed by a retraction.

We urge BMC Public Health to stop immediately all steps leading to a retraction of our article. If the entire Editorial Board wishes to review the critique of our paper and our responses to that critique, we would be willing to participate. Meanwhile, an apology would be welcomed. The precipitate proposal to retract a paper that has been in the public domain for more than 2 years on the basis of a single reader with inadequate understanding of the research, not only wrongly undermines the integrity of the authors but also risks damaging the otherwise good reputation of the journal itself.

Studies like ours, making use of the best available data, are standard practice in an effort to generate information that may allow for the appropriate directing of resources in the interest of public health and harm prevention. In global health, acting on the precautionary principle in order to save lives means that waiting for perfect estimates is not ethical, nor is it feasible. Withdrawing the paper is likely to do more harm than good, which is against the ethos of global health. Given the apparent conflict of interest of the reader, the letter to the editor by Dunn et al., and that the paper was so rigorously peer reviewed-- a retraction by the journal undermines the integrity of the scientific process.

04.05.2023 Wolfgang Bödeker, Meriel Watts, Peter Clausing, Emily Marquez