IMPRESS: Improving exposure assessment methodologies for epidemiological studies on pesticides

Meeting with ECPA
12th December 2018
IOM, Edinburgh, UK

Agenda
Remit of meeting as per Project Governance, Section F.

Time	Item
10.00-10.30	*Arrivals / coffee*
10.30-12.00	*Brief overview of 2018 activities*
	WP1: Review of EA methods (15 min)
	Literature review results
	WP2 and WP3 progress (10 to 15 min per project)
	PIPAH
	Historical
	Malaysia
	SHAW
	Ethiopia
12.00-12.30	*Project time scales / invoicing schedule*
12.30-13.00	*Advisory Board feedback*
13.00-13.30	*Lunch*
13.30-14.30	*Discussion*
14.30-14.45	*Next steps / AOB*
14.45-15.00	*Closing remarks - farewell*

Notes:

- *Times are allocated as way of indication and flexibility to accommodate discussions should be expected*
- WP4 – analytical plan to be presented at next meeting.
- Hans Kromhout leaving at 11.30 am

Attendees: Karen Galea (KG) (IOM), Ioannis Basinas (IB) (IOM), Andy Povey (AP) (UoM), Kate Jones (KJ) (HSL), Hans Kromhout (HK) (IRAS) (till 11.30am), Aaron Blair (AB) (Advisory Board Chair), Stéphanie Nadzialek (SN) (ECPA), Alistair Morriss (AM) (representing ECPA), Phil Botham (PB) (representing ECPA), Carol Burns (CB) (representing ECPA)

Apologises: Anne-Helen Harding (HSL), Roel Vermeulen (IRAS), John Cherrie (IOM), Martie van Tongeren (UoM)

Meeting Chair: Aaron Blair (AB)

Minutes: Karen Galea (KG)

Presentation shown during the meeting is provided separately

Agenda update

KG advised that the agenda had been amended since the version circulated so that 'invoicing' was discussed alongside 'timescales'. She also advised that HK needed to depart early and that discussions would be prioritised to cover Work Package (WP) 1 and updates on the Ethiopia cohort.

1. Brief overview of 2018 activities

KG presented this overview.

Questions raised were as follows:

- Who are the Advisory Board (AdB) members? The IMPRESS project website was shown which lists the AdB members, their completed conflict of interest forms, as well as copies of the AdB independent report and meeting minutes.
- Do we track usage of website? Advised that this is not done but was considered that it should be possible via Google Analytics. Action: KG to find out if usage can be tracked and if so, number of hits.
- Have we had much interest in project from stakeholders? Yes, approached by several people to provide input to their work and explore collaborations but so far have not actively moved this forward as concentrating efforts on the core IMPRESS study.
- What is the scope of the registry where the project has been registered? It was highlighted that there are currently just under 4000 registered studies, despite the resource appearing to be fairly new. It was also apparent that new studies were being registered on an almost daily basis. Further details provided following meeting are as follows: It allows registration of a wide range of study types and claims to be more comprehensive than any other registries. It also conforms with WHO requirements, International reporting guidelines, is compliant with the EU-U.S. Privacy Shield Framework and EU General Data Protection Regulation (GDPR)

2. WP1: Review of EA methods

HK presented to WP1 review. Key points highlighted included:

- The review has focussed on publications, not studies e.g. Agricultural Health Study has a lot of publications associated with it.
- Focus was on occupational, not environmental, studies.
- Review will be a valuable resource which will be used in the other WPs.
- For WP1 the methods used over the last 25 years were reviewed, their quality will be considered more in depth in WP4.
- It presents an opportunity for additional publications to be drafted (time and resources permitting).
- Overall, the type of exposure assessment methods being used has not changed over time.
- Differences in the types of methods used by type of epidemiological study were apparent.

Further work that HK highlighted as currently underway was as follows:

- Review of study locations (e.g. do results differ in Low-Middle Income Countries) following feedback received at the X2018 conference.
- Investigate combinations between methods to obtain a sense of what was being used in studies where more than one method was employed (which would lend itself to an offshoot paper on how well these perform to instances when only one method is used).
- Potentially look at results in relation to research sponsor.

Questions raised were as follows:

- GIS? Mainly used in environmental studies so not included in the reviewed articles.
- Is the absolute number of studies going up? Get a sense that this is the case (KH noted subsequently that it is double in the last lustrum compared to first.
- Double review has so far only been on a certain % of articles – is this considered enough? Ideally one would independently double review all papers but not possible due to time and resources. The reliability exercise performed showed that paper misclassification is likely low. Using this we will try to be as convincing as possible when drafting the manuscript and we will await feedback from journal reviewers.
- Did the team use machine-reading? No did not do this, review was undertake using typical standard methods.
- Has there been a move from blood (long-term exposure) to urine sampling (short-term) over time? Not sure.
- Have the team looked at study size (older studies may be smaller; use of methods may differ by size)? Some of that information is available and looking at cross tabulating, one drives the other and inter-related.
- Use of methods such as linear regression to investigate trends? The work has been descriptive, looking at absolute numbers and fractions and to change this to a more formal analysis will slow down WP1. This could be a follow up study for WP4.
- So paper will be a factual description of the use of exposure assessment methods, with no judgement being made on them at this time? Yes, this is correct for the WP1 work. The paper will not present the outcome of what exposure assessment method is best for which type of study
- In the proposal some other data categories were suggested would be extracted – what has happened to these? These are considered within other categories that have been included.

In summary, it was highlighted that the overall remit of the project is to move the discipline forward. This works highlights that nearly 40% of published research in the study period involves self-reported exposure, which has well recognised limitations, either as the sole methodology applied or in addition to other hybrid or surrogate methods of assessment. It was considered that combining methods may lead to better classification, also that a series of further papers will emerge, in due course, from this WP.

3. WP2 and WP3 progress

Progress with respect to each of the cohorts was discussed in turn.

Ethiopia presented by HK

Key points highlighted included:

- Samuel Fuhrimann recruited to undertake fieldwork. Very experienced with this type of work.
- Political situation in Ethiopia has changed and it's unstable. Large turnover in workers, therefore hard to re-interview the same workers that were studied earlier (which will impact WP2).
- In most occasions, applicators will not know what they are applying. With respect to the biomonitoring, HK advised that it will not be possible to only go when they are applying particular pesticides. The strategy, at least for small Ethiopia farms, will be to collect samples when they are spraying /re-entry, record what was being applied and then make a decision on what to analyse at a later date once we see what we have.

Questions raised were as follows:

- What products are they using - registered or counter-fit? The list of products used is not the same as in the UK. The Government of Ethiopia has funded a project to set up a registration board for pesticides (https://www.wur.nl/en/show/Pesticide-Risk-Reduction-Programme-in-Ethiopia-PRRP.htm). In many instances, the applicators will not know what they are applying.
- When will it start (if proceeds)? Can start as soon as have necessary permissions in place as spraying occurs all year round (no spray season as such).
- Decision point for continuing with Ethiopia is around March, what is the backup plan if it falls through? Samuel is also working on a Swiss government funded study in Uganda. Whilst this would present fewer challenges, they are typically small-scale farmers and there are no large green houses. Would not have the continual spraying such as that observed in Ethiopia and there are no health analysis available at present, which will affect WP4 contributions.

HK then left meeting

PIPAH / PUHS presented by KJ

Key points highlighted

- Ethical approval for WP2 in place, for WP3 this will soon be requested. Approval for linkage between PIPAH / PUHS studies also in place.
- Sending out packs in Feb / March to avoid PIPAH cohort mailing which happens in Jan 2019
- Two populations: PIPAH – 2016 follow up (769 participants); PUHS – 2004 / 2006 – questions about these years will be followed up (328 participants)
- Process will be managed by external company (who also managed PIPAH cohort).

Historical BM presented by KJ

Key points highlighted

- 115 participants identified as having biomonitoring data relating to pesticide exposure in HSL database
- Not previously had a questionnaire, team need to generate a questionnaire.
- Will be applying to HSL research ethics committee for approval early 2019.
- Process will be managed by HSL staff.

Malaysia study presented by AP

Key points highlighted

- Study started early due to PhD student activities
- Sample collection nearly complete, will stop end Jan 2019.
- Analysis of pilot study samples ongoing and results should be available to the team shortly.
- All small-scale farmers.
- Sample collection occurred regardless of the type of pesticide being applied. Have established analytical methods for samples from at least 30 participants. Highlighted that for samples provided by 12 participants may not have established methods that can be used

Questions raised were as follows (these were not all specifically related to the Malaysia study):

- Sample storage, stability studies and results from these? Once samples collected they are stored frozen and transferred on dry ice. HSL undertaking lab based stability studies for short term high temperatures (worst-case) and also at room temperature. Pilot study samples may assist with this.
- Information on storage stability under frozen conditions? Yes have this for some pesticides from previous studies, where samples have been stored for more than one year frozen. If including new analytes then further studies would need to be undertaken.
- Parent compound or metabolite? Most of the methods will be based on metabolites although glyphosate is the exception here - the parent compound will be analysed. There may be an issue if new actives are included where metabolites might not be present.
- By focussing on metabolites, could we be underestimating exposure? Study is trying to focus analysis on the agents that we have good knowledge and understanding and trying to minimise inclusion of new actives because of the uncertainties that they present.
- When are urine samples collected? Pre and post to working activities – i.e. application/spray or re-entry.
- Where are they collecting the samples in Malaysia – is it at the home or in the field? Don't know. Action: AP to obtain information on this.
- How is the project team planning on including blanks? Empty sealed bottles will be distributed and participants asked to fill with water. This will be provided at the same time as when collect urine samples and will give an indication of potential cross-contamination.
- Inclusion of spikes? It was considered that asking people in the field to prepare spikes was adding an unnecessary layer of complexity and that we would not be learning anything further to the knowledge gained in the lab spike studies. A range of spike and stability tests will be done at HSL and will include a range of temperatures and conditions.
- What information is being collected from the Malaysian applicators at this time? They are being asked to provide a diary and they are monitored through video recording for a 10 min period during actual work.
- How can we determine exposure related to the application period? Will be collecting pre-shift as well as post-shift samples. The post-pre difference in concentration levels is the result of the exposure to the pesticide in question.
- Is the Malaysia study looking at health of the participants? Health information is being collected but this is not specifically part of the IMPRESS study
- Are the Malaysia pilot study results high? The pilot results not include high levels, which raises no concern for presence of an immediate hazard due to exposure.
- What will be the team's data entry checks and what are considered acceptable error rate? In revised protocol, 10% of data entries will be checked and providing less than 5% errors this will be judged acceptable. If above this % then other measures will be initiated, e.g. increase number of duplicate checks. It was highlighted that the team are considering the use of methods for restrictive data entry such as Visual Basics, which can help facilitate reduced errors and automatic checks.
- Have the ethics committees raised any issues about observation of participants carrying out dangerous practices? No, ethics committees have not raised any issues about this. ECPA expressly highlighted that, as part of their product stewardship practices, they cannot condone bad practice with respect to pesticide usage. The team highlighted that the protocol states that in the event of bad practice being observed that this would be raised with the participant at the time and any reputational damage would be on them, rather than ECPA.
- Will there be feedback / educational component within the cohort studies? Yes, this will be included in Ethiopia however nothing is explicitly planned in Malaysia. Action: AP to consider inclusion of appropriate participant feedback at the end of the study (field collection is due to stop end Jan 2019)

SHAW study presented by AP

Key points highlighted

- 234 people available for IMPRESS
- Need to redesign questionnaire as can't use prompts. Will send info out before telephone interview and try, so far as is reasonably practicable, to replicate what was done in-person, over the phone.

Questions raised were as follows

- How are we controlling for age related memory loss? There were standard cognitive evaluation questions, which were used in the previous study and so will be included here too.

4. Project time scales / invoicing schedule

Prior to the meeting a memo requesting a one-year no cost extension to the project was issued to ECPA, along with proposed new timelines and invoicing schedule. A summary of these documents was presented during the meeting.

Questions / points raised were as follows:

- If we had funds available, is there a benefit of including the Uganda cohort in the study as well? Need to discuss with HK however no funds currently available to include this in addition to Ethiopia (project team prefer to continue with Ethiopia and have Uganda as the back-up).
- Would be helpful to document the areas / aspects of the project that are out with the project team's control. KG suggested that the team put together a risk registry, which will detail the various project risk, mitigating measures etc.
- It was highlighted that the project team may wish to rethink the invoicing schedule with respect to the publications. They are presented as 'overall' papers linked to various work packages when it is likely (and very much intended) that multiple papers will emerge from each.

It was agreed by the ECPA representatives that a one-year no cost extension would be granted.
Action: KG / IB to send Peter Day / SN the final update timelines and invoicing schedule.

5. Advisory Board feedback

AB provided feedback from the Advisory Board, following their 2nd Meeting held on 11th December 2019, with key points being as follows:

- Four Advisory Board members, have met in-person twice and provide feedback and comment to the project team.
- They like the project and recognise that it is a complex study, which has the potential to proportionally increase understanding on how we do exposure assessment in such studies.
- Progress is, and will be, hard but it has the potential to generate a lot of useful info.
- Comparing different methods in different areas will, in some way, tell you how different components will work, helping fill the knowledge gaps.

Questions raised were as follows:

- How many times do the Advisory Board meet? In person once a year, comment on documents as necessary throughout the year.
- Is once a year enough? AB considered yes, as the Advisory Board are reviewing materials between times. It was highlighted that there is flexibility and that ad hoc meetings could be requested if considered necessary to do so.

KG raised that one of the Advisory Board members had asked why ECPA were interested in funding this project and it would be helpful to have their responses in relation to this. ECPA representatives providing the following views:

- Shared aim to go as far as can to make studies robust in way in which causation is established.
- ECPA received feedback from their advisory board that there was a need to establish work focussed on the veracity of exposure assessment in epidemiological studies. This need was placed as a request for proposals in the public domain.
- Good science is good business. Better exposure assessment leads to better studies, which leads to better business, with everyone winning.
- Recognition that epidemiological studies will be used more and more from a regulatory perspective and there are limitations associated with them. Only thing industry can do is improve science – the ECPA representatives involved are scientists, not concerned with any political aspects.
- Although the efforts are from Europe it does have an International perspective. Considered that it would be good for the project team to look at Crop Life International and reach out to those involved.

6. Discussion

Two items were formally tabled for discussion, these being:

a. Design components for WP3
b. Further outreach / dissemination

a. Design components for WP3

There was discussion about the comments raised by ECPA on the WP3 protocol and how ECPA will receive feedback on these.

KG stated that this had been formally discussed at the Advisory Board meeting on the 11th December. The project team had responded to each of the comments and forwarded their responses (and updated protocol) to the Advisory Board who were satisfied with this. Due to project team disagreement on the provision of direct feedback in response to ECPA's comments, and to ensure complete transparency, it was agreed during the Advisory Board meeting that the updated protocol and response to comments would be made publically available on the website and that ECPA would receive these documents via this channel.

ECPA representatives clearly expressed that they do not wish to impact on the science but considered it important that they have the opportunity to raise any suggestions for improvement / points of concern and for it to be clear that these have been considered by the project team.

It was discussed what the procedure would be if there was a clear disagreement between the project team and ECPA representatives with respect to the proposed science to be used in the IMPRESS project. It was considered that this situation would be unlikely however if that were the

case then the Advisory Board would more formally step in and review the respective view points and arguments put forward. It was considered that a meeting with all three parties may be necessary in this situation.

There was concern raised about the Ethiopia study, the difficulties it presents, that there are several groups being investigated (small farmers, green houses, re-entry) and that this may be spreading the project resources too thinly. It was also raised that these different exposure groups (e.g. applicators in greenhouses vs small-scale farmers) should not be combined into a single group, must be kept separate.

b. Further outreach

Points raised / discussed were as follows:

- Merit in increasing accessibility to project information (design, results, dissemination) beyond Europe and North America, e.g. developing countries, need to think about how people can find out information relating to it – e.g. websites, other communication etc.
- Raised that there is a need to disseminate to epidemiology community as to be mostly exposure related forum. Highlighted has symposium at EPICOH last year and will try to hold another symposium session at EPICOH at the end of the project. Think about 'using' the teams epidemiologists more to assist with dissemination to this community.
- KG highlighted that an article in literature such as 'Outlooks in Pest Management' may be useful in bringing the project to another audience.
- Consider use of Tweets, Linkedin to spread the work and highlight various outreach projects.
- KG mentioned intention to present overview of presentation at ISES conference in 2019.

7. Next steps / AOB

Next steps slides shown

AOB – date and time for next IMPRESS/ECPA teleconference. This is scheduled for 21st March, 1.30-3.30pm UK time. (Note that due to calendar conflicts the date and time will now need to be changed).

Meeting closed.

Addendum

The text below was provided by ECPA, 18th January 2019, following receipt of the draft minutes from the meeting. The text is included here for completeness.

Dear Karen,

Thank you for having drafted the minutes of our face-to-face meeting held in IOM, Edinburgh on Dec. 12th, 2018. We, as ECPA, reviewed the draft minutes and we would propose to include some comments addressed in the course of the presentations.

1. Data collected *versus* project proposal achievements

It was noticed that the current data collected does not appear to fully cover project expectations as described in the project proposal. So far, best example is WP1 where key indicators listed in the proposal were not reported in the data presented. Specifically, going back to review the funding source of each publication is outside the scope of this project:

WP1: Review the methods of exposure assessment used in occupational epidemiology
« This WP aims to prepare an inventory of methods and techniques that have been used for exposure assessment in epidemiological studies either community-based (case-control or cohort) studies or in studies among farmers, farm workers and other occupational exposed workers. ….Emphasis will be given to identify, extract and register the critical components of the used exposure assessment methods that are most commonly used in assigning exposure to individuals or groups of study subjects. The reliability and validity of these components will be evaluated in order to arrive at an overview where the limitations and possibilities for improvement will be reported. »

From our perspective, the project proposal, as initially planned and agreed amongst parties, was reaching a satisfying quality standard. Therefore, we would be displeased to meet only the overall concept of each single WP. A higher level of focus on these objectives will not result in unnecessary time and energy consumptions but instead guarantee to increase worldwide visibility (e.g. higher number of publications), acceptance (e.g. reduce room for negative feedback) and recognition (e.g. enroll future project/future financing support).

2. Technical quality and accuracy issues making us concerned not using best practices could jeopardize the fundamental objective of exposure assessment.

Some examples were addressed during the meeting. A selection from the WP3 objectives are listed below. As noted in the discussion the quality recommendations for biomonitoring of short-lived chemicals (BEES-c) as developed by LaKind et al (2014, 2015) and now part of US EPA recommendations should be incorporated into the data collection protocol.

Examples:

- **Field fortifications/spikes data**. As mentioned during the open discussion, field spikes and blanks within an exposure study is essential. Also, as suggested, providing field spikes taken in UK to reflect Malaysian conditions should undergo additional confirmation that the assumptions are valid.
- **Control samples**. For analytical recoveries, the usual approach is for a blank urine to be taken from volunteers in the field – i.e. not the applicators but others in the local vicinity that will be exposed to the same background levels as the applicators. . As mentioned above, taking control urine from UK volunteers will not give a meaningful field blank. From previous field study experience, it has already been observed elevated general population levels of pesticides in the field before, showing the importance of these samples.
- **Half-life data**. As raised during the discussion, the samples are "spot samples" and, therefore, we will not be able to know if the source of the measured exposure is from the application. From experience it often happens on a biomonitoring study and if we get one unexplained high concentration, this data may skew the overall result. Additional samples would provide more robust data to meet the WP and overall project objectives (i.e. back to the quality *versus* quantity discussion).

WP3: Assess the reliability and validity of individual-based exposure assessment methods
« The aim of this WP is to assess the reliability and validity of the most advanced individual-based exposure assessment methods available to date comprising of a semi-quantitative approach based an algorithm utilising existing information on exposure determinants such as mixing conditions, duration and frequency of application, application methods, maintenance or repair of mixing and application equipment and work practices. …We intent to examine the ability of the algorithms to predict exposure intensity during application and re-entry using the results of an extensive field monitoring study that will include the collection of biological samples from workers of a series of different farming systems. …Task 3.1. Urinary biomarkers will be selected based on extent of use within the study populations, validity of biomonitoring methods (availability, specificity, robustness, quality assurance) and knowledge of toxicokinetics parameters (see LaKind et al, 2014; 2015) and will follow our recommendations from a current EFSA study on this topic.»

3. Finally, we do understand your requirement for a transparent separation of the project governance as provided by the Advisory Board, from the input of the industry sponsor, and we will continue to fully respect this separation. However, we are concerned about the present way of working where our technical comments, such as those we have reiterated in point 2 above, are answered indirectly by posting your responses after discussion with the Advisory Board on the project website. As we said in the meeting, we would like you to consider a more direct response to these detailed scientific or technical questions (in our regular calls or face-to-face meetings) and, in situations where we are not able to agree, to then have the possibility of a three-way discussion between ourselves, the project team and the Board. Please be assured that, in suggesting this way of working, we are trying to seek a scientific consensus to facilitate the success of the project, especially as it undergoes external peer-review of the quality of the project data and conclusions. We would not attempt to influence or demand any changes to protocols or reports for political reasons.

If you feel that, in the light of our comments, we should have an ad hoc discussion with yourself and possibly the chair of the Advisory Board before our next planned phone call on March 21st, we would be more than willing to do this.

Kind regards,

Stephanie Nadzialek
Science & Technical Manager