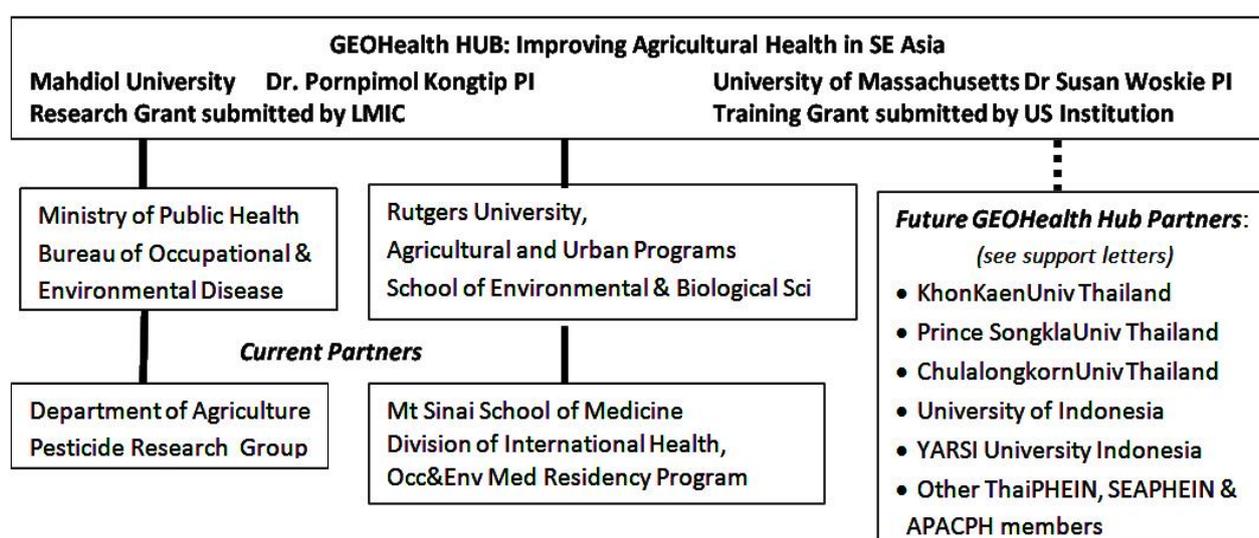


Mahidol and UMass Lowell Joint Center for Work, Environment, Nutrition and Development (CWEND)

GEOHealth Hub for Occupational and Environmental Health:

Improving Agricultural Health in Southeast Asia.

The U.S. National Institutes of Health (NIH) through the Fogarty International Center has funded two paired grants to the GEOHealth Hub, one for research and one for training focused on a core set of common research and training topics that address agricultural health issues in the region. The GEOHealth Hub partners are the focal point for all proposed research, research capacity-building, training, and collaborative activities, in which partner institutions may participate.

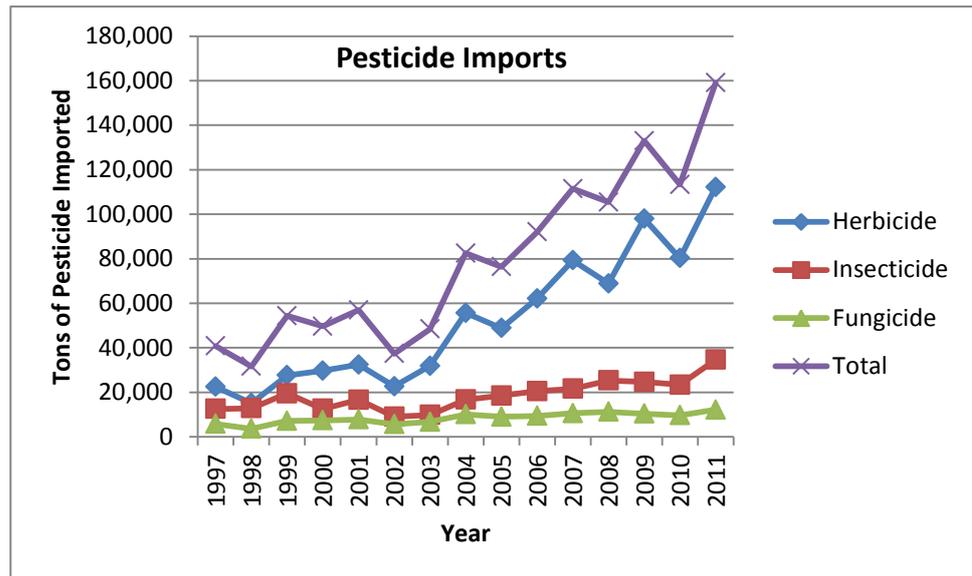


Scientific Topic and Rationale for Research

In 2012 the International Labor Organization (ILO) reported that there are approximately 1.3 billion agricultural workers worldwide. This represents half of the total world labor force. Almost 60% of these agricultural workers were in developing countries, with a great majority found in the Asia-Pacific region. In Thailand, agricultural work is an economic foundation of the nation and rural areas are home to more than 70% of the population. Among the working population, over 40% work in agriculture (16.7 million), with 93% of these agricultural workers in the informal sector and 44% female.

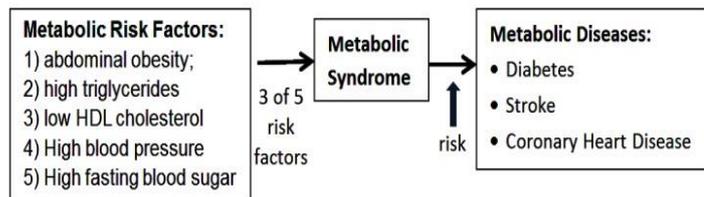
Thailand continues to increase its annual import of pesticides. The most common type of pesticides imported are herbicides, followed by insecticides, and fungicides. Currently there is no data available in Thailand on the manufacture or use of pesticides within the country. The most commonly imported herbicides were glyphosate, paraquat dichloride, 2,4-D, ametryn, and atrazine. The most commonly imported insecticides were chlorpyrifos, fenobucarb, cartap hydrochloride, cypermethrin, and methomyl In our planning grant agricultural worker questionnaire (n=212) we also found that the most commonly used pesticides were herbicides, with 73% of the products used containing glyphosate, 49% gramoxone/paraquat and 20% 2,4-D. In our previous NIH cohort of pregnant women in agriculture, 76% of our subjects reported using paraquat, compared to 38% reporting use of OP pesticides.

Yet, to date there have been very few studies of chronic disease among Thai agricultural workers. In Thailand, non-communicable diseases, especially metabolic-related diseases and related conditions such as



hypertension and diabetes, are rapidly increasing. In our planning grant agricultural worker questionnaire (n=212) self-reported disease prevalence was 25% for hypertension, 8% diabetes, 2% cardiovascular disease, which is considerably higher than the prevalence reported among hospitalized patients in Thailand.

Persons with metabolic syndrome are at increased risk of metabolic diseases such as diabetes, stroke and coronary heart disease. Thus the underlying risk factors that comprise metabolic syndrome are of much concern, especially as

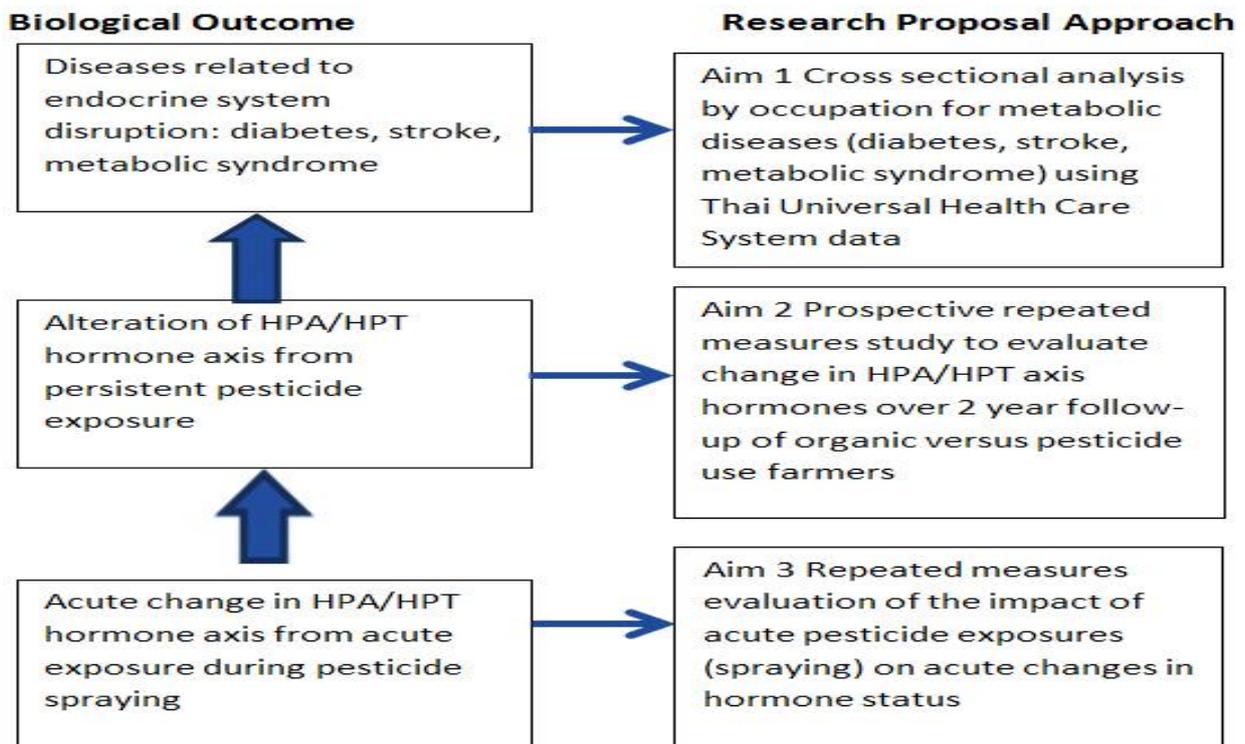


rates of obesity continue to increase at alarming rates across the globe. Although metabolic diseases are complex, endocrine hormones are known to play an important role in regulating adipose development, lipid and glucose metabolism, heart and blood pressure, and insulin sensitivity. Hypercortisolemia has been linked with increased abdominal obesity and changes in cortisol levels have been linked with increased risk of type 2 diabetes. There is increasing evidence linking exposure to endocrine disrupting chemicals (EDC's) with obesity and metabolic syndrome in animals, especially when exposures occur early in life. For diabetes, there is growing evidence from human studies linking exposure to EDC's with type 1 & 2 diabetes. In a meta-analysis of 14 epidemiologic studies, there was an increased risk of coronary heart disease among those with subclinical hypothyroidism (normal T4 with high TSH). Triglycerides, total cholesterol and low density lipoproteins (LDL) have been shown to increase with increasing thyroid stimulating hormone (TSH) levels, and high density lipoproteins (HDL) decrease with increasing TSH levels. In addition, as TSH levels increase, both systolic and diastolic blood pressure increases. Exposure to a number of EDC's have been linked with thyroid hormone disruption. **Our hypothesis is that Thai agricultural workers are at increased risk of metabolic disorders and endocrine function disruption through the use of common pesticides**

Almost 60 pesticides are listed as potential endocrine disrupters by the US Endocrine Disrupting Screening Program. However, most of the evidence is based on in vitro studies. Nevertheless, there is some in-vivo evidence linking pesticides with disruption of the

hypothalamic–pituitary–thyroid (HPT) axis (effecting thyroid hormone levels) and the hypothalamic-pituitary-adrenal (HPA) axis (effecting cortisol hormone levels). Altered homeostasis of these important endocrine axis's is postulated to be a biomarker of risk for the development of metabolic disorders.

This proposal is designed to provide a comprehensive examination of the potential linkages between acute and semi-chronic disruptions in the HPA and HPT axis endocrine hormones and the development of endocrine associated chronic diseases.



Specific Aims.

1. Use Thai Universal Health Care System (UCS) data to conduct cross sectional analysis by occupation for metabolic diseases (diabetes, stroke, coronary heart disease, metabolic syndrome and associated risk factors).
 - a. Conduct pilot project to develop model of environmental pesticide contamination (soil, water) using Material Flow Analysis with geospatial mapping that could be widely applied in Thailand and used in conjunction with UCS data to examine pesticide links of a wide range of diseases.
2. Prospective repeated measures study to evaluate sub-chronic change in hypothalamic–pituitary–thyroid (HPT) axis and hypothalamic-pituitary-adrenal (HPA) axis hormones and risk factors for metabolic syndrome comparing organic and pesticide use farmers over a 2 year follow-up.
 - a. At 8 month intervals over 2 years (n=3), measure HPT axis (thyroid hormones (TSH, fT4, fT3, T4, T3) and HPA axis (salivary cortisol) hormones, risk factors for metabolic syndrome (BMI, waist circumference, blood pressure, triglycerides, glucose and cholesterol levels) and collect data on volume and type of pesticides applied to create pesticide exposure indices.
 - b. With a final estimated cohort of 170 organic and 170 pesticide use agricultural workers, model hormone levels as the outcome using linear mixed models for repeated measures including covariates for organic vs pesticide use and/or

- cumulative volume of each type of pesticide used after controlling for gender, age and other covariates.
3. Repeated measures evaluation of the impact of acute pesticide exposures (spraying) on acute changes in HPT/HPA axis hormone status among 100 pesticide using farmers (from aim 2).
 - a. On 2-4 (average 3) occasions when target pesticides are sprayed measure HPT axis (thyroid hormones (TSH, fT4, fT3, T4, T3) and the HPA axis (salivary cortisol) before and after spraying.
 - b. On the same occasions when pesticides are sprayed measure urinary metabolites of target pesticides (2 types insecticides, 3 types of herbicides) before and after spraying.
 - c. Model hormone levels as the outcome using linear mixed models for repeated measures including covariates for urinary pesticide metabolite concentration after controlling for gender, age, etc.
 - d. Conduct pilot project to measure home contamination through pesticide analysis of home soil, water, indoor surfaces and children's hands (also used in Aim 1a).
 4. Evaluate the impact of genetic polymorphisms of xenobiotic metabolizing enzymes related to target pesticides on pesticide urinary metabolite levels and HPT/HPA axis hormone levels from Aim 3.
 5. Expand the research capacity of the GEOHealth Hub

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More details on the program, research areas and application procedures can be found at our website: <http://www.geohealthseasia.org>

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