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Meta-analysis on occupational exposure to pesticides – Neurobehavioral impact and dose–response relationships

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ABSTRACT

While the health impact of high exposures to pesticides is acknowledged, the impact of chronic exposures in the absence of acute poisonings is controversial. A systematic analysis of dose–response relationships is still missing. Its absence may provoke alternative explanations for altered performances. Consequently, opportunities for health prevention in the occupational and environmental field may be missed.

Objectives were (1) quantification of the neurotoxic impact of pesticides by an analysis of functional alterations in workers measured by neuropsychological performance tests, (2) estimates of dose–response relationships on the basis of exposure duration, and (3) exploration of susceptible subgroups.

The meta-analysis employed a random effects model to obtain overall effects for individual performance tests. Twenty-two studies with a total of 1758 exposed and 1260 reference individuals met the inclusion criteria. At least three independent outcomes were available for twenty-six performance variables.

Significant performance effects were shown in adults and referred to both cognitive and motor performances. Effect sizes ranging from $d_{RE}=-0.14$ to $d_{RE}=-0.67$ showed consistent outcomes for memory and attention. Relationships between effect sizes and exposure duration were indicated for individual performance variables and the total of measured performances. Studies on adolescents had to be analyzed separately due to numerous outliers. The large variation among outcomes hampered the analysis of the susceptibility in this group, while data on female workers was too scant for the analysis.

Relationships exist between the impact of pesticides on performances and exposure duration. A change in test paradigms would help to decipher the impact more specifically. The use of biomarkers appropriate for lower exposures would allow a better prevention of neurotoxic effects due to occupational and environmental exposure. Intervention studies in adolescents seem warranted to specify their risk.

1. Introduction

Due to the ban of some organochlorine pesticides in the 1970s (e.g. DDT), organophosphates (OPs) became the principal means of agricultural-pest control (U.S. Department of Agriculture, 2006). Despite some decrease in their use in the US since 2000 (U.S. Environmental Protection Agency, 2012) they remain an important tool for pest-control worldwide. While clinical symptoms due to high exposures are primarily experienced by occupationally exposed individuals, sequelae of low-level exposures are of importance in the context of occupational and environmental exposures. Beside farm workers also their families, the communities as a whole, and even non-rural populations undergo exposures (Barr et al., 2005; Bradman et al., 2011; Coronado et al., 2011). Neurobehavioral deficits were shown in rural and non-rural children (Guillette et al., 1998; Rauh et al., 2011; Rohlman et al., 2005).

There is agreement about the serious neurological consequences of high exposures to pesticides (Alavanja et al., 2004; Keifer and Firestone, 2007; Lotti and Moretto, 2005), but the assessment is less unequivocal in terms of chronic exposures that do not result in acute poisoning. Inconsistent outcomes across studies are considered as challenging the neurobehavioral impact of lower concentrations. Not fully consistent (Alavanja et al., 2004), discordances (Colosio et al., 2009), or contradictory evidence (Costa, 2006) were some of the descriptions. What was the background? Many studies investigated the impact of chronic

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pesticide exposures by means of neuropsychological performance tests that are capable of reflecting the altered nervous system functioning due to toxic effects. Lower scores in exposed workers were not shown by every study and not always for the same performance test across studies. However, this situation characterizes research in general. Outcomes from individual studies usually show some heterogeneity. Efficient approaches for assessing heterogeneity among studies (e.g. I^2 statistics) and estimating common effects in the presence of heterogeneity (e.g. random effects models) were developed and could quantify the evidence. A rigorous attempt to relate outcomes to exposure concentrations across studies might also help to reconcile inconsistent results.

The existing reviews by Rohlman et al. (2011), Ismail et al. (2012), and Ross et al. (2013) summarized the epidemiological evidence in general, but they appear unsatisfactory with respect to the analysis of dose-related differences across studies. Due to their narrative approach Rohlman et al. (2011) did not quantify dose–response relationships across studies. Despite their meta-analytical approach Ross et al. (2013) did not analyze the relationships. Instead, several studies were excluded, duplicate papers and a study of workers in litigation were included, and results were averaged in a way that finally there was no heterogeneity between studies that required explanations; a relationship between effect and exposure was assumed. Ismail et al. (2012) regressed effect sizes to duration of exposure. The result might be biased since samples of adolescents were included. There are indications that they should be analyzed separately as will be shown by our meta-analysis.

The importance of dose–response relationships for the proof of causal relationships has been highlighted by Hill (1965) and their analysis recently emphasized by Loomis (2012). The estimate of such relationships is an obstacle to a summary of epidemiological studies on the neurobehavioral impact of pesticides for several reasons: (1) the acute toxicity of OPs and carbamates is triggered by the inhibition of the enzyme acetylcholinesterase (AChE). Some studies measured the inhibition of cholinesterase activity, but already in 1999 the inadequacy of the biomarker for the reflection of chronic low level exposures was known (He, 1999). During the last decades additional molecular targets and modes of action have been discussed that might explain the impact of lower concentrations (Hernandez et al., 2004; Lockridge and Schopfer, 2010; Pancetti et al., 2007; Ray and Richards, 2001; Terry, 2012), but alternative biomarkers have not yet been employed. (2) Urinary metabolites of pesticides reflect acute exposures and are not helpful when the effect is protracted or cumulative. (3) A job-exposure matrix provides serious obstacles since different formulations of OPs are common and combinations of OPs and carbamates or pyrethroids frequent. Moreover, migratory and illiterate workers who are included in several studies are not always informed which pesticides they use. Consequently, many investigators faced difficulties for their attempt to describe exposure more precisely.

Due to the vague quantitative exposure characterization, exposure duration is the only available surrogate measure that is supposed to approximate the cumulative exposure of the workers. It is a crude measure, but previous studies showed that sometimes simple classification schemes are not worse than empirical models derived from exposure measures when it comes to a retrospective exposure assessment, for example on solvent exposure (Kromhout, 2012).

Considering the current scientific state of knowledge, the analysis had the following objectives: (1) to quantify the impact of chronic exposures on neuropsychological performances and (2) to analyze relationships between performances and exposure duration. The evidence that age and/or gender might modify the impact of pesticides (Eckerman et al., 2007, Levin et al., 2010, Litteljohn et al., 2011, Rohlman et al., 2007, Rothlein et al., 2006) demanded the exploration of a third question: are there susceptible sub-groups? For the analyses of these topics we focused on epidemiological studies in the occupational field that investigated chronic exposure to organophosphates in the absence of acute poisonings.

2. Methods and materials

2.1. Search strategy

Electronic searches were built around three groups of keywords: exposure, occupation, test performance. Keywords used included "pesticide*", "insecticide*", "organophosph*", "carbamate", "occupat*", "work*", "agricult*", "psychol*", "neuropsychol*", "neurobehav*", and "nervous*". Databases were PubMed, Scopus, PsycINFO, SocINDEX, Web of Science. All records included in the databases were exploited until December 2012. Manual searches included screening of reference lists of identified reports and reviews.

2.2. Inclusion criteria

Eligible studies were required to (1) investigate occupational exposure in an epidemiological study; (2) investigate pesticide exposure where at least one ingredient was an organophosphate; (3) aim at the investigation of chronic exposures that did not evoke cholinergic symptoms; (4) examine random samples of exposed and unexposed participants (no suspected occupational disease); (5) examine neurobehavioral performance by means of at least one standardized neuropsychological test that was employed by at least two further studies; (6) report means and standard deviations (SDs) of test results for exposed and reference groups or provide them on request; and (7) be published in English, French or German by December 2012.

2.3. Identification of relevant studies

Potentially relevant articles were selected by reviewing titles and/or abstracts. Where this did not allow conclusions the entire article was reviewed. Means and standard deviations of performance tests were requested from the authors where non-reporting of these was the only obstacle for the inclusion of a study.

2.4. Risk of bias

To examine the possibility that the summarized data did not adequately reflect the existing studies, a feasible publication bias was analyzed. The effect estimates were plotted against the standard error of the individual studies and the symmetry of the funnel plot tested by adding the standard error as a moderator to the random effects model (Sterne et al., 2011).

The tool for assessing the risk of a within-study bias in randomized trials (Higgins et al., 2011) was adapted to epidemiological studies and employed to assess the included studies. For each study five domains were scored with high, low or unclear risk for bias: representativeness, exclusion criteria, blinding of examiners, control for confounders, and exposure measurement. Low risk was scored 0, unclear risk was scored 0.5, and high risk was scored 1. A median split provided two groups of studies with higher or lower risk for within-study bias.

2.5. Meta-analysis

The analysis was based on effect size estimates (Hedges and Olkin, 1985) defined as the standardized difference between mean values of exposed and reference group. Neuropsychological test variables were the unit of analysis. The availability of 3 results for the same test was deemed a minimum required for an analysis that aimed at searching for repeated evidence. Individual effect sizes, overall effects and the assessment of their statistical significance were obtained as follows:

(1) Individual effect sizes (d) were calculated for each neuropsychological test in each study. Signs of effect sizes were reversed when reaction times or errors were analyzed. Negative effect sizes therefore always indicate lower performances in the exposed group.
(2) A check for outliers (values exceeding mean $\pm 2 \times$ interquartile range) was conducted among the individual effect sizes of each test.