IMPRESS: Improving exposure assessment methodologies for epidemiological studies on pesticides

2nd Project Advisory Board meeting
11th December 2018
IOM, Edinburgh, UK

Agenda

Time	**Item**
09.00-09.30	*Arrivals / coffee*
09.30-09.45	*Brief overview of 2018 activities*
09.45-10.15	*WP1 - Review of EA methods* Literature review results and how outputs will feed into later work packages *(15 min)* Discussion (*15 min*)
10.15-10.45	*Overview of general protocols* *WP2 - Recall of past PPP exposure and determinants (15 min)* *WP3 - Reliability and validity of individual-based EA methods* (*15 min*)
10.45-11.00	*Coffee*
11.00-12.00	*WP2 and WP3 progress (≤15 min per cohort)* PIPAH; Historical; Malaysia; SHAW; Ethiopia
12.00-13.00	*Discussion on WP2 and WP3*
13.00-13.30	*Lunch*
13.30-14.00	*Continue discussions on WP2 and WP3*
14.00-14.30	*WP4 - Comparing the performance of exposure assessment methods in existing epidemiological studies* Possibilities overview and discussion
14.30-14.45	*Review of project time scales*
14.45-15.15	*Advisory Board feedback*
15.15-15.30	*Coffee*
15.30-15.45	*Next steps / AOB*
15.45-16.15	*Time for AB to prepare note for client meeting*
16.15-	*Departure*

Note: Times are allocated as way of indication and some flexibility to accommodate discussions should be expected

Attendees: Karen Galea (KG) (IOM), Ioannis Basinas (IB) (IOM), Martie van Tongeren (MvT) (UoM), John Cherrie (JC) (IOM), Andy Povey (AP) (UoM), Kate Jones (KJ) (HSL), Samuel Fuhrimann (SaFu) (IRAS), Hans Kromhout (HK) (IRAS), Aaron Blair (AB) (Advisory Board), Mark Montforts (MM) (Advisory Board), Silvia Fustinoni (SF) (Advisory Board), Len Levy (LL) (Advisory Board)

Apologises: Anne-Helen Harding (HSL), Johan Ohlander (IRAS), Roel Vermeulen (IRAS)

Chair and minutes: Karen Galea (KG)

Copies of the slides presented at the meeting will be provided separately.

1. Brief overview of 2018 activities

Advisory Board asked whether project team require their input with respect to project extension discussions. This was considered unnecessary as European Crop Protection Association (ECPA) had been broadly receptive to the request when it was first raised in Sept 2018.

2. WP1 - Review of EA methods

HK presented the Work Package (WP) 1 review methods and results

Points highlighted

- Work presented at x2018 in September. Since then further Quality Control (QC) work has been undertaken. It was also suggested here that study location be included (Low to Middle Income countries vs. other countries) and this is still work in progress.
- Noted that there has been an increased in self-reported exposure - study location may play a role here. Increases in one thing may be linked to decreases in other, e.g. Job title and expert assignment usage has decreased over the study period but the use of Job Exposure Matrix (JEM) has on the contrary increased.
- Blood samples – mostly cholinesterase inhibition.
- Big differences in outcome and Exposure Assessment Method (EAM) usage.
- Methods only mentioned in full text might have been missed in a few cases.
- Draft paper has looked at results in different ways although the overall picture is that there is not a large change over time with respect to the type of methods being applied.

Comments / questions raised by Advisory Board:

- What proportion of articles reporting indirect EAM also had direct methods? Not known at this time but will have this information in the database and will look into this.
- Has there been a change in the type of studies being run over time? Don't think so and nothing obvious has emerged but will check.
- Should the quality of the papers be scored in some way? This would require a lot of additional work which is considered unnecessary as the work is not about the quality of the studies, but reviewing which exposure assessment methods have been used.
- How will results feed into the work? Results provide with a landscape we should look at combining different methods and have fewer misclassified individuals Use of more objective information would be better.
- What are the genetic outcomes? Biomarkers of effect, DNA adducts (grouped together)
- Does a more comprehensive QC exercise need to be undertaken? Think not and will proceed with what has been done to date and see if journal reviewers request anything further. Advisory Board was also supportive to the opinion that a double review of all articles would be too much additional work and for not enough gain.

Next steps for review work

- Action: HK will circulate draft manuscript to Advisory Board before the end of 2018. The intended journal for submission is OEM

3. Overview of general protocols

3a WP2 – presented by KJ

Highlighted that ethical approval has been obtained to progress with Prospective Investigation of Pesticide Applicators' Health (PIPAH) and Pesticide Users Health Study (PUHS) cohorts. KJ advised that the team has to wait until Feb / March 2019 before they can approach participants as the PIPAH study are issuing a questionnaire in January. It was highlighted that it is unsure whether the same people are being approached in Jan for the PIPAH study and Feb/ March for the IMPRESS study as we are following up those who responded in 2016 (~800 people).

Comments / questions raised by Advisory Board:

- Wish to interview people again, we know that there is bias so what is the value of the information? Value when evaluating difference from immediacy.
- Does the team have a hypothesis that we are testing? Have we looked at literature on recall bias? It depends on what you are asking. Lot of literature on job histories, that is relative easy, gets more difficult with differences in years and types of info being requested. It was highlighted that whilst there may be a lot of literature relating to recall for exposures in general there is little relating to exposure to pesticides.
- Do we state in the participant information leaflet that we are testing recall? No, project team had a discussion about this and removed wording which explicitly stated this.
- Do PIPAH participants keep application records and use these to help complete the questionnaire? Keeping records is the law but experience of PIPAH cohort is that participants don't use these records to complete the questionnaire. The project team acknowledges that participants could use them but will not ask if they have done so.
- Is there some way of finding out if they go back to records to complete? Not at the same time as asking them to complete the questionnaire but potential to ask at a later date.
- How are questions asked? Study of Health in Agricultural Work (SHAW) and PIPAH have a mixture of different question types – tick and free text – but always format is the same as asked previously.
- Are we selecting people? Team is sending invitation to all in relevant cohort (e.g. those who completed 2016 questionnaire for PIPAH).
- Response rate by demographic characteristics? Action: KJ to ask if PIPAH study have any information about response rate vs. age, socio-economic outcomes etc.

3b WP3 – presented by IB

Advisory Board have seen a copy of the protocol (twice). ECPA was also given the opportunity to comment on the protocol and identified some points that they would like the project team to consider. The project team have considered the comments, updated the protocol and sent these documents to the Advisory Board for review, who were happy with the responses and updates made

Following discussion with the Advisory Board, it was agreed that the updated WP3 protocol and project teams response to ECPAs comments would be added as appendices to the 2nd Advisory Board meeting minutes, which will be made available on the IMPRESS project website. These documents are publically available to anyone for reference and review, including ECPA.

There was more detailed discussion on some of the points that ECPA had raised, which led onto other discussions concerning the protocol, e.g.

- Spikes and blanks – should they be included and how? It was decided to include field blanks involving participants being provided with empty vials and asked to fill with tap water. For spikes HSL will be undertaking lab spikes as consider no benefit including field spikes. Spikes will include different storage stabilities.
- In the current version of the protocol, five different pesticides are listed because of methods /knowledge available on these. There was a lot of discussion about whether this should be increased and that in Ethiopia, Malaysia other pesticides may be used and it is not possible to ask participants to only provide samples relating to selected pesticides. It was decided that for the Ethiopia and Malaysia fieldwork where other pesticides are being used and where it is not possible to collect samples related to specific pesticides that other pesticides might be analysed (dependent on what pesticide was being used during the urine sample collection, availability of suitable analytical methods and numbers of samples collected).
- Advisory Board highlighted that it is good to have some preferred pesticides but that we may have to sample what we get. A judgement call will be needed on what to actually analyse for, when methods, QC, Quality Assurance (QA) costs of multiple active ingredients are considered.
- What are the aims of WP3? Really need to have several measurements for same pesticide in order for this WP to work. Make sense to have large groups of samples for the same pesticide.

There was a lot of discussion regarding the algorithms to be used in WP3 (and how they will be applied)and it was agreed that this discussion would continue following the meeting. Some key points mentioned are summarised below:

- In the process of developing country/study specific algorithms for where they do not already exists e.g. PIPAH, Malaysia studies
- Taking an established algorithm, applying it in another situation and observing that it does not perform well is useful. How well it works in a new dataset is a good step forward.
- Need to consider what contrast in exposure intensity these algorithms are able to predict.
- Highlighted that biomonitoring itself is not predictable and therefore it was questioned as to whether it should be considered as being a gold standard.
- Apply all algorithms to each cohort and see what the difference is? In process of adapting algorithms for UK and Malaysia situation. See how they work and then also looking to see if can optimise them in a generic form. Team are in the initial steps.
- It was raised by HK that the algorithms and weighing factors have to be ready before the field work starts. It was mentioned that Malaysia field work is nearly finished.
- If using biomonitoring to validate model – what is low, medium, high for biomonitoring methods? In order to compare we need an external scale.
  AB summarised the work is being two parts – Firstly supply the algorithms and apply to the population and secondly, how they can be applied in populations external to the IMPRESS project. AB suggested that the team apply all three available algorithms to all studies and see if the performance of components of algorithms differ in some way. AB suggested a possible sub activity to consider, this being a sensitivity analysis to see what works and does not work with respect to the algorithms.

4. WP2 and WP3 cohort progress

PIPAH – KJ presented the slides

KJ advised that they are waiting for a quotation for sending out packs, uploading etc from the company who deals with the administration of the PIPAH study. Historical cohort have biomonitoring results but have not received a questionnaire previously. Participants in this will be issued with a common set of question and materials set to HSLs internal ethical committee.

The Advisory Board asked what response rate is anticipated. KJ advised that PIPAH typically achieves a 25% response rate and for the historic cohort we have no way of knowing. SF asked what the response rate is expected to be for the biomonitoring element of the work. KJ advised that we are unsure but that it is expected to be lower than 25%. (Although not discussed during the meeting KJ has provided the following information - A previous postal recruitment and sampling biomonitoring campaign had a response rate of 7.5% in the general population (Bevan et al, 2012). The project team expects an engaged population such as the PIPAH cohort to potentially be in excess of this.

Malaysia study – AP presented the slides

AP highlighted that these are all small-scale farmers. LL asked whether participants live on the farm. AP replied that this information will be available but at present he was unable to provide with the relevant info. SF considered that it would be interesting to collect general population samples. AP advised that this is outside the scope of the study but the study has collected pre-pesticide application urine samples. The PhD student will finish all the field work in Jan 2019 and so the project will have all the available samples by that point. Participants are providing a urine sample when they apply a pesticide, irrespective of what it is. Videos are being collected of the tasks undertaken. Spray and urine collection times are recorded.

SHAW – AP presented the slides

SF asked what is the time period between Phase 1 and 2 (which was one year) and how many people will be approached to participate (which is the maximum of 234). LL asked whether people kept spray records back to that time and it was considered that no, they did not. The Advisory Board highlighted that there may be issues with interviewing elderly people – how good is their memory in general, never mind their ability to recall pesticide related work?

AP mentioned that the plan is to recruit someone full time to assist with the recruitment and interviews. To evaluate cognition status standard cognitive evaluation questions, which were used in the previous study, will be included in this evaluation too.

Ethiopia – SaFu (IRAS) presented slides

Discussions are still ongoing, with a 'go- no go' decision to be taken early summer at the very latest. Mentioned that whilst three farming systems were included in the previous study, this might not be possible for the follow up. A potential alternative study was discussed but due to potential sensitivities, this is not elaborated in these minutes.

5. WP4 - Comparing the performance of exposure assessment methods in existing epidemiological studies

HK presented the WP4 slides. This WP will start in about a year from now. During 2019 the analysis plan will be worked up for the three components of WP4 and this will be circulated to the Advisory Board for comment.

AP highlighted that UoM have unpublished health data from Thai study, although it is available in the PhD thesis. He also highlighted that the Malaysia health data will be available later. Action: AP to provide HK with details of health data available from these studies.

6. Review of project time scales

KG discussed the relevant slides.

LL asked whether a year extension is sufficient. The project team considered that yes; this was, providing that the team keep control of the aspects of the project within their control. The team highlighted that they were committed to achieving the new timelines and would communicate at the earliest opportunity if it appears that any further slippage is occurring.

7. Advisory Board feedback

MM asked whether the project team has a clear understanding of why the sponsor wants the study carried out, highlighting that he had asked this question at the previous meeting. Advised that there was a need to be clear about this and how it is advancing science. LL considered that the project was funded for good reason and that it was considered that they wish to have better designed studies done in the future.

LL and SF highlighted some concerns that there was still a need for the project team to resolve some key practical and scientific issues, which they hoped would have already been addressed.

SF highlighted that she felt there was a need to ensure that significant numbers of samples were collected for each pesticide – too many active ingredients will result in too few data points for each. KJ highlighted that we will only be analysing active ingredients with sufficient sample numbers.

AB mentioned that he is not concerned about slippage in project timescales. The project is data pooling on a difficult scale. He raised the point of whether project spending is fast in comparison to the amount of work done (and still to be done). It was considered that whatever the projects findings, these will be important. It was considered that the role of the Advisory Board is to guide the investigators, where necessary, to ensure that the 'right science' is used to address the study aims and objectives.

8. Next steps / AOB

No additional points raised here as all had been discussed earlier.

9. Meeting closed and time given for Advisory Board to prepare their Advisory Board note