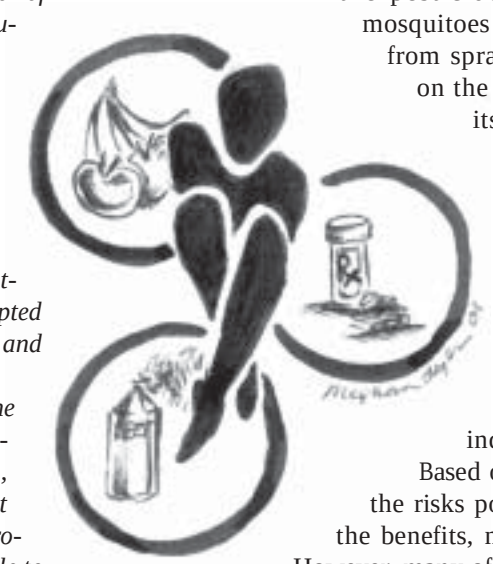
Synergy: The Big Unknowns of Pesticide Exposure

Daily combinations of pesticides and pharmaceuticals untested

By John Kepner

Pesticide exposures in the real world are not isolated incidents. Rather, they are a string of incidents marked by combinations of exposures. As a result, scientists have argued for years that toxic exposures to pesticides should be measured as they would normally occur, in combination with one another. Yet, current federal law does not require this type of testing for pesticides on the market, except in very limited instances. This issue has been fueled during the recent West Nile virus spray programs by researchers at Duke University's School of Medicine, who found that exposure to a popular insect repellent when combined with exposure to a popular insecticide caused a synergistic, or magnified, effect greater than the individual chemical effects added together. The debate has also heated up around the question of potential interactions between pesticides and pharmaceuticals. A law requiring the testing of drug-pesticide combinations was adopted by Congress and then dropped by the Food and Drug Administration (FDA) in the 1960's.



How much do we really know about the pesticides that are widely used in our communities, schools, homes, offices, hospitals, parks, on lawns and golf courses and in West Nile virus and other mosquito spray programs? Not as much as we should to be able to make sound decisions that are protective of public health and the environment. Sometimes limitations in protection are a function of a regulatory failure to carry out the mandate of a federal statute. But, in this case, the underlying statutes that govern pesticide use, allowable residues (and exposure), and risk assessment are wholly deficient. The laws simply do not require testing that is ultimately essential in determining the safety of pesticide use, as typically used every day. No amount of improved enforcement of law or additional dollars for EPA will correct this situation until the mandates in law change.

This piece by John Kepner tracks the current situation and history on this critical issue of public health and safety. It leaves us with a greater sense of the importance of efforts to eliminate on a daily basis exposure to pesticides and opt for alternative pest management approaches that do not rely on pesticides. The burden must shift to those who want to use pesticides to show that basic questions of health protection have been answered. Pointing to a pesticide label or citing an EPA pesticide product registration is no assurance of safety. —JF

Introduction

In the summer of 2001, the mosquito-borne West Nile virus hit Maryland. As the media fueled a local panic, the Maryland Departments of Health and Agriculture worked together to monitor, treat, contain and eradicate the disease. Permanone, a synthetic pyrethroid-based insecticide containing the active ingredient permethrin, emerged as the pesticide of choice for combating the adult mosquitoes that could be carrying the virus. Aside from spraying Permanone from foggers mounted on the backs of trucks, the state also instructed its residents to empty standing water on their property to reduce mosquito breeding grounds, and encouraged residents to use mosquito repellants containing the active ingredient N, N-diethyl-m-toluamide (DEET).

Both DEET and permethrin are registered as pesticides by the Environmental Protection Agency (EPA) and have been, or are in the process of being, individually tested for adverse health effects. Based on these results, EPA has determined that the risks posed by these pesticides do not outweigh the benefits, namely killing and repelling mosquitoes. However, many of the residents of Maryland will not be exposed to these pesticides individually. Real world pesticide exposures rarely occur as individual, isolated incidents. Many residents could have applied DEET to their bodies as recommended by the state when the mosquito trucks fog their neighborhoods. Or because permethrin has a half-life of 30 to 38 days, they could be exposed to the combination anytime they are wearing DEET for weeks to come. Although not all pesticide combinations show increased toxicity, recent studies out of Duke University's School of Medicine suggest that the residents of Maryland should be concerned about the potentially damaging synergistic effects of this particular pesticide combination. These studies will be discussed in greater detail below.

What is synergy?

The concept of interaction is fundamental to understanding the processes by which chemical mixtures act. If the effect is simply additive, the sum of the effects is the same as if we were exposed to each chemical individually. Synergy occurs when

the effect of a mixture of chemicals is greater than the sum of the individual effects.[1] (If the effect of a mixture is less than the sum of the individual effects, it is called antagonism).

For example, a population exposed to neither "Pesticide A" nor "Pesticide B" experiences a background level of a certain health effect at 5%. In a population exposed only to "Pesticide A," the effect is seen at 10% (5% + the 5% background). In a population exposed only to "Pesticide B," the effect is seen at 20% (15% + the 5% background). If the two pesticides are simply additive, and not synergistic, we would expect the effect to be observed at 25% (5% + 15% + the 5% background). If the observed effect is greater than 25%, the combination is synergistic.

Prior to 1957, the combined effects of exposure to a group of pesticides was assumed to be additive. However, a study[2] published that year documented for the first time a case of pesticide synergy. The authors postulated that the combined effects of exposure to the organophosphate insecticides ethyl*p*-nitrophenyl benzenethiophosphate (EPN) and malathion would be additive. Instead, there was a 10-fold synergistic effect in rats and a 50-fold synergistic effect in dogs for the acute toxicity of EPN and malathion administered simultaneously.

Regulatory history

Faced with potential interactions between pesticides and pharmaceuticals, the *Food, Drug and Cosmetic Act* was amended with the following in 1962: "Pesticide chemicals that cause related pharmacological effects will be regarded, in the absence of evidence to the contrary, as having an additive deleterious action. For example, many pesticide chemicals within each of the following groups have related pharmacological effects: chlorinated organic pesticides, arsenic-containing chemicals, metallic dithiocarbamates, cholinesterase-inhibiting pesticides." While this language assumed only additive and not synergistic effects, it still considered, for the first time, the adverse impact of cumulative chemical exposures. However, in 1967, FDA abandoned the regulation on the grounds that the "requirement has failed to serve any useful purpose."

During its first 85 years, federal pesticide law did not require testing for adverse health effects of pesticide combinations. In 1996, EPA was required for the first time to consider cumulative pesticide exposures in limited circumstances under the *Food Quality Protection Act* (FQPA). FQPA, which amends the *Federal Insecticide, Fungicide and Rodenticide Act* (FIFRA), recognizes that real-world pesticide exposures do not occur as single discrete exposures to a specific pesticide, but rather in combination to several pesticides at once. Considering dietary exposure alone, U.S. Department of Agriculture (USDA) data shows that apples surveyed from across the U.S. contained 22 different pesticide residues, and peaches surveyed contained 40 different pesticide residues. Many of these residues remain even after thorough washing and preparation of food.

To address the issue of multiple pesticide exposures, FQPA directs EPA to consider combinations of pesticides that have a common mechanism of toxicity when setting tolerances. This means that only if EPA determines that two chemicals have the same toxic mechanism in the body will the agency aggregate the exposure value in its risk assessment calculation. The first result of this mandate was released in June 2002 when EPA published its *Revised Organophosphate Cumulative Risk Assessment,14* in which the agency examined the combined hazard of exposure to all organophosphate pesticides. Although the report was seen as incomplete by the environmental community and criticized by FIFRA's Scientific Advisory Panel, the intent of the report is an important first step in evaluating the combined effects of several pesticides. Unfortunately, the current *Guidance on Cumulative Risk* requires that only chemicals sharing both a common toxic effect and a common mechanism of toxicity be considered in determining pesticide tolerances. In the real world, a liver cannot tell the difference between two cancer-causing chemicals because of the biochemical route each chemical takes to cause that cancer. In other words, if a number of pesticides and other substances cause liver cancer via a number of different pathways, the end result is the same, a diseased liver. EPA should not use common mechanisms of toxicity as a filter to decrease the number of chemicals it considers. This leaves the majority of potential pesticide interactions untested and potentially dangerous.

Medical studies: proof of pesticide synergy

While the first study showing pesticide synergy was published in 1957, the topic has not been studied at the level necessary to adequately inform officials making decisions regarding human health. Despite the lack of depth, many studies demonstrating synergy between pesticides and other commonly used chemicals have been documented in medical literature. In the late 1960's and early 1970's, researchers Samuel Epstein, MD, at the time with the Children's Cancer Research Foundation in Boston, MA and Keiji Fujii, MD, of the National Institute of Hygienic Sciences in Tokyo, Japan published a series of papers[3,4] on the synergistic effects of carcinogens and co-carcinogens found in a variety of common pesticide products. "Co-carcinogens" is a term used to describe non-carcinogenic chemicals that increase the rate of cancer when used in combination with carcinogens. These papers highlighted carcinogenicity between two chemicals used in combination, even when the individual dosages were applied at sub-carcinogenic levels. One study produced the effect even when the chemicals were applied as far as 200 days apart.

Much of the latest research on the synergistic effects of pesticides used in combination has come out of the Duke University Medical Center in Durham, NC. In 2001, researchers in the Department of Pharmacology and Cancer Biology published

a series of papers in the *Journal of Toxicology and Environmental Health* and *Experimental Neurology* looking closely at the synergistic health effects of DEET, the active ingredient in most insect repellents, and permethrin, a pesticide commonly used in community mosquito spray programs, as well as many household bug killers.

To determine the effect of subchronic dermal application of these chemicals on the brain, the researchers evaluated neurological indicators after daily dermal doses of DEET, permethrin or a combination of the two pesticides for varying periods of time, from 24 hours to 60 days. The neurological indicators included: sensorimotor performance and permeability of the blood-brain barrier,[5] increased urinary excretion of 6*B*-hydroxycortisol (a marker chemical poisoning),[6] release of brain mitochonrial cytochrome-c (a result of cell death)[7], and diffuse neuronal cell (cells specialized to conduct nerve impulses) death and cytoskeletal (structural components of the cell) abnormalities.[8] In the first study, DEET alone caused a decrease in the permeability of the blood-brain barrier and impairment of sensorimotor performance, and permethrin alone showed no effect. In combination, the effect on the blood brain barrier and sensorimotor performance was amplified, a "0+1=2" example of pesticide synergy. This "0+1=2" pattern was also seen in the study examining increased urinary excretion of 6*B*-hydroxycortisol. When the researchers looked at the release of cytochrome c as an indicator of brain cell death, no effect was seen when the pesticides were used individually. However in combination, a significant increase in the release of cytochrome c was seen 24 hours after dosing, a "0+0=1" example of pesticide synergy. In the study examining neuronal cell death, damage was seen in all treatment groups, but was accelerated in rats treated with both DEET and permethrin.

The purpose of the Duke studies was to determine a possible link between pesticides and other chemicals used during the Persian Gulf War and "Gulf War Syndrome," neurological disease characterized by headache, loss of memory, fatigue, muscle and joint pain, and ataxia, which causes an inability to coordinate muscular movements. The first work in this area by this team of researchers, published in 1996, studied the combination of DEET and permethrin with pyridostigmine bromide, a drug taken prophylactically to counteract toxic gas warfare agents.[9] The study found that test animals exposed to the three chemicals in combination experienced neurological deficits similar to the symptoms of the Gulf War veterans. However, when the chemicals were administered alone, even at doses three times the level soldiers received, no effects were observed, a "0+0+0=1" effect. The researchers theorized that many of the symptoms might be seen without the pyrido-stigmine bromide and continued to study the interactions of DEET and permethrin.

Neurology experts give three possible reasons for the synergistic effects seen in the above experiments. First, the stress endured by animals when exposed to a combination of chemicals undermines the protective role of the blood brain barrier, allowing the level of toxics to cross into the brain to be 100 times higher. Second, tissue that has been exposed becomes more sensitive and receptive to other toxic substances. Third, certain chemicals bind to enzymes that detoxify the body, making the enzymes unavailable to protect the body from other intruding chemicals. Dr. Goran Jamal, a neurologist at the West London Regional Neuro-Science Center of the Imperial College of Medicine, makes the following comparison, "It's like releasing 200 criminals in London and taking away the police officers that are usually on duty. There is bound to be some damage."

Pesticide-Drug Synergy

In the summer of 1985, 30 year-old Thomas Latimer was leading a good life in the suburbs of Dallas, TX. He was a vigorous, athletic man with a promising engineering career. On one particular Saturday afternoon, Mr. Latimer spent the day mowing the lawn, picking up the clippings and edging the walkways. After about an hour, he began to feel dizziness, nausea, tightness in his chest and a pounding headache. Ten days later, he felt even worse and went to see his doctor.

Over the next six years, Mr. Latimer found himself unable to exercise and suffering from brain seizures. He visited 20 different doctors and underwent numerous tests to determine the source of his medical problems. His symptoms were consistent with organophosphate poisoning, most likely from the insecticide diazinon that had been applied to his lawn. But because his symptoms were so severe and the amount of pesticide he was exposed to was so low, the doctors continued to look for a complicating factor. After further research, a toxicologist, three neurologists and two neuro-ophthalmologists all concluded independently that the popular ulcer drug Tagamet that Mr. Latimer was taking had suppressed his liver, making him more susceptible to pesticide poisoning.

Alfredo A Sudan, a professor of neurology and ophthalmology at the University of Southern California, who conducted extensive tests evaluating an eye disorder that Mr. Latimer developed, estimates that taking a medication like Tagamet "can make a person 100 to 1,000 times more sensitive to organophosphate poisoning."[10]

Conclusion

Synergistic effects between multiple pesticides and/or other chemicals represent one of the greatest gaps in EPA's ability to protect the public from the adverse health effects associated with pesticide use and exposure. The U.S. government recognizes that pesticide exposures occur in combinations and not as unique events, yet has rules and regulations to test only a

limited number of possible interactions. Given that there are over 875 active ingredients currently registered for use, it would be impossible to test all possible combinations, but we must start somewhere. One approach would be to prioritize pesticides most likely to act in combination. The following recommendations would serve as a basis for beginning to look at this very important aspect of pesticide safety:

- **Test for interactions between pesticides commonly used in combination in both agricultural and non-agricultural settings.** This would include testing of groups of pesticides that are commonly used on the same crops, like atrazine and chlorpyrifos, the most common herbicide and insecticide applied to corn.[11] Another example would be DEET, used as an insect repellent and permethrin, used as a mosquito fog.

- **Test for interactions between agricultural pesticides and the most persistent food contaminants.** FDA data shows chlordane, DDE (a breakdown product of DDT), DDT, dieldrin, dioxin, endrin, heptachlor, hexachlorobenzene, and toxaphene are frequent contaminants of the typical U.S. diet.[12]

- **Test for interactions between the pesticides that most commonly contaminate drinking water.** Like all pesticide use patterns, water contamination will vary greatly around the country, so it is imperative that these combinations are tested for synergistic effects. The Wisconsin State Laboratory of Hygiene has found 14 different pesticides contaminating state water supplies.[13]

- **Test pesticides that are most likely to drift and cause non-target exposure.** Based on formulations and methods of application, pesticides often drift far from their point of application. A July 2000 survey of air samples in Fresno, CA, on four separate sampling dates, detected carbaryl, chlorpyrifos and trifluralin.[14]

- **Test interactions between the most common pharmaceuticals and the most common pesticides.** According to the National Defense Research Institute, DEET has been reported to accelerate the dermal absorption of pharmaceuticals and possibly other pesticides.[15]

Recognizing the unlikely reality of testing even the most common pesticide combinations, another approach would be to reduce pesticide risk by limiting exposure. When weighing the benefits of a pesticide against the risks to public health, we must err on the side of safety. In registering pesticides, EPA should assume interactions between chemicals will occur. Limiting exposure, and therefore limiting synergistic health effects, could be accomplished through decreased pesticide use and tighter restrictions to minimize pesticide drift and runoff. For example, ban drift-prone application technologies, like cropdusting and ultra-low volume foggers; establish buffer zones around populated areas; require notification to nearby residents before a pesticide application, so appropriate precautions may be taken; and encourage lower exposure formulations such as containerized baits. By taking the appropriate steps, we could minimize harmful synergistic health effects.

Overall, this deficiency in data and the difficulty associated with its collection calls for a national policy of pesticide use reduction and national adoption of the Precautionary Principle that seeks to avoid pesticide use in favor of alternatives.

John Kepner, project director at Beyond Pesticides, has been with the organization since 1999. He graduated with a B.S. in biology from Pennsylvania State University minor in Human Environmental Relations in 1998.

Endnotes

For a fully cited version of this article, see www.beyondpesticides.org.

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