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For Science-Based Public Policy

"Our greatest responsibility is to be good ancestors."
…Jonas Salk

How Scientific Uncertainty Affects Food Safety Evaluations of Pesticide Residues

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We are pleased to attribute the cover photograph of the earth to Harrison H. Schmitt, Ph.D. This photograph was taken during the 1972 Apollo 17 flight on which Dr. Schmitt served as Lunar Module Pilot. Dr. Schmitt, the last person to step onto the moon, is Chairman Emeritus of The Annapolis Center.

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Introduction

"Consumer opinion surveys indicate that much of the U.S. public believes that pesticide resides in food are a serious cancer hazard[i]". To address these concerns, the Federal government "assures" the safety of food by placing limits on the amount of synthetic pesticide residues found in food. These limits, known as tolerance levels, represent the maximum level of synthetic pesticide residue allowed in raw and processed foods. Tolerances have been set for specific chemicals on specific food commodities. A single synthetic pesticide may have many tolerances, depending on different crop uses. If residues in or on a food product exceed the established tolerance levels, existing law authorizes the government to seize foods and impose civil penalties or even seek criminal charges.

Contrary to the opinions of an overwhelming majority of scientists, polling has shown that much of the public believes that there is a "cancer epidemic". Since many Americans have been led to believe pesticides are a major cause of cancer, one focus of pesticide regulatory policies has been on exposure and the potential of a pesticide to cause human cancer, usually based on animal tests. However, regulatory policy that focuses on traces of synthetic chemicals is based on misconceptions about those animal cancer tests. Although 99.99% of the pesticides humans ingest are natural, the focus of regulatory policy is on synthetic pesticides. Plants in the human diet contain thousands of natural "pesticides" produced by plants to protect themselves from

99.99% of the Pesticides Americans Consume are Natural

Each day a person consumes 1.5 grams of natural pesticide vs. 0.09 milligrams of synthetic pesticide

If you drink 13 grams of roasted coffee per day, you are ingesting 765 milligrams of natural toxins

Several hundred milligrams of a natural toxin (phenolics) are found in other plant foods such as:

- 100 milligrams flavonoids and glucosinolates
- 100 milligrams saponins and legumes
- 100 milligrams potato and tomato toxins
- several hundred milligrams of whole wheat, rice, grains

insects and other predators: 71 have been tested and 37 are rodent carcinogens.[ii] Many thousands of natural pesticides have been identified in food, and each plant contains its own set of such defenses. By definition, natural pesticide levels in a plant can greatly increase in order to defend the plant if it is stressed or damaged, such as during a pest attack.[iii]

Some people assume that since natural chemicals are part of human evolutionary history, whereas synthetic chemicals are recent, the mechanisms that have evolved in animals to cope with the toxicity of natural chemicals will fail to protect against synthetic chemicals and pesticides. This assumption is flawed. "Humans have many natural defenses that buffer against normal exposures to toxins and these are usually general, rather than tailored for each specific chemical. Thus they work against both natural and synthetic chemicals. Examples of general defenses include the continuous shedding of cells exposed to toxins — the surface layers of the mouth, esophagus, stomach, intestine, colon, skin and lungs are discarded every few days; DNA repair enzymes, which repair DNA that was damaged from many different sources; and detoxification enzymes of the liver and other organs which generally target classes of chemicals rather than individual chemicals. That human defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world. If a herbivore had defenses against only a specific set of toxins, it would be at great disadvantage in obtaining new food when favored foods became scarce or evolved new chemical defenses."[iv]

Humans have not had time to evolve a "toxic harmony" with dietary plants. The human diet has changed greatly during the last few thousand years. Very few of the plants that humans consume today, e.g., coffee, cocoa, tea, potatoes, tomatoes, corn, avocados, mangos, olives and kiwi fruit, were present in a hunter-gatherer's diet. Natural selection works far too slowly for humans to have evolved specific resistance to food toxins in such newly introduced plants.

Development of the Regulatory Process

In 1996, Congress changed the approach to regulating synthetic pesticide residues when it enacted the Food Quality Protection Act (FQPA). Instead of establishing tolerances for raw food (i.e. agricultural commodities) and processed food according to distinct cancer-related criteria as under the Delaney clause in the Federal Food, Drug, and Cosmetic Act, the new law established a single health-based standard for synthetic pesticide residues in raw and processed food. The new standard takes into account the aggregate risk from dietary exposure and other non-occupational sources of exposure. This would include drinking water and residential lawn uses, and the cumulative risk from exposure to residues from multiple pesticides having a common mechanism of toxicity. The 1996 statute also changed the standard by which the tolerance is set. Under the new law, the U.S. Environmental Protection Agency (EPA) may only establish a tolerance if there is *a reasonable certainty of no harm*, considering all combined sources of exposure. In addition, when establishing a new tolerance or when reevaluating an old tolerance,

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EPA must now explicitly focus on the exposure and risks to children. Finally, the revised statute also requires EPA to develop and implement a comprehensive screening program specifically for estrogenic and other endocrine effects.

Taken together, FQPA dramatically changes the way pesticide tolerances are set. Because of the significance of these changes, Congress directed EPA to review all old pesticides by 2006 to assure that pesticide residue limits and uses meet the new tolerance safety standard. EPA must reassess more than 9,700 tolerances that were in effect in 1996 for more than 450 pesticide active ingredients. EPA has the authority to revoke tolerances now in effect if the Administrator finds that the sum of the exposure from all the tolerances for a given active ingredient exceeds "safe" levels.

When President Clinton signed the FQPA on August 3, 1996, he called it "the peace of mind act," in the belief that it will give parents and consumers much greater confidence in the safety of their food supply. More than six years after passing this new law, many are now assessing how well it is protecting public health and whether it has truly provided the peace of mind originally intended.

The Challenge in Assessing Risk

Because there is rarely direct human health data on the potential impact of exposure to pesticide residues in food, risk assessors must often rely on animal toxicity tests and rough estimates of potential exposure to estimate the possible impact on humans. Almost everyone involved recognizes that this estimation process is fraught with uncertainties. Animal sensitivities to chemicals often differ dramatically among species. Furthermore the animals tested in laboratories are often exposed to very high levels of the pesticide, raising questions about the nature of the effect seen and its relevance to the low doses that humans generally receive.

The practical limits on data acquisition and the inherent uncertainties in pesticide risk assessment make EPA and other government risk assessors dependent on certain assumptions to bridge the data uncertainties. Many of these assumptions, however, are not neutral in predicting the likely risk. Some may tend to underestimate the likely risk, though most over-estimate it.

As discussed by the General Accounting Office (GAO) in its October 2000 Report to Congress, *Environmental Protection Agency, Use of Precautionary Assumptions in Health Risk Assessments and Benefits Estimates*, many of the assumptions used in EPA's risk methodologies are selected with the intent to err on the side of over-estimation. GAO reasons that EPA's use of precautionary assumptions is influenced by its mission to protect human health and safeguard the environment, and by key statutory requirements, which require EPA to assure protection with an "adequate margin of safety." The National Research Council in a 1994 report, *Science and Judgment in Risk Assessment*, affirmed the conservative nature of these assumptions. According to the NRC report, EPA's assumptions "lead to risk estimates that, although plausible, are

believed to be more likely to overestimate than to underestimate the risk to human health and the environment." The end result, however, has been a risk assessment process built on a series of protective assumptions that may be several orders of magnitude above the true estimate of risk. Many risk assessment experts question how well these numbers inform the public and whether these numbers should be used to make decisions.

How Far Under No-Effect Levels?

Most pesticide residue tolerances, however, are based on animal toxicity testing. Risk assessors review the animal data to determine the "no observed adverse effect level" (NOAEL) and "lowest observed adverse effect level" (LOAEL). As explained in its guidance[v] on setting tolerances, for the past thirty years EPA has routinely used at least two ten-fold safety or uncertainty factors when relying on animal testing to assess the potential for human hazard posed by exposure to chemicals. The two ten-fold factors used most often are designed to address both the extrapolation of the results of animal studies to humans, and the variability and sensitivity within the human population. Three additional safety factors may then also apply to address: (1) uncertainty in extrapolating from subchronic to chronic data; (2) absence of data; and (3) uncertainty in going from a LOAEL level to a NOAEL level. Finally, an *additional* safety factor may be applied to address other scientific uncertainties in the study (such as small sample size or poor exposure characterization) if the risk assessor believes existing factors do not explicitly account for the uncertainty. According to the Agency, the composite uncertainty/modifying factor can be as high as 10,000, and often is as high as 1,000[vi].

This conservatism of two to four orders of magnitude, however, is often compounded by the use of "worst-case" exposure data.[vii] The Pesticides Data Program with the U.S.D.A. has built up considerable body of data on pesticide residues on foods. That, combined with use of probabilistic models has led to significant improvements in dietary safety.

In the areas of drinking water and residential exposure, the agency's capabilities lagged behind the capabilities of dietary exposures. In those situations, assumptions sometimes lead to "worst-case" exposure scenarios rather than scenarios derived from actual use practices, such as actual application rates, numbers of applications, percent crop treated, and pre-harvest intervals.

FQPA Builds in Additional Conservative Factors

Despite the clearly conservative, health-protective nature of the risk assessment methodologies in place, FQPA added two additional conservative factors – the need to address cumulative and aggregate risks, and the need to develop a separate safety factor for children.

Under the new law, the agency must assess aggregate exposures (including exposure from dietary, drinking water, and non-occupational residential sources) and conduct cumulative risk assessments (combined exposures from pesticides having a common mechanism of toxicity). In

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other words, instead of looking at the incremental risk posed by exposure to one pesticide on one food source, the new Act requires EPA to assess the risk from a class of pesticides on all food sources. In addition, the EPA must also develop an exposure model to calculate the likelihood that an individual will be exposed from nonfood sources, such as through pesticide lawn or household applications. The complexity of these requirements is significant. When the law was passed, the Agency did not possess the tools or the scientific knowledge to accomplish this assessment. This has resulted in a difficult and demanding catch-up game.

The first class of pesticides to undergo cumulative risk assessment is the organophosphates – older pesticides that are still used in agriculture but are mostly no longer used in homes and gardens. Because of the prevalence of the pesticides, the agency will have to assess all possible exposures from the food supply as well as possible exposures from other unrelated sources.

FQPA also requires EPA to add a new safety factor to assure protection adequate protection for children if there is insufficient data on how the pesticide can affect their health. EPA must (1) consider children's potential special sensitivity and exposure to pesticide chemicals; (2) explicitly determine that the tolerances are safe for children; and (3) use an additional ten-fold safety factor to account for uncertainty in the data with regard to children, unless it determines that a different safety factor is adequate. Finally, the new law also requires EPA to assess the ability of a pesticide chemical to disrupt the human endocrine system.

Based on EPA's implementation plan published in 1997, EPA would impose the 10-fold safety factor if the agency lacked complete and reliable data to assess pre-or postnatal effects. A safety factor between 3 and 10 would be applied if the data were incomplete, depending on how much information was missing. No safety factor would be required if there was sufficient data to demonstrate a lack of potential pre-or postnatal effects. Of 105 tolerance decisions made by EPA between August 1996 and March 2000, EPA required an additional safety factor for children in 49 cases.[viii]

When Does Too Much Conservatism Become a Bad Thing?

Most scientists view the use of safety factors as appropriate in addressing uncertainties; the question, of course, is one of degree. Narrowly focused regulatory agencies, such as EPA, have little incentive but to err on the side of extreme safety, even if it means compounding safety factors and assumptions to the point where even common sense would question the validity of the process and the value of the resulting estimate. In other cases, lowering safety factors is deterred by the work required in conducting or reviewing new studies. FQPA compounded this problem by requiring the application of yet another safety factor that arguably was already accounted for in the pre-existing tolerance setting process.

If unnecessarily reducing use of synthetic pesticides makes fruits and vegetables more expensive, thereby decreasing consumption, then the cancer rate may increase.

Decisions that are based on overly conservative estimates could place at risk the availability of wholesome foods, such as fruits and vegetables, or at a minimum create the impression of increased risk from their consumption – an outcome that would actually thwart public health efforts aimed at improving the diets and health of Americans. While there is no convincing scientific evidence that synthetic chemical pollutants are important as a cause of human cancer, regulations targeted to eliminate minuscule levels of synthetic chemicals are enormously expensive. The EPA has estimated that environmental regulations cost society $140 billion/year.[ix] Others have estimated that the median toxic control program costs 146 times more per hypothetical life-year saved than the median medical intervention. Attempting to reduce tiny hypothetical risks has other costs as well. If unnecessarily reducing use of synthetic pesticides makes fruits and vegetables more expensive, thereby decreasing consumption, then the cancer rate may increase.[x] Similarly, overly protective risk estimates may also force from the market the very products needed to combat the spread of vectors of potentially deadly viruses, such as the West Nile virus. Such potentially negative results for our society would appear to be a classic example of the "law of unintended consequences" brought about by extreme precaution.

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For additional information about Rational Thinking vs. Emotional Responses, see the Center's first paper in this series, "*How Can I Tell Good Science?"* which outlines the Center's *Annapolis Accords for Risk Analysis* and *Cost-Benefit Analysis.* In addition, please see The Center's *Progress, Precaution, and the Precautionary Principle* paper.

Websites for Additional Information:
http://www.epa.gov/opppsps1/fqpa/backgrnd.htm#background
http://www.gao.gov
http://www.gao.gov/archive/2000/he00175.pdf
http://potency.berkeley.edu/listofpubs.year.html

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[iv] Gold LS, Slone TH, and Manley NB, Pesticide Residues in Food and Cancer Risk: A Critical Analysis, in *Handbook of Pesticide Toxicology*, Second Edition (R. Krieger, ed.) Academic Press, (2001). http://potency.berkeley.edu/text/handbook.pesticide.toxicology.html

[v] "Office of Pesticide Program's Policy on Determination of the Appropriate FQPA Safety Factor(s) For Use In Tolerance-Setting Process" February 28, 2002. http:www.epa.gov/pesticides/trac/science/determ.pdf

[vi] *Ibid*., page 26

[vii] Gold LS, Slone TH, and Manley NB, Pesticide Residuals in Food and Cancer Risk: A Critical Analysis, in *Handbook of Pesticide Toxicology*, Second Edition (R. Krieger, ed.) Academic Press, (2001). http://potency.berkeley.edu/text/handbook.pesticide.toxicology.html

[viii] "Children and Pesticides: New Approach to Considering Risk Is Partly in Place" September 2000, GAO/HEHS-00-175, page 4. http://www.gao.gov/newitems/he00175.pdf

[ix] Ames BN, Gold LS, Misconceptions about Pollution, Pesticides, and the Prevention of Cancer, in *The Standard Handbook of Environmental Science, Health, and Technology*, J. Lehr ed. (2000)

[x] *Ibid*.

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