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Neurobehavioral and neurodevelopmental effects of pesticide exposures

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ABSTRACT

The association between pesticide exposure and neurobehavioral and neurodevelopmental effects is an area of increasing concern. This symposium brought together participants to explore the neurotoxic effects of pesticides across the lifespan. Endpoints examined included neurobehavioral, affective and neurodevelopmental outcomes among occupational (both adolescent and adult workers) and non-occupational populations (children). The symposium discussion highlighted many challenges for researchers concerned with the prevention of neurotoxic illness due to pesticides and generated a number of directions for further research and policy interventions for the protection of human health, highlighting the importance of examining potential long-term effects across the lifespan arising from early adolescent, childhood or prenatal exposure.

1. Introduction

The focus of this symposium, part of the International Neurotoxicology Association (INA) and International Commission of Occupational Health (ICOH) Joint International Neurotoxicology Conference in Xian, China, June 5–10, 2011, was to highlight some of the current challenges and advances in our understanding of the health effects of pesticide exposure across the lifetime. In featuring topics ranging from developmental toxicity studies using animal models to on-going epidemiological studies of the effects of pesticide exposure at all stages of the human life course, this symposium signaled the importance of adopting a lifecourse approach to disease epidemiology (Ben Shlomo and Kuh, 2002). Organized by Leslie London and Cheryl Beseler, the symposium, comprising 5 papers, began with a discussion of the inherent limitations in developmental toxicity testing before moving into studies of neurobehavioral deficits and Attention Deficit and Hyperactivity (ADHD) in children, neurobehavioral changes in adolescents applying organophosphate (OP) pesticides to cotton in Egypt and concluding with studies of depression and suicidality in adults with a history of pesticide poisoning and cumulative low-dose exposure to OPs.

Developmental neurotoxicity studies have been informed by the epidemiological data showing that prenatal exposure to OP pesticides may be associated with an increased risk of pervasive developmental disorders, delays in cognitive development, and attentional deficits. Postnatally, children are at greater risk from

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OP toxicity than adults because the brain is rapidly developing, the dose of pesticides per body weight is likely to be larger in children and children have a reduced capacity for detoxifying xenobiotics. In children, OP exposure has been associated with behavioral problems, poorer short-term memory and motor skills, and longer reaction time. Given ubiquitous exposures to OPs in the environment, the need for further toxicological and epidemiological data to characterize the nature of the risk to children is evident.

Among older subjects, such as adolescent and adult agricultural workers, workplace injuries and exposure to pesticides pose health hazards. Pesticides are widely used in developing countries where child labor remains a feature of many countries' agricultural sectors. High levels of exposure, including poisoning, may result in an elevated risk of agricultural injury and neuropsychiatric sequelae. Pesticide poisoning is thought to alter neurotransmitter systems in the adult brain leading to increased anxiety and depression. Further, suicide is a major public health problem in developing countries, often involving the use of pesticides as the agent for suicide. Recent work suggests that exposure to organophosphate pesticides affecting non-cholinergic systems may contribute to depression, impulsivity or some combination of these disturbances in mood and could explain an elevated association of organophosphate exposure with suicide.

Drs. Moretto and Colosio provided a starting point for the symposium with a discussion of the issues associated with developmental neurotoxicity studies currently conducted for regulatory purposes. These studies are conducted according to approved guidelines and indications for the interpretation of the results are available. Many pesticides, especially organophosphates, have been studied according to experimental protocols using varying doses and assessing different parameters. These studies were reviewed with the aim of identifying toxicity endpoints that may help in understanding the results of epidemiological studies.

Drs. Harari and Grandjean presented a study using an expanded battery of neurobehavioral tests in 87 children attending two grades in a local public school in northern Ecuador, where floriculture is intensive. Children with prenatal exposure from maternal greenhouse work showed consistent deficits particularly for motor speed, motor coordination, visuospatial performance and visual memory. These associations corresponded to a developmental delay equivalent to 1.5–2 years. These findings support the notion that prenatal exposure to pesticides, at levels not producing adverse health outcomes in the mother – can cause lasting adverse effects on brain development and contribute to a "silent pandemic" of developmental neurotoxicity.

Dr. Bouchard and colleagues examined the association between urinary concentrations of dialkyl phosphate metabolites of organophosphates and ADHD in children (8–15 years) representative of the general US population. They found that children with higher urinary dialkyl phosphate concentrations, especially for dimethyl alkylphosphate, were more likely to be diagnosed as having ADHD.

Dr. Rohlman and colleagues discussed their study of pesticide exposure among adolescents in Egypt hired seasonally to work as pesticide applicators for the cotton crop. Adolescent pesticide applicators ($n = 58$) and controls who did not apply pesticides were recruited from the same villages ($n = 40$) to participate in a 10-month longitudinal study from April 2010 to January 2011. The results showed depression in both plasma butyrylcholinesterase (PChE) and red blood cell acetylcholinesterase (AChE) levels in applicators followed by recovery after the application had ended. Applicators had impaired performance compared to controls on the majority of tests on the neurobehavioral battery developed for the study. Work practice questionnaires indicate limited use of personal protective equipment. This study provided data to characterize chlorpyrifos exposure and identified numerous behavioral deficits in an adolescent population occupationally exposed to pesticides.

Drs. Beseler and Stallones presented evidence that a history of pesticide poisoning and depression are risk factors for farm injuries. A total of 1637 Colorado farm residents were assessed to address associations between pesticide poisoning, depressive symptoms, safety behaviors and injury in a Structural Equation Model. This work provides evidence that pesticide poisoning differentially affects the negative affect, somatic and retarded activity dimensions of depression, but not positive affect to the degree that health or financial problems do. The negative affect symptoms feeling depressed, fearful, sad and lonely and the retarded activity symptoms feeling unable to "get going" and that everything was an effort showed the most robust association with injury.

Dr. London and colleagues presented their cross-sectional study of 810 workers on commercial grape farms in the Western Cape province of South Africa showing an association between reported past poisoning by pesticides and depression as measured on the GHQ, but no relationship with long term cumulative exposure. Structural Equation Modeling did not improve the exposure–effect characterization nor identify any relevant causal pathways. Whereas this study confirmed the association of affective disorders with past poisoning consistent with the literature, the contribution of long-term low-dose exposures to depression and suicidality remains uncertain.

1.1. Evaluation of experimental data for developmental neurotoxicity of pesticides

The development of the central nervous system occurs both in utero and postnatally, and requires an adequate environment that depends on a complex relation between different factors that have different spatial and temporal roles. Disturbances of development may have genetic as well as external factors acting during any of the phases of development (Connors et al., 2008). Many groups of pesticides act through a neurotoxic mechanism that is relevant both to target and non-target mammals, including humans. The majority of such neurotoxic compounds are included in the groups of anticholinesterases, i.e. organophoshates (OP) and carbamates, pyrethroids, and organochlorines, although other groups or individual compounds might also show neurotoxic properties. Consequently, the issue of possible effects by pesticides on the normal development of the central nervous system was raised and ways of addressing the identification and prevention of these effects have been discussed (Barlow et al., 2007; Eskenazi et al., 2008; Fitzpatrick et al., 2008; Raffaele et al., 2010). In particular, in the USA the passage in 1996 of the Food Quality Protection Act mandated an increased effort on the assessment of the potential toxicity of pesticides to children, and a special focus was given to developmental neurotoxicity (Raffaele et al., 2010).

A number of epidemiological studies have been performed to identify possible consequences on the neurological development after perinatal exposure to pesticides, and results have been subject to several criticism regarding the relevance of the findings (for a review see e.g.: Bjorling-Poulsen et al., 2008; Jurewicz and Hanke, 2008; Weselak et al., 2007). In particular, it has been concluded that many of the studies suffered from poor exposure estimation, that the effects were inconsistent, and that there was limited or inadequate evidence to support causality between neurodevelopment and perinatal low level repeated pesticide exposure. Given these uncertainties, a review of the experimental evidence was undertaken in order to assess whether animal data support the hypothesis of specific neurodevelopmental effects of pesticides; in other words the question asked was that of a particular sensitivity of the developing organism to neurotoxic effects, that occur at doses that are lower than the