Editorial

Pesticides, human health, and food security

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The worldwide population is projected to increase to 9 billion by 2050 (United Nations 2015). To accommodate this increase, food production will necessarily need to increase as well. However, new agricultural land is limited, so sustainable production and increasing productivity of existing agricultural land is an important aspect to addressing global food security (Popp et al. 2013).

Food security has been described as a condition of humanity “…when all people, at all times, have physical and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life.” (Food and Agriculture Organization 1996). Increases in the terrestrial agricultural production of food and fish farming will be necessary to ensure adequate food availability, but this is only part of the larger concept of food security that also comprises food access, utilization, and stability (Food and Agriculture Organization 2006). Given that there is limited additional land available for agriculture and sites for fish farming coupled with increasing economic pressures to produce agricultural commodities for industrial purposes, including fiber and biofuels, strategies to increase agricultural yield will need to be used to meet the increase in food demand for the immediate future. For the near and foreseeable future, pesticides may be an important component of a comprehensive strategy to increase crop yield by preventing both pre and postharvest loss to pests.

With the role that pesticides may have to play to provide food security for an increasing world population, our commentary focuses on the important contribution epidemiology can make in helping to inform environmental health policy to safely meet the many challenges involved with ensuring food security.

Pesticides and Food Security in the Context of Risk Assessment and Risk Management

“Pesticides are substances used to prevent, destroy, repel or mitigate any pest ranging from insects, animals and weeds to microorganisms” (Grube et al. 2011), but inadvertent exposure to pesticides may adversely affect human health. Determining the balance between benefit and harm from pesticide use is complicated because it has been argued that the use of pesticides, broadly, has increased the quality and quantity of fruits and vegetables and consequently has improved public health, in spite of the potential adverse health effects (Ames 1983). We take a more nuanced view, that is, effective use of some carefully selected pesticides should be considered after having been scientifically evaluated in a comprehensive health risk assessment. Only then should an environmental health policy be developed in a clearly considered, written “risk management plan” that reflects competing disease risks (including the risk to particularly vulnerable subpopulations), and the economic feasibility for that particular political entity.

We believe this more cautious action plan is warranted in light of the limitations of current health and ecological research in this area. For example, in a recent News at a glance article in Science entitled “Few Studies of Synthetic Chemicals” (Anonymous 2017), it has been reported that “U.S. government funding for studies of synthetic chemicals—such as pharmaceuticals and pesticides—that affect the environment lags behind the rapidly expanding use of these substances…..”. Meanwhile, <3% of grants from the National Science Foundation Division of Environmental Biology-the nation’s major funder of ecological research by academics-focus on the issue, …” Consequently, this lack of investment in or commitment to such research, severely hampers meaningful risk assessment and optimal risk management plans that could increase benefits while mitigating risks.

A definition of Health Risk Assessment that consists of four parts, namely Hazard Identification, Dose–Response Assessment, Exposure Assessment, and Risk Characterization will be used in this discussion. This definition was developed by the National Academy of Sciences in 1983 (National Academy of Sciences (NAS) 1983). In the context of pesticide use, hazard identification is a process of determining whether human exposure to a pesticide’s active ingredient could cause an increase in

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the incidence of a health condition (e.g., cancer, birth defects, heart disease, immune disorders, neurological injury) or whether exposure to a nonhuman receptor (domestic animals or animals in the wild) might be adversely affected.

Dose–Response Assessment is the process of characterizing the relationship between the dose of a specific pesticide administered or received and the incidence of an adverse health effect in the exposed populations and estimating the effect as a function of the pesticide dose. This process also includes assessing the intensity (or dose) of exposure, duration of exposure, personal protective equipment (PPE) used, age pattern of exposure, and other lifestyle factors that may modify risk. Extrapolations of risk to lower exposure levels and an estimate of uncertainty associated with these extrapolations are also included in this step as necessary.

Exposure Assessment is the process of measuring or estimating the intensity, frequency, and duration of human or animal exposure to a specific pesticide currently present in the environment or estimating hypothetical exposures that might arise from the release of new pesticides into the environment. This is important because in population settings, population attributable risks are partly a function of the prevalence of exposure. Consequently, certain pesticides may have weak, albeit causal associations on the relative risk scale, but relatively large population attributable risks because of the ubiquitous presence of that pesticide.

Finally, Risk Characterization is the process of quantitatively estimating the potential incidence of a health effect using the dose–response assessment in conjunction with documenting the various conditions of human (or animal) exposure present in the population under evaluation that would influence the incidence of the health risk.

The National Academy of Science’s report emphasized the need to separate the function of Risk Assessment and risk management (National Academy of Sciences (NAS) 1983). The objective of Risk Management is to systematically consider the options that may be taken to reduce risk, and then to select an option that balances the benefits of actions while mitigating potential health, ecologic, and economic risks.

Investigations of pesticides carried out in experimental animals assume relevance only when they can be extrapolated with confidence to humans. However, there has been relatively little knowledge of human metabolism of any class of xenobiotics other than clinical drugs (Cole et al. 1982; Bogen and Spear 1987; Falls et al. 1997; Coleman et al. 1999, 2000; Usmani et al. 2004). While studies of animals have been useful for decades in predicting human health hazards associated with pesticide use, studies in rodents have sometimes been misleading, since gender, strain, and species differences in several pharmacological parameters related to the metabolism, distribution, and toxicity of pesticides have been described in the literature (Bogen and Spear 1987). Nonetheless, risk assessment and risk management of essentially all occupational/environmental-related chemicals has historically depended heavily on extrapolations from studies on experimental animals (Fenner-Crisp 2001).

**Pesticides and Chronic Diseases**

It should be noted that for chronic diseases such as cancer there are relatively few reliable epidemiologic studies that allow us to directly estimate health risks from dietary exposure to pesticides or contaminated drinking water. While acute health effects caused by high-dose exposure to food contaminated with pesticides are better documented, they are not necessarily relevant to understanding the toxicological mechanisms involved in low-dose chronic exposure (Fenner-Crisp 2001).

Determining if there are any adverse health consequences to specific low-level, long-term exposure to the vast array of pesticides on the market is a complex task.

The epidemiological literature identifying and describing dose–response relationships of particular pesticides to cancer in the occupational literature has only recently been judged to be sufficient by the International Agency for Research on Cancer (2016, 2017) in their monograph series. As recently as 1991, an IARC monograph stated that “occupational exposures in spraying and application of non-arsenical insecticides” as a group are classified as “probable human carcinogens” (category 2A) (International Agency for Research on Cancer 1991), yet the identification of specific pesticides as human carcinogens has not been made. While this IARC conclusion was an important early step in the process to identify risk, it was insufficient to target-specific agents and therefore of little value to formulate a meaningful risk management plan.

Fortunately, risk assessments that rely on more recently published epidemiological studies focused on cancer endpoints among more highly exposed occupational-populations are better suited to provide more informative science-based risk assessments (Alavanja et al. 2013). These studies are characterized by more complete chronic disease ascertainment, more reliable exposure assessment (including the role of PPE in reducing exposure), more complete assessment of relevant concomitant exposures that may affect disease incidence, and some prospective studies also provide biological material collected prior to the onset of disease. Moreover, the epidemiologic studies with information on human genetic polymorphisms can be important to help define populations at particularly increased risk (Koutros et al. 2010, 2013; Barry et al. 2011).
In an earlier article we wrote: “Since disease vectors, weeds and insect pests in agriculture and commerce have developed resistance to widely used pesticides and since these pests have periodically been introduced to new geographic areas that do not have natural controls, societal response has frequently been the introduction of new chemical to control these new pest problems” (Alavanja et al. 2013). It might seem, therefore, that the science of epidemiology might be an ineffective tool for helping to set meaningful environmental health and food safety policy, since epidemiology is in an endless catch-up cycle while new chemicals are regularly being introduced to the market place. The situation may seem particular troubling for cancer epidemiologists who must wait 10 or more years before the “natural experiments” linking a particular pesticide exposure to a particular cancer produces meaningful epidemiological observations (Alavanja et al. 2013). We do not believe this is the case.

Although pesticides have a diverse set of chemical structures and exhibit a wide range of biological modes of action, considerable progress is being made identifying the relevant “modes of action” for a number of pesticide-induced human diseases.

Among pesticides found to be human carcinogens or probable human carcinogens, for example, lindane (Group 1, human carcinogen) has been shown to cause immunosuppressive effects that can operate in humans (International Agency for Research on Cancer 2016). DDT (Group 2A, probable human carcinogen) has also been shown to have immunosuppression effects in human cells and it has also been shown to increase oxidative stress in human peripheral blood mononuclear cells and stimulates human colon cancer cells and liver cancer cell proliferation in vitro (International Agency for Research on Cancer 2016). Estrogenic effects and androgen-receptor antagonism were observed in human cells in vitro (International Agency for Research on Cancer 2016). The insecticides malathion and diazinon and the herbicide glyphosate were classified as ‘probably carcinogenic to humans’ (Group 2A) (International Agency for Research on Cancer 2017). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. Malathion is rapidly absorbed and distributed and then metabolized to the bioactive malaoxon which induces DNA and chromosomal damage in humans (International Agency for Research on Cancer 2017). Diazinon has been widely used in agriculture and for home and garden insect control. Diazinon induces chromosomal damage in human cells (Hatjian et al. 2000). Glyphosate is a broad-spectrum herbicide, currently with the highest production volumes of all herbicides. For example, increases in micronuclei, a biomarker of chromosomal damage, in several communities after spraying with glyphosate has been reported (Bolognesi et al. 2009). Validly identifying the mode-of-action of pesticides in human disease will ultimately result in testing methods to effectively evaluate chemicals premarket.

These early attempts to identify the mode-of-action of suspected environmental carcinogens, must nonetheless be evaluated cautiously. Human exposure to xenobiotics frequently produces a multiplicity of metabolic byproducts and these byproducts often result in a cascade of additional biological effects. While these relatively early molecular epidemiologic findings are an important step forward and they provide more data for a weight-of-evidence evaluation, and some of these biomarkers can be observed long before clinical disease can be diagnosed; it is suspected that not all of these biomarkers lie along the causal path of carcinogenesis (Alavanja et al. 2013). Additional work by molecular epidemiologists and toxicologists needs to be conducted to isolate and identify the actual pathogenic pathway, but once this is accomplished powerful new tools will be available to provide timely evaluations of pesticides prior to their use in a public health and or commercial agricultural context.

**Pesticides Used for Public Health and Food Security**

Pesticides are used to directly benefit public health by reducing vector-borne disease, such as malaria and Zika virus that are transmitted to humans via mosquitoes. An unanticipated consequence of these efforts to control mosquito populations may result in serious harm to pollinators, such as honeybees, which may harm crop production that relies on these pollinators. Quantifying the indirect consequences of our potential action is currently fraught with uncertainty and requires balancing short-term risks (e.g., Zika virus infection) with long-term risks (e.g., cancer risks and diminished crop yields) in the risk management plan.

**Pesticide Use in Developing Countries**

In developing counties, quantitative risk assessment is further complicated by the lack of regulatory oversight of pesticide sales and safe usage. Consequently, appropriate handling and use of PPE during pesticide applications are not adhered to widely. For instance, among adult Egyptian pesticide applicators with documented limited use of PPE extremely high urinary concentrations of the chlorpyrifos-specific metabolite 3,5,6-trichloro-2-pyridinol (TCPy) (Farahat et al. 2003, 2010, 2011; Callahan et al. 2014) during seasonal applications were found. Similarly, adolescent Egyptian pesticide applicators have also been
shown to have limit PPE use and correspondingly high concentrations of TCPy (Crane et al. 2013). Adolescent chlorpyrifos applicators had a median TCPy level of 137 μg/g creatinine at the end of applications, whereas the nonapplicators had a median TCPy level of 16.8 μg/g creatinine. Correspondingly, short-term deficits in neurobehavioral tests have also been documented among these Egyptian pesticide applicators, adult (Farahat et al. 2003), and adolescent (Rohilman et al. 2016) alike. While these deficits maybe considered subtle on a major morbidity and mortality scale, the longer term consequences have not been adequately investigated.

In addition to identifying highly exposed adults and adolescents working as pesticides applicators, adolescent nonapplicators were also observed to have increased urinary levels of TCPy that corresponded to chlorpyrifos applications in the field, suggesting that considerable environmental or bystander exposure could be occurring among the general population during periods of pesticide application (Crane et al. 2013). The implication of these observations in developing comprehensive food security plans is that risk estimates from the developed world may underestimate the actual risks in developing countries.

**Conclusions**

While we have begun to increase our rate of progress in identifying specific associations of pesticides with specific health outcomes, our task is largely incomplete. To help provide food security, we need more epidemiological research that evaluates specific pesticides and their mode of action on a number of health outcomes. Identification of the most sensitive outcomes, coupled with balancing the short- and long-term risks is necessary to develop risk management strategies that will optimize benefit and mitigate risks. We need to recognize that our understanding of the risks and benefits of specific pesticide use as well as the uncertainties around our estimates will evolve as more rigorous research is conducted. In the absence of absolute certainty about risks and benefits of pesticide use, the precautionary principle has been advocated to guide decision making. The 1992 Rio Declaration describes the precautionary principle, as follows: “In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.” (United Nations 1992). Of course, applying the precautionary principle to the use of pesticides in the context of food security is challenging because of the potential economic impact and the uncertainty in identifying and quantifying health risk and benefits. As more molecular epidemiologic research is conducted to more precisely determine and quantify risks associated with specific pesticide use, we will less frequently have to default to the precautionary principle because of the lack of scientific certainty. If careful use of pesticides can minimize health risks while increasing nutritional quality and quantity of foods, then a beneficial consequence of pesticide use could be improved nutritional status and a corresponding improvement of public health (Shlisky et al. 2017).

The epidemiologic contribution to identifying and quantifying health risk associated with pesticide uses are issues that concern food availability, but these are not the only issues in comprehensibly addressing food security. Food security policy must also address issues of food access, utilization, and stability – all-important components that contribute to food security that goes beyond issues of environmental health.

**Conflict of Interest**

None declared.

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