The Effect of Chronic Exposure to Insecticides on Cognitive and Physical Neural Function.

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Hypothesis: Increased chronic cumulative exposure to carbamate, organophosphate, and pyrethroid insecticides is associated with decreased performance on neurobehavioral (e.g., IQ) and neuromuscular (e.g., postural balance) measures. Subhypothesis: The levels of these insecticides or their metabolites in body tissue are directly related to identifiable environmental factors.

Public Health Significance:

Members of the pyrethroid and organophosphate classes of synthetic insecticides have been identified as toxic to developing nervous systems (Olson et al. 1998; Roy et al. 1998; Weiss 2000). Data from animal models and epidemiological studies suggest that even low levels of exposure during critical periods of development could cause subtle neurological effects in humans (Dam et al. 1999; Miller 1999; Auman et al. 2000; Dam et al. 2000; Rice and Barone 2000; Ritz and Yu 2000). For example, permethrin, a commonly used pyrethroid insecticide in the United States (Landrigan et al. 1999), adversely impacts synaptogenesis in the developing nervous system (Rice and Barone 2000). The human central nervous system develops from the first few weeks of gestation through puberty with synaptogenesis occurring most rapidly during gestation through 4 to 5 years of age (Rice and Barone 2000).

Clinical outcomes resulting from cumulative insecticide exposure are unknown. However, diagnoses of several outcomes such as autism and ADD have been on the rise. This study will investigate relationships between such outcomes and levels of insecticide exposures. The relationship between insecticide exposures and decreases in IQ, effects that impact an individual's Quality of Life, will also be investigated.

In addition, a report by the General Accounting Office indicates that Federal, state, and local public health agencies are in better need for estimates of reference values for human exposure to chemicals and the variability in these values (GAO, 2000). This research will generate high quality data on exposures of the U.S. Population to insecticides and the geographic and temporal variability in those exposures.

Justification for Large prospective Study

The time windows of greatest vulnerability to disruption of neural development vary by substance, dose of the substance, and mechanism of action (Adams et al. 2000). Thus, an in-depth understanding of numerous variables, including short-, intermediate-, and long-term intake of insecticides is needed to investigate potential exposure-disease relationships. A prospective longitudinal cohort study is the most powerful design for investigating relationships of this type.

The types and quantities of pesticides used are highly variable by region of the country. Since cumulative exposure to several pesticides is of interest, any analysis will be multi-variate. Individuals diagnosed with the health effects of interest, however, will

be relatively few in number. Because of the relatively rare outcomes and because of the large gradients in exposure, a large sample size is warranted.

A large sample size will allow those components of this hypothesis that are related to validation of exposure estimation methods (e.g. GIS, surveys, etc) to be tested on a smaller sub-sample of the study population. An additional benefit of a large sample size is that it will provide meaningful data to and encourage support from state and regional health departments, who might otherwise have little interest.

Scientific Merit

The goals of this hypothesis will be two-fold: 1) to assess potential neurodevelopmental effects associated with cumulative exposure to pesticides in the environment, and 2) to better understand trends in pesticide exposure over time and the factors responsible for any changes.

Pesticide exposures in children are highly variable, not only among different children but also for the same child measured at different time points (Quackenboss *et al.*, 2000; Rigas *et al.*, 2001). As a result, many measurements are needed to accurately characterize average, long-term exposures. Using a repeated measures design will increase the accuracy and precision of the estimates and will increase the likelihood of observing a relationship between the exposures and neurodevelopmental health outcomes, if one exists. . The repeated measures design combined with a large sample size will also allow us to gain a better understanding of variability in the relationship and the factors related to it..

In order to better understand the relationship between cumulative insecticide exposure and health effects in a large group over a long period of time, and in order to suggest mitigation strategies, better information is needed on the determinants of personal exposure. This is the basis for our sub-hypothesis. There is currently very little information available on the predictors (or determinants) of long-term average exposures to insecticides in the general population and virtually no reliable, consistent information for infants and very young children. Yet, in terms of the risks for chronic disease, and the ability to identify and classify population groups who are at greater risk, this is important. Researchers have frequently relied upon short-term average measurements or questionnaire/diary information on a few different individuals to estimate long-term exposures for all segments of the population (Quackenboss *et al.*, 2000).

Potential for Innovative Research

This hypothesis has a high potential for innovative research. Methods to better characterize cumulative exposure to insecticides from surrogates such as GIS maps (indicating proximity to agriculture) as well as from simple questionnaires will be validated.

Typically studies of cumulative effect focus on chemicals with the same mechanism of action. In this case, both organophosphate and carbamate insecticides operate by reducing cholinesterase activity while pyrethroids act by blocking sodium channels. This will be a unique opportunity to examine the health effects arising from cumulative exposure to chemicals with differing mechanisms but perhaps affecting the same endpoint, neurodevelopment.

Feasibility

This research involves critical periods that extend for a period of years, with a high degree of uncertainty regarding specific windows, if any, during those critical periods. This research will also require environmental sampling (including in the home). Pilot work and current work underway at EPA and other institutions may allow for reduced amounts of environmental sampling, as a better understanding of the important pathways for insecticide exposure is gained. Properly designed questionnaires may serve as a surrogate for some environmental sampling. This research will also require periodic sampling of blood and/or urine during the critical period. The necessary time interval between biological monitoring is uncertain, but will probably coincide with blood sampling and medical examinations related to other hypotheses in the NCS. To assess neurodevelopment, outcome measures will need to be determined in consultation with the neurodevelopment working group. The study is feasible but, perhaps, costly. Careful consideration of information gained by repeated environmental measurements will need to be weighed against costs and participant burden.

These three classes of insecticides (organophosphate, carbamate, and pyrethroid) have very short half-lives in blood and are thus generally monitored in urine as metabolites. Since 28 of the 39 organophosphates that are approved by EPA for agricultural use metabolize into 6 common metabolites, they can be monitored nonspecifically, but more specific metabolites may be measured as well. The collection of urine samples is noninvasive and, although a challenge in the very young, is generally simple to perform.

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