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The Value of Human Testing of Pesticides

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ABSTRACT

Recently, the issue of using human volunteers as subjects for studying the potential toxicity of pesticides has received public attention through the media and subsequently in the regulatory arena. The debate has focused on whether such studies are ethical *per se* and if data from these investigations should be used for regulatory decisions. The precipitating event that prompted the current debate was the enactment of the Food Quality Protection Act (FQPA) of 1996. The FQPA, which amended the two laws governing the regulation of pesticides in the United States, requires the Environmental Protection Agency to reassess all of the nearly 10,000 tolerances (maximum allowable residues in food) and exemptions from tolerances that were in place when the law went into effect. When reassessing tolerances the U.S. Environmental Protection Agency (USEPA) reviews the data, including toxicology, available on each pesticide to determine if they are adequate to allow the Agency to make the necessary safety finding. Historically, it had been considered acceptable to conduct and use data from studies of exposure to chemicals (including pesticides) of human volunteers if these studies were conducted according to specific criteria as outlined in the Helsinki Declaration and Common Rule. Now this philosophy is being challenged and the USEPA is faced with answering the question of whether pesticides should be viewed as different, from an ethical standpoint, from other chemicals, and how such data should be used in the risk assessment process.

The following paper makes an argument for the use of human volunteer testing of pesticides applying the logic that, if one wants to protect humans from the potential harm that may occur from eating foods containing pesticides, one must use the best possible data available. There can be little doubt that the best data for predicting the toxicity of a chemical in humans is to obtain and use human data, as long as it is obtained in an ethical manner.

Key Words: testing, human, pesticides.

INTRODUCTION

In my opinion, it seems only sensible to use human data, whenever possible, when determining the potential toxicity of any chemical to which the public is exposed.

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This is particularly so for pesticide residues on foods because we are all potentially exposed to such foods. After all, pesticides, like many nonpesticide chemicals, are inherently toxic! One could make the argument, as some have, that the logical solution to this potential problem is to just ban the use of pesticides in food production. However, I submit that this is neither practical nor desirable. First, eliminating the use of pesticides in food production would dramatically increase the cost of most, if not all, types of food. While this increased cost would not be an undue hardship on affluent members of our society, it certainly would be for the less fortunate. Many pesticide-free foods (labeled as "organic") are increasingly available, and one should have the right to buy and consume such foods if he/she desires.

In addition to the economic considerations, in my view many types of food would not be as safe as they are with the use of pesticides. For example, before the development of pesticides that prevent damage to corn and peanuts with resulting mycotic infestation, mycotoxin contamination of these crops was a serious problem. Many of these mycotoxins are highly toxic and remain the cause of liver toxicity and liver and esophageal cancer in many parts of the world. Another example of how the use of pesticides has improved the quality and healthfulness of food is through the use of rodenticides and fumigants. Prior to their use, the loss due to bacterial contamination of food from rodents and insects during storage and handling was much greater than today. It would be impossible to store and ship foods as efficiently and safely as we do today without them.

I share the view of others that the abundance and relative low cost of foods that we enjoy today is a direct reflection of a combination of the use of pesticides, fertilizers, more efficient agricultural methods and the development of new and more productive strains and species of plants and animals. To delete pesticides from this equation would be counterproductive. That being the case, i.e., that pesticides are an integral part of our food production and will continue to be for the foreseeable future, it is incumbent that we make sure that any residues that are present on food do not present a health hazard to humans consuming those foods. As noted before, pesticides are toxic chemicals, not unlike other chemicals to which we are exposed in our air, water and working environment.

In this context, I offer the following arguments in support of the value and need for the testing of pesticides in human volunteers. The logic underlying this view can be summarized in the simple paradigm below.

Protecting Humans = Human Risk Assessment = Best Possible Data = Human Data

PROTECTING HUMANS FROM THE POTENTIAL HAZARDS OF PESTICIDES

There is a long history in the United States of legislative and regulatory efforts to protect humans against the deleterious health effects from exposure to pesticides, as well as other chemicals. Before the Food Quality Protection Act was enacted (FQPA 1996), which probably represents the most significant and far-reaching piece of environmental legislation of the decade[1,2], pesticide residues in some processed foods were considered to be "food additives" and regulated under Section 409 of the

Federal Food, Drug and Cosmetic Act (FFDCA). If the pesticide residue was expected to exceed the tolerance level for a "raw" agricultural commodity allowed under FFDCA 408, it became necessary to establish a separate food "additive" regulation for the "processed" food under FFDCA 409. However the *Delaney Clause* in FFDCA 409 prohibited the establishment of food additive regulations for any substance "..."*if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal*". One of the primary reasons for enacting the FQPA was to address what was termed the *Delaney Paradox*, *i.e.*, regulating the presence of pesticides in *raw* and *processed* food differently.

FQPA solved this problem by unifying the setting of tolerances. Pesticide residues in both raw and processed foods are now regulated only under Section 408 of FFDCA, which does not contain a prohibition against setting tolerances for carcinogens. The Delaney Clause is no longer applicable for pesticides. Instead, FQPA provides for a single uniform health-based standard for pesticide residues in both types of foods; that is, that there should be "*reasonable certainty of no harm*" associated with exposure to residues in the food for which the tolerance is established.

Other noteworthy features of the FQPA are that this new safety standard, unlike the Delaney Clause, applies to *all health risks*, not just cancer. It also directs the USEPA to consider *cumulative effects* and *common mechanism of action* in its risk assessment. In practice "cumulative effects" involves the combining of exposures from the different routes of exposure, *e.g.*, inhalation, oral and dermal. Although a given source of pesticide exposure may involve primarily a single route of exposure, other routes may add to the overall dose. For example, if a person uses a can of insecticide spray in his/her house, there is a potential for inhaling the pesticide, getting it on one's skin or even on food in the vicinity. The total of these routes represents the true exposure to the individual. "Common mechanism of action" requires the Agency to combine, for risk assessment purposes, different kinds of pesticides if they work through a common mode of action. For example, if a person were exposed to several different types of organophosphate pesticides (OPs) that act via a common mode of action, *e.g.*, choline-esterase inhibition, then the different OPs would be totaled for exposure purposes in the risk assessment.

RISK ASSESSMENT

The object of this section is not to define or restate the risk assessment process, but to draw on those issues that impact the use and need for human data. There are essentially two separate evaluations that occur before one can be confident that a pesticide residue on food does not present a health hazard to the people consuming that food. The first step is to establish a *reference dose*, usually expressed in mg/kg body weight/day, which is a hazard value derived from the available toxicology database. This "reference dose" represents the maximum amount of daily exposure to all sources of that pesticide that can occur with "reasonable certainty of no harm". The second step is to establish a *tolerance level* for the pesticide. The "tolerance level" represents the amount of pesticide that is expected to remain on a given food at the time of harvest. Different tolerances may

be established for the same pesticide for different crops. If exposure at the tolerance level for a specific use were estimated to be greater than the reference dose, then it is likely that this particular application of the pesticide would not be allowed. If anticipated exposure from a new use would yield an *aggregate exposure* that exceeded the reference dose for the pesticide, this new use would not be approved unless adjustments, *i.e.*, exposure reduction or cancellation, were made in the already existing uses.

To establish the reference dose, the USEPA depends primarily on a series of required toxicity studies conducted in laboratory animals to characterize the potential human health risks that may ensue from exposure to pesticides. From these studies, the Agency selects the most appropriate endpoints of toxicity to use in risk assessment. If a "most appropriate" endpoint or species cannot be determined from the data set, then the Agency defaults to the use of the most sensitive endpoint(s) measured in the most sensitive sex/species to identify the highest dose that produces no adverse effects for this endpoint; referred to as the "No Observed Adverse Effect Level" (NOAEL). The Agency then uses this value as the basis for a series of mathematical exercises to estimate a "safe level" or, in the case of the FQPA, a level that would provide "reasonable certainty of no harm" in a similar fashion as is done by the Food and Drug Administration for setting safe levels for nonpesticide food additives.

As part of this mathematical exercise for setting the reference dose, the Agency uses additional "safety" or "uncertainty factors". First, if the best NOAEL is derived from an animal study, this NOAEL is divided by an uncertainty factor (10× is the default) to extrapolate from the animal to the human. This is referred to as the "*10× interspecies uncertainty factor*" and assumes that the human is more sensitive to exposure to the chemical than is the test animal. Then this number is divided further by another uncertainty factor (10× is again the default) to account for the range of sensitivities within the human population. This is called the "*10× intraspecies uncertainty factor*". In other words, the NOAEL by default is divided by at least 100 to set a reference dose for a given pesticide. Other uncertainty factors might also be required, if the data warrant. Traditionally, these additional factors were not needed when deriving a chronic reference dose (also known as the "acceptable daily intake" or an "acute reference dose") for a food use pesticide. This is what was required until passage and implementation of the FQPA.

However, another major part of the FQPA that is unique, and directly impacts on the issue of human testing, requires the USEPA to apply an additional "safety factor" of 10× when setting a pesticide reference dose for food to provide for special protection to children. In practice, this means that the NOAEL could be divided by 1000 or more for setting tolerances. The only way the additional 10× safety factor can be set aside (*not used*) is to have reliable scientific data that show that the developing fetus, infant and child are not uniquely different from adults in terms of the dose that produces a given effect. While this safety factor seems reasonable and supported by science (the young are often more at risk to harm than adults at a given dose), it can have profound ramifications on a given pesticide when setting the reference dose.

BEST POSSIBLE DATA

If the goal of the risk assessment process is to assure "reasonable certainty of no harm" from a pesticide residue in foods, then by default the most reliable data should be those that provide the most certainty that the risk assessment is an actual representation of potential risk. Although data from a myriad of animal and *in vitro* studies are submitted to the USEPA by the registrant, it needs to be remembered that these are not human data, although they certainly have application to humans. While animals have many of the same characteristics as humans in that they are reasonable surrogates for many of the toxicity endpoints of importance, they are not humans! Because of this, there is always, by necessity, a certain amount of uncertainty as to just how applicable the animal data are to humans. The best possible data to predict what would happen in humans as a result of exposure to pesticides from the handling and ingestion of foods are human data.

HUMAN DATA

There are two essential questions that need answering before discussing human data *per se*. First, what type of human studies provides the most relevant data for risk assessment, and second, can such data be obtained in an ethical manner? In practice, these two questions cannot be isolated from each other, but need to be considered in concert. For example, while there may be a given toxicology endpoint of interest, it may be impossible to obtain such data without causing harm to the human test subject. Obviously, one would not be interested in obtaining this type of data. In contrast, if one can obtain human data in a way that will not cause harm to the human subject, and if such data could benefit a risk assessment, then such data could be obtained and used.

While it is not the object of this paper to outline the procedures that are required for human studies, suffice it to say that human volunteer studies with pesticides, as with other chemicals, can be conducted in an ethical manner. There are several thoughtful arguments for why human testing is ethical, and highly specific criteria for how such studies should be conducted have been delineated (Declaration of Helsinki 1964, 1975, 1983 and 1989; Common Rule 1991). It needs to be remembered that there is nothing inherently unique about a pesticide in terms of its biological interaction that would suggest that human studies with such chemicals are any different than those conducted with nonpesticide chemicals. Once a pesticide enters the body, it behaves as would any other xenobiotic that interacted with the same organ, tissue or cell. As with other chemicals, pesticide toxicity is a direct reflection of its dose and biological target. Typically, the exposure chosen for human studies is a fraction of the most sensitive NOAEL or endpoint of interest derived from the animal studies. The human volunteer usually does not exhibit any clinical manifestation of exposure other than the presence of the material in his/her blood and urine.

In my opinion, as noted in the recent joint report of the USEPA FIFRA Science Advisory Panel and USEPA Science Advisory Board (USEPA 2000), the most appropriate type of data at this point would be in the area of absorption, distribution, metabolism and excretion (ADME). ADME data are easily obtainable in human

subjects without undue risk to the human volunteer participating in these studies. The value of these studies is that one can compare the findings with the same endpoints in the animal studies, thereby providing more or less confidence that the animal data are predictive of what might occur in humans. Additionally, such human data could provide insight for conducting additional animal studies that would give further assurance that the "total" data package provides the best chance to assure the public that their food supply has a "reasonable certainty of no harm" as required by the FQPA.

It may surprise the reader of this opinion that human studies are already required in some situations by the USEPA. The focus of these studies is to establish the level of exposure of workers engaged in mixing, loading, application and workers entering the field after pesticide application. It is noteworthy that these workers would be considered "volunteers" in that they have to give informed consent, *etc.* before the exposure analysis. However, the exposure conditions are not "controlled", in the same way as they would be in a toxicity study, *i.e.*, no pre-specified dose is "applied" to the worker. Exposure is only controlled and minimized by the use of specific types of clothing and other personal protective equipment. In addition, these studies typically do not include any toxicological evaluations, although measurements of biomarkers of exposure are increasingly being incorporated into the study design. However, logic would suggest that a well-controlled, scientifically based human volunteer toxicity study would be more appropriate to conduct *prior* to exposing workers. This view is particularly convincing when considering "new" pesticides that have not yet been introduced into commerce. The same could be said for pesticides that are used in and around the home. Why would one want to wait until the pesticide is already being used and people are being exposed before understanding the potential hazard to humans?!!

In summary, if, as noted previously, the seminal reason for conducting a risk assessment for pesticides in or on foods is to *protect humans* consuming these foods, then it only makes sense to obtain and use human data. If fact, one could make the argument that it is "unethical" not to use human data, as long as it is acquired in an ethical manner.

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FOOTNOTES

1 The reader is directed to the USEPA OPP Website (http://www.epa.gov/pesticides) for more information on the FQPA.

2. The reader is directed to Robertson and Gorovitz (2000) for a detailed summary of the legislative and political history of the FQPA.