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Pesticides Use and Exposure Extensive Worldwide

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Introduction

Worldwide it is estimated that approximately 1.8 billion people engage in agriculture and most use pesticides to protect the food and commercial products that they produce. Others use pesticides occupationally for public health programs, and in commercial applications, while many others use pesticides for lawn and garden applications and in and around the home (1, 2). Pesticides are defined as “chemical substances used to prevent, destroy, repel or mitigate any pest ranging from insects (i.e., insecticides), rodents (i.e., rodenticides) and weeds (herbicides) to microorganisms (i.e., algicides, fungicides or bactericides)” (1,3).

Over 1 billion pounds of pesticides are used in the United State (US) each year and approximately 5.6 billion pounds are used worldwide (1). In many developing countries programs to control exposures are limited or non-existent. As a consequence; it has been estimated that as many as 25 million agricultural workers worldwide experience unintentional pesticide poisonings each year (4). In a large prospective study of pesticide users in the United States, the Agricultural Health Study, it was estimated that 16% of the cohort had at least one pesticide poisoning or an unusually high pesticide exposure episode in their lifetime (5).

Although attempts to reduce pesticide use through organic agricultural practices and the use of other technologies to control pests continue, exposure to pesticides occupationally, through home and garden use, through termite control or indirectly through spray drifts and through residues in household dust, and in food and water are common (6). The US Department of Agriculture has estimated that 50 million people in the United States obtain their drinking water from groundwater that is potentially contaminated by pesticides and other agricultural chemicals (7,8). Children from 3-6 years old received most of their dermal and non-dietary oral doses from playing with toys and while playing on carpets which contributed the largest portion of their exposure (9-12).

Previous Hazard Assessment Inadequate

Pesticides are commonly referred to by the functional class of the active ingredient and the type of organism that they are designed to control (e.g. organophosphate insecticides, thiocarbamate herbicides, triazine herbicides). Nearly all commercial formulations of pesticides are complex mixtures of active and other ingredients. These “other ingredients” include a wide variety of substances added to increase the efficacy of the product in a cost-effective manner. Information regarding these other compounds is considered proprietary business information and is not publicly available (6). The health effect of a commercial pesticide product may be a consequence of the active ingredient, the other ingredients in the formulation, or both. Toxicological testing, unfortunately, is usually restricted to the active ingredient. Epidemiological surveillance of the health effects of pesticides identifies adverse effects of the combined ingredients. Disparity between epidemiological evaluations of

pesticides and toxicological evaluations may, in part, be due to this difference in scientific focus.

The International Agency for Research on Cancer (IARC), a component of the World Health Organization, and its monograph series on the Evaluation of Carcinogenic Risks to Humans is widely used to identify environmental carcinogens and to help guide government policy in protecting people from the risk of cancer due to dietary, environmental and occupational carcinogens. Currently, lARC classifies two pesticides as human carcinogens namely, the arsenical insecticides and 2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD, a contaminant of the phenoxy herbicide 2,4,5-T) (13). However, IARC also states that "occupational exposures in spraying and application of non-arsenical insecticides" as a group are "probable human carcinogens". This group of non-arsenical chemicals is used world-wide and includes scores of active ingredients in hundreds of different commercial formulations. Most of the pesticides on the market today are considered non-genotoxic. IARC characterizes most previous epidemiology studies as inadequate to assess human carcinogenicity because of small sample size, limited follow-up, or a retrospective design with poor exposure assessment.

In the United States before a pesticide can be marketed or sold, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) requires the EPA to ensure that when used according to label instructions, the pesticide can be used with a reasonable certainty it will not harm health or the environment. To achieve this, the EPA assesses carcinogenic risk by relying primarily on animal genotoxicity studies and/or short-term mutagenicity assays. This is based on our understanding that genotoxicity and mutagenicity play a major role in carcinogenesis (6). Of particular concern is the situation that arises when a pesticide is determined to be non-carcinogenic based on genotoxicity/mutagenicity assays (thus labeled by the US EPA as *"Not Likely to Be Carcinogenic in Humans"* or *"Evidence of Non-Carcinogenicity for Humans"* (14), yet cancer incidence has been found to be increased in epidemiologic studies (15).

Recently, the Agricultural Health Study has produced some evidence of increased incidence of cancer of the prostate, lung, colon, pancreas, bladder, leukemia, and multiple myeloma with increasing lifetime exposure to certain pesticides (16-31).

Use of in-vitro and in-vivo toxicological testing has undoubtedly kept many dangerous pesticides destined for agricultural, commerce, public health and household use off the market. Accumulating experience suggests that post-market epidemiological surveillance of pesticide safety is essential to ensure public health (6). Post-market surveillance has revealed that as many as 25 million agricultural workers worldwide experience unintentional pesticide poisoning each year (32) and it has also been suggested that pesticides on the market currently may cause cancer in humans (16-32).

The epidemiologic evaluation of individual pesticides for human carcinogenicity has been hampered by inadequate exposure assessment. Early occupational epidemiological studies inferred pesticide exposures from occupational or industrial classifications of work histories (14-32). Exposure assessment methods have progressed from using crude surrogates, such as farming or living on a farm, to identifying specific chemicals that may contribute to disease risk. Additionally, information on determinants of exposure, such as application methods, use of personal protective equipment, and attitudes regarding safe work practices can be collected by questionnaire or personal interview. Exposure estimates can be further improved through the use of integrated metrics such as exposure algorithms that have been used in the Agricultural Health Study (14,32,38). Pesticide exposure assessments are more accurate and precise when information is collected prior to disease onset, because most exposure cannot be assessed

accurately (32). Time since application and disease can influence recall of exposure as well as interpretation.

The primary' goal of exposure estimation in epidemiology is to correctly rank individuals with regard to exposure level in the study population (32). To reduce exposure misclassification, it is critical to separate the non-exposed from the low- exposed, moderately exposed, and highly exposed individuals.

POPULATIONS DISPROPORTIONATELY AFFECTED BY AGRICULTURAL WORK-RELATED CANCERS

Workers with occupational exposures to pesticides on average have significantly greater exposure than the rest of the population. In the United States, pesticides with the highest acute toxicity are know as 'restricted use' pesticides, and can only be sold to individuals with certification in the safe handling of these chemicals. Applicators who apply these pesticides are generally required to obtain formal instruction in the safe use, handling and storage of these chemicals. Workers in developing countries and migrant or seasonal agricultural workers in the United States rarely have adequate training in the use of 'restricted use pesticides'. These populations are probably disproportionately affected by the adverse health effects of these pesticides. These populations are difficult to study epidemiologically because cancer tends to take about 10 to 20 years to develop in an individual exposed to a biologically sufficient dose (33). Further studying the association of exposures in transient seasonal agricultural workers and their families (34-37) with cancer has rarely been possible. Innovative study designs coupled with modern technology may allow us to conduct studies of cancer risk among seasonal workers in the future; however studies with adequate statistical power and rigorous exposure assessment, have yet to be fully developed.

PROSPECTIVE COHORT STUDIES: SOME IMPROVEMENTS IN DESIGN

In order to mitigate the limitations of previous epidemiological efforts scientists at the National Cancer Institute in collaboration with other federal agencies (i.e., NIEHS, USEPA, and NIOSH), designed and initiated the previously-mentioned prospective study known as the Agricultural Health Study (AHS) of occupationally exposed pesticide applicators in two important agricultural states (i.e., Iowa and North Carolina) (38). Both farmers and commercial pesticide applicators and the non-occupationally exposed spouses of farmer applicators constitute the study population of 89,658 participants. A more complete discussion the AHS is contained in the report by Dr. Laura Beane-Freeman (this issue).

In summary, thirty heavily used pesticides have been evaluated by the Agricultural Health Study as of September, 2008 (14-31). Because the observed exposure-response associations for many of these pesticides were not hypothesized *a priori* and because of the limited study of their biological plausibility, study findings should be interpreted with caution. Nonetheless the results are provocative. Twelve of the thirty pesticides used by millions of people world-wide were observed to show an increased risk of some cancer with increasing use of the pesticide based on limited numbers. Significant associations were observed for prostate, lung, bladder, pancreas, and colon cancer as well as for, leukemia and multiple myeloma. The pesticides observed to show significant positive effects included herbicides, insecticides and chemical fumigants. While a wide variety of chemical were involved, not all chemicals from the same chemical class showed significant associations with cancer. The AHS is evaluating the consistency of these findings by re-evaluating the links between pesticides and cancer and by assessing the mode of action of these pesticides. Studies with a prospective design and comprehensive exposure assessment can provide valuable information concerning the potential link between pesticides and cancers. However, it is essential that an independent panel of

experts such as those convened by IARC or the USEPA make a determination about the adequacy of evidence regarding the human carcinogenicity of a particular pesticide.

CAN NON-GENOTOXIC CHEMICALS BE HUMAN CARCINOGENS?

The majority of pesticides observed to show a significant exposure-response association with a particular cancer in recent epidemiological studies were not observed to be genotoxic in the standard battery of laboratory test currently used in pre- market screening of commercial products (14,32). This perplexing observation may suggest recent epidemiological findings are erroneous. Alternatively, it may indicate although the existing battery of tests used for regulatory purposes have successfully kept a large number of genotoxic human carcinogens out of the market place; some non-genotoxic human carcinogens have passed through the existing screening procedures (14).

ALTERNATIVE BIOLOGICAL MECHANISMS

Several alternative mechanisms are being explored within the AHS and other studies:

Epigenetic mechanism

Epigenetic events are responsible for both normal and vital processes that keep cells working in a healthy state and also for abnormal and pathological processes associated with cancer development. Epigenetic events include heritable alterations in gene and chromatin expression without accompanying changes or mutations in the DNA sequence. Knowledge of epigenetic mechanisms within the cells is developing rapidly and holds great promise for research related to cancer etiology, prevention, early diagnosis and treatment.

Although other mechanisms are being explored, three major mechanisms seem to account for the major vital epigenetic cellular control measures within the cell including: DNA methylation, covalent post-translational modifications of historic proteins, and RNA-mediated gene silencing. Once epigenetic patterns of DNA methylation and histone acetylation have been established, they are propagated over many cell generations. Disruption of one of these two epigenetic mechanisms will automatically affect the other and this close communication seems to be at work in both the normal and the diseased cell (38-41).

Current research *suggests* that aberrant epigenetic changes such as those discussed above can promote tumor development. Better understanding of the environmental and the endogenous factors that trigger these epigenetic changes is vitally needed. Environmental pollutants such as pesticides, metals (arsenic, nickel, cadmium), aflatoxin, ionizing radiation, tobacco smoke, and different infectious agents are suspected to have a potential effect on DNA rnethylation, chromatin organization and function, and histone as carriers of specific epigenetic information. Growing evidence suggests that the deregulation of epigenetic information in somatic cells caused by environmental pollutants can alter gene expression in a heritable manner, leading to malignant transformations (39-42).

Gene-environment interaction

Prostate cancer is significantly more frequent in farm populations compared to the general population (14). In the AHS, we observed a significant elevation in risk among men with a family history of prostate cancer (42) that used chlorpyrifos, fonofos, phorate, coumaphos, pymethrin, and butylate, suggesting genetic susceptibility among these subjects. To better understand this observation, we have launched a nested case-control study within the AHS cohort. Buccal cell DNA will be used to determine if selected pathways could help explain the observation by means of a gene-environment interaction. By using the latest biotechnology

available, we will explore a large number of pathways including metabolic, hormone regulatory, lipid metabolism, telomere regulatory and others.

Telomere length

Since some leukemia's and lymphomas are often preceded by chromosome instability, several studies are evaluating the length of the chromosome telomeres in relation to environmental exposures and cancer risk. Telomeres shorten with age and with exposure to some exogenous agents. Telomere length controls the stability of the chromosome and shortening the telomere after exposure to selected pesticides may explain, in part, the epidemiological associations observed between selected pesticides and cancer risk (14).

CONCLUSION

Exposure to pesticides is very common world-wide. Currently, only two pesticides, arsenical insecticides and TCOD (a dioxin) have been designated by IARC as known human carcinogens, but many others with world-wide use are suspected human carcinogens. Few pesticides on the market today are directly genotoxic and their role in human carcinogenesis will be questioned as long as the epidemiologic data are limited and alternative non-genotoxic mechanisms are not established. Rapid progress in our understanding of non-genotoxic carcinogenic mechanisms is being made in the biomedical research arena. While no one study can provide all the evidence needed to evaluate the carcinogenicity of pesticides as human carcinogens, prospective cohort studies with comprehensive exposure assessment are likely to greatly increase our understanding. A prospective cohort study also allows for pertinent biological specimens to be collected at appropriate periods of time to examine the biological plausibility of the epidemiological observations. The design strengths of prospective studies should help increase our scientific understanding of the links between pesticide exposure and cancer and other diseases. Better scientific understanding coupled with effective public health programs should greatly reduce the human disease burden currently caused by pesticide exposures.

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