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COMMENTARY

Reflections on the process of using systematic review techniques to evaluate the literature regarding the neurotoxicity of low level exposure to organophosphate pesticides

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Abstract

We undertook a systematic review (incorporating meta-analysis) of the literature concerning the neurotoxicity of cumulative low level occupational exposure to organophosphate pesticides, which was published online by the journal Critical Reviews in Toxicology in 2012. As far as we are aware, we were the first research team to attempt quantitative evaluation of study findings on this topic, using meta-analysis. We wish to encourage others to apply systematic review techniques in chemical risk assessment to reduce bias, increase transparency and better inform public policy. We thought it would be useful to share our experience of undertaking a systematic review in the hope of dispelling misconceptions about the complexity, time and resource issues involved along with the view that meta-analysis is meaningless when studies are not homogeneous. In this commentary paper we reflect on aspects of the process which were relatively straightforward; aspects which were more challenging; the advantages of using systematic review techniques; and the advantages and limitations of using statistical techniques such as meta-analysis in this context.

Key words: Systematic Review, Meta-analysis, organophosphates, low-level exposure, neurobehavioural function.

1.1 Introduction

Organophosphate pesticides (OPs) are the most widely used group of pesticides in the world and concern about their effects on human health have been growing as they are increasingly used for a variety of agricultural, industrial and domestic purposes (WHO, 1990). The neurotoxic effects of acute poisoning are well established, but research concerning the neurotoxicity of cumulative low level exposure has produced inconsistent results (see reviews by Alavanja et al, 2004; COT Report, 1999 and COT Statement, 2014; Freire & Koifman, 2013; Kamel & Hoppin, 2004; Mackenzie Ross et al, 2013; Ontario College of Family Practitioners, 2012; Takahashi & Hashizume, 2015). Narrative reviews of the literature published over the last three decades, have failed to resolve the debate so in 2010 we employed systematic methods (including meta-analysis) to see if we could integrate the studies in a more systematic way to give an answer to the question of whether low level occupational exposure to OPs is associated with deficits in neurobehavioural function.

Systematic review methodology aims to identify and summarise the findings of relevant studies using a strict protocol which minimises bias and provides a more reliable appraisal of research evidence (Centre for Reviews and Dissemination, 2009). Meta-analysis is a useful method of summarising and quantifying the results from different studies and provides a more reliable estimate of whether an association exists between specified variables than one study alone (Lipsey & Wilson, 2001). As far as we are aware, we were the first research team to attempt quantitative evaluation of study findings using meta-analysis to evaluate the literature regarding the neurotoxicity of low level occupational exposure to OPs. In 2012 our findings were reported online by the journal *Critical Reviews in Toxicology* and published in January 2013 (Mackenzie Ross et al, 2013). In summary, we reviewed literature published between 1960 and 2012, and assimilated data from 14 studies incorporating more than 1600 participants, using meta-analysis. We found the majority of well-designed studies reported a significant relationship between low level exposure to OPs and impaired neurobehavioural function which is small to moderate in magnitude and concerned primarily with cognitive functions such as psychomotor speed, memory, visuo-spatial and executive function. In addition we identified a number of unresolved issues in the literature requiring further investigation.

In November 2014, the lead author attended an ‘International Expert Workshop’ regarding the implementation of systematic review techniques in chemical risk assessment, in which the opportunity and challenges of implementing systematic review techniques in this arena were discussed. Many experts involved in reviewing evidence in order to inform Government policy, expressed reservations about using systematic review methodology in toxicology due to uncertainty as to where systematic review fits into the multi-faceted process of chemical risk assessment, the cost effectiveness of systematic reviews, resource issues and lack of training in systematic review methodology.

We found systematic review techniques useful in evaluating the literature regarding the neurotoxicity of OPs and hope to encourage others to apply systematic review techniques in chemical risk assessment / risk characterisation to reduce bias, increase transparency and better inform public policy. We thought it would be useful to share our experience of undertaking a systematic review with readers and so in this commentary we reflect on aspects of the process which were relatively straightforward; aspects which were more difficult and challenging; the advantages of using systematic review techniques in terms of what we learnt about the literature by systematically appraising it; the advantages and limitations of using statistical techniques such as meta-analysis in this context; and unresolved issues in the literature which need addressing by future research.

According to organisations like the Cochrane Collaboration and the Centre for Reviews and Dissemination, a systematic review should focus on a well-defined question, undertake a comprehensive search of the literature, have clear criteria for the selection/rejection of studies, make explicit criteria for assessing the quality of studies, clearly describe the extraction and synthesis of data and explore the similarities/differences between studies and the possible reasons for variation in study findings. Ideally the review team should have expertise in systematic review techniques, research methods and statistical analysis, in addition to the topic under review (CRD, 2009).

2.1 Straightforward aspects of the process

Our research team has considerable expertise in neuropsychology, clinical psychology, toxicology, systematic review techniques, research methods and statistical analysis. Indeed, all of us have been involved in teaching advanced research methods and statistical analysis at postgraduate level and Professor McManus has completed a number of systematic reviews incorporating meta-analysis over the last decade (Bourassa et al, 1996; McManus et al, 2013; Van Horn et al, 1992; Woolf et al, 2011). The research question we chose to focus on was *the effects of cumulative low level exposure to OPs on neurobehavioural function in occupational settings,* a topic which has been debated for decades. Inclusion and exclusion criteria and criteria for assessing the quality of studies were relatively easy to identify and agree on given our knowledge of the literature. The process of undertaking a comprehensive literature search was also relatively straightforward and in terms of time and resources, no different from the amount of time we would have spent locating articles for a less formal narrative review. Another aspect which was not particularly onerous was the statistical analysis of the data which yielded a considerable amount of useful information, not least because most studies provided multiple effect sizes from different measures. However, data extraction and synthesis were more challenging and will be discussed later on in this paper. As far as software are concerned, we used the Mix software for Excel, but if repeating the study would now use the *metafor* package in R, which is very versatile (Viechtbauer, 2010).

2.1.1. What did we learn by systematically appraising the literature?

The systematic appraisal of study quality was very revealing. Our criteria stipulated that study designs must adequately address the question of whether cumulative low level exposure to OPs has adverse effects on neurobehavioural function; that researchers provide adequate information about exposure history, particularly whether participants show evidence of prior acute poisoning; that studies use reliable, valid, objective outcome measures (not subjective symptom questionnaires) and suitably matched comparison groups.

Out of a total of 644 potentially relevant articles which were retrieved from database searches, only 45 met our inclusion criteria. Of particular interest was the fact that several studies appeared, from an initial review of titles and abstracts, to be concerned with the effects of cumulative low level exposure, but involved study designs that did not adequately address this issue. For example, several studies looked at the impact of low level exposure by examining participants before and after a single season or episode of exposure but failed to provide information regarding exposure history prior to the study time frame (Albers et al, 2004; Bazylewicz-Walczak, Majczakowa & Szymczak, 1999; Daniell et al, 1992; Maizlish, Schenker, Weisskopf, Seiber & Samuels, 1987; Misra, Prasad & Pandy, 1994; Rothlien et al, 2006; Salvi et al, 2003). Others studies used proxy measures of exposure such as occupational group or area of residency so causality and dose-response relationships could not be determined (Beseler et al 2006; Browne et al 2006; Cole et al 1997; Kamel et al 2003; Parron et al, 1996;

Rohlman et al 2007). Seven studies failed to provide detailed information about exposure history (Bosma et al, 2000; Dimich-Ward et al, 1996; Kilburn, 1999; Korsak & Sato, 1977; Kurlycheck & Morrow, 1989; Richter et al, 1992; Starks et al, 2012); and eight used subjective symptom questionnaires (Ahmed & Davies, 1997; Ciesielski et al, 1994; Cox et al, 2005; Davies et al, 1999, Kamel et al, 2007, Ohayo-Mitoko et al, 2000; Smit et al, 2003; Solomon et al, 2007). Previous reviews of the literature regarding the neurotoxicity of low level exposure to OPs have included these studies without discussing the fact that they do not adequately address the issue of whether cumulative low level exposure to OPs is associated with neurobehavioural impairment (COT, 1999 and 2014).

Overall, the literature we reviewed encompassed considerable variation in study methodology leaving us with a sample of only 16 relevant studies, which adequately addressed the issue of whether long-term low level exposure to OPs is associated with neurobehavioural deficits. However, these studies recruited different occupational groups and sample sizes, ranging from 23-380 participants. Exposure history also varied considerably from 2-20 years. We provided a narrative synthesis of these studies so that readers were aware of the variation in study methodology, before undertaking a quantitative synthesis of the data using meta-analysis.

2.1.2 Challenging aspects of the process

Data extraction was challenging on occasion as (1) several studies, failed to provide the relevant statistical information required for meta-analysis (means and standard deviations) and a decision had to be made about how to code them. Two studies had to be excluded as it was impossible to extract any meaningful data. Three studies failed to provide relevant statistics for all the comparisons made and simply stated that some of their findings were not significant. We were concerned that the exclusion of these studies would introduce bias into the analysis so we coded them as having an effect size of zero. It is important to note that this procedure leads to effect size estimates that are small and is very conservative in nature (Rosenthal, 1995) (2) a large variety of outcome measures have been used in previous research, some requiring statistical transformations to make them comparable. One technical subtlety is that we used Glass's delta rather than the more usual Cohen's d, since this is more common in studies where a control group is compared with a 'pathological' group which may well be much more variable than the controls. Meta-analysis was performed in several stages. Firstly multiple effects sizes were calculated for each study incorporating data from all the outcome measures. Then, to reduce bias from a small number of studies producing multiple effect sizes, we calculated an overall effect size per study by adding the effect sizes for each variable and dividing by the number of comparisons made. The second stage of the analysis involved establishing the variance of effect size distributions (i.e. heterogeneity) and the influence of possible moderator variables such as outcome measures, population characteristics, publication date.

2.1.3. Pros and cons of meta-analysis

Meta-analysis is a useful method of summarising and integrating the results from different studies, thereby increasing the number of participants, reducing random error and increasing statistical power to detect small effects that may be missed by individual studies (CRD, 2009; Zhou et el, 2002). Critics argue that meta-analysis is not meaningful if studies are not strictly comparable, and often see it as a process that yields a single answer; but technical advances in meta-analysis have made it possible to explore the homogeneity of studies and allows researchers to include and exclude studies with questionable methodology to determine which aspects of study design alter the overall findings (Lipsey & Wilson, 2001). We explored a number of issues in our analysis which we will now highlight using an extract from our paper. Figure 1 is a Forest plot depicting the effect sizes, 95% confidence intervals and the amount of variation between studies. The first interesting thing to note is the direction of effect sizes, eleven showing a negative effect and only two showing a positive effect (and that alone is statistically unlikely with $p<.05$). This predominantly negative pattern indicates poorer performance in exposed workers relative to controls. The second thing to note is the studies by Srivastava (2000) and Mackenzie Ross et al (2007) which showed the largest effect sizes. We were able to explore and discuss possible reasons for the differences noted between studies and we undertook meta-analysis with and without the Mackenzie Ross et al study (2007) included, since it may have been biasing the overall results, but excluding this study did not render the overall findings non-significant. We were also able to explore a number of other potentially moderating factors in our analysis such as the influence of publication date (studies published after 1995 were more likely to report negative effect sizes), the file drawer problem (Field & Gillett, 2010), population characteristics and the influence of outcome measures (some cognitive tasks were found to be more strongly associated with a history of low level exposure to OPs than others). In other words, we got a lot more out of the data than an overall single effect size and we were able to see more clearly the issues that need to be tackled by future researchers.

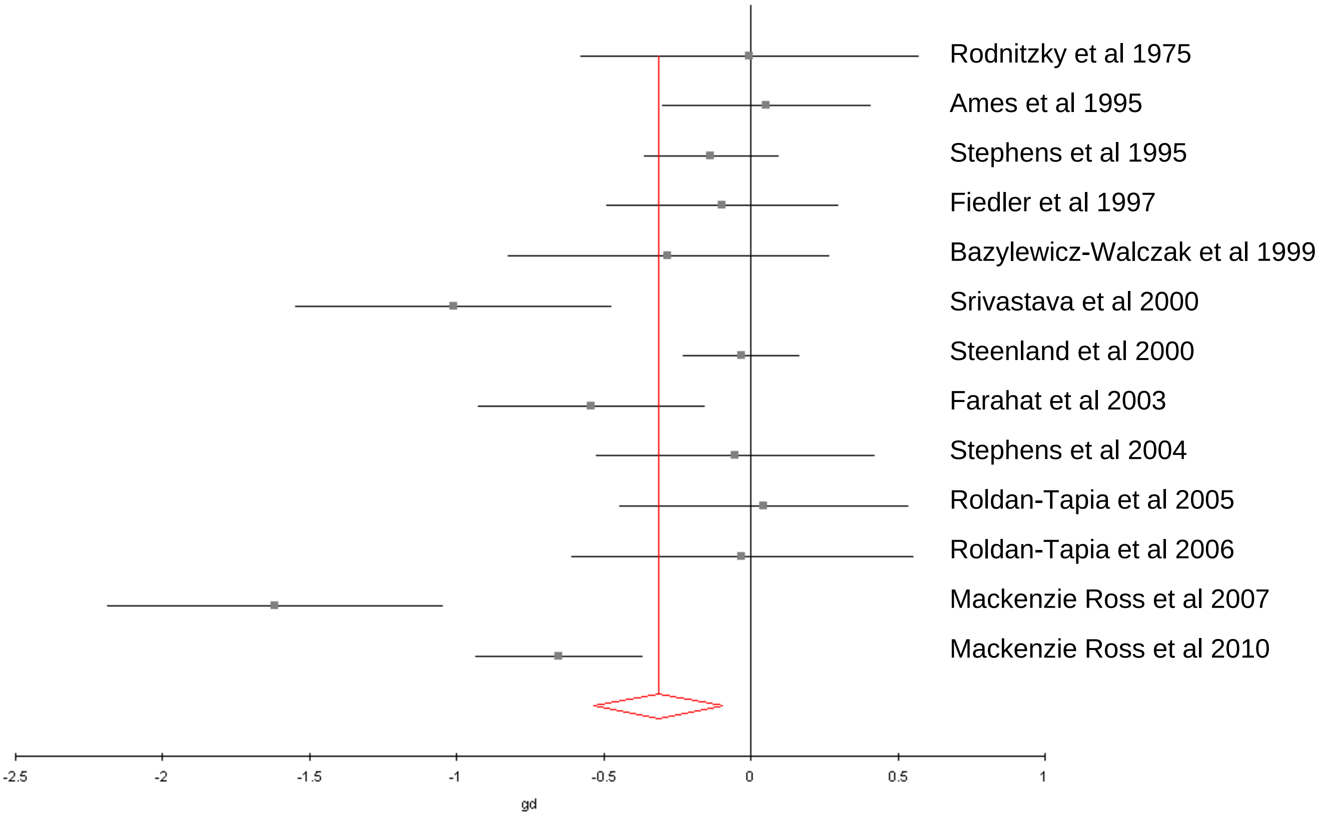

Figure 1. Forest plot depicting effect sizes for each of the studies in date order and 95% confidence intervals.

3.1 Conclusions

We found Systematic Review Techniques (incorporating meta-analysis) extremely useful in evaluating research findings concerning the neurotoxicity of cumulative low level exposure to OPs, a controversial topic for which numerous narrative reviews published over the last three decades, have failed to resolve. Although challenging at times due to variation in study methodology, populations, comparison groups, sample sizes, multiple outcome measures, poor characterisation of exposure history and studies failing to report statistics required for meta-analysis; these difficulties were not necessarily fatal and are in fact quite common to many systematic reviews and meta-analyses of the literature in behavioural, social and health sciences. Some critics argue that meta-analysis is meaningless when studies are heterogeneous, but we would like to argue that this is not necessarily the case as contemporary meta-analysis can help identify the reasons for variation in study findings and thus focus future research efforts and funding. It is also important to acknowledge the risks in terms of not using systematic methods to evaluate large or complex bodies of literature. Given the limits of human memory and decision-making, those involved in reviewing large quantities of literature are likely to use heuristics (either consciously or unconsciously) to reduce the effort associated with a task, such as integrating less information, inconsistent treatment of material, or examination of fewer alternatives (Shah & Oppenheimer, 2008), thus introducing bias, which is apparent in earlier reviews of the literature on OPs (COT, 1999 & 2014). It is impossible to remove bias altogether as a subjective component remains in the process of systematic review, in the decisions as to which studies to include or exclude, criteria for appraisal and focus of analysis, but protocols for the systematic appraisal of evidence and statistical analyses of the data reduce bias and improve transparency. Nevertheless, findings should be interpreted within a wider context taking account of theory and criteria such as those propped by Bradford Hill (Hill, 1965), for example whether results are biologically plausible and consistent with other sources of research such as animal work and laboratory findings. Finally, every effort should be made, when conducting a systematic review, to identify studies with null results which may have not been published.

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