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Unidentified Inert Ingredients in Pesticides:

Implications for Human and Environmental Health

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Abbreviations:

DHHS	U.S. Department of Health and Human Services
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
NCAP	Northwest Coalition for Alternatives to Pesticides
NPTN	National Pesticide Telecommunications Network
NRC	National Research Council
OECD	Organization for Economic Co-operation and Development
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey

Manuscript Outline

Abstract

Introduction

Inadequate Assessment of the Hazards of Pesticide Formulations

Inert Ingredients Can Increase Toxicity of Pesticide Formulations

Inert Ingredients Can Increase Exposure to Pesticide Formulations

Inert Ingredients Can Increase Ecotoxicity of Pesticide Formulations

Discussion

References

Abstract

Background: By statute or regulation in the U.S. and elsewhere, pesticide ingredients are divided into two categories, active and inert (sometimes referred to as other ingredients, adjuvants or co-formulants). Despite their name, inert ingredients may be biologically or chemically active and are labeled inert only because of their function in the formulated product. Most of the tests required to register a pesticide are performed with the active ingredient alone, not the full pesticide formulation. Inert ingredients are generally not identified on product labels and are often claimed to be confidential business information.

Objectives: We describe the shortcomings of the current procedures for assessing the hazards of pesticide formulations and demonstrate that inert ingredients can increase the toxicity of and potential exposure to pesticide formulations.

Discussion: Inert ingredients can increase the ability of pesticide formulations to affect significant toxicological endpoints, including developmental neurotoxicity, genotoxicity, and disruption of hormone function. They can also increase exposure by increasing dermal absorption, decreasing the efficacy of protective clothing, and increasing environmental mobility and persistence. Inert ingredients can increase the phytotoxicity of pesticide formulations, as well as toxicity to fish, amphibians, and microorganisms.

Conclusions: Pesticide registration should require full assessment of formulations. Evaluations of pesticides under the National Environmental Policy Act, the Endangered Species Act, and similar statutes should include impact assessment of formulations. Environmental monitoring

for pesticides should include inert ingredients. To enable independent research and risk assessment, inert ingredients should be identified on product labels.

Introduction

Pesticides are toxic chemicals that are both ubiquitous and unique. Unlike other toxic chemicals, they are designed to kill, repel or otherwise harm living organisms (U.S. EPA 2005b), and they are one of the few toxic substances that are intentionally applied to the environment (NRC 1993). Monitoring programs conducted in the U.S. have found pesticides in "one or more samples from every stream sampled" (Gilliom et al. 2006), in over 70 percent of common foods (USDA 2006), and in over half of adults and children (CDC 2005).

In the U.S., the pesticide regulatory system differs from other toxic chemical regulatory programs. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), active ingredients, those which "prevent, destroy, repel, or mitigate any pest," are subject to greater scrutiny than inert (or sometimes other) ingredients (FIFRA, 7 U.S.C. §§2a and 2m, U.S. EPA 1997). The combination of active and inert ingredients, as marketed and used, is called a formulation (U.S. EPA 2006b). In Organization of Economic Co-operation and Development countries a similar distinction is made although terminology can be different: adjuvants and formulants are sometimes used to describe inert ingredients, and formulations can be called preparations (OECD, 1994 and 1998).

In ordinary usage, the word inert refers to something that is physically, chemically, or biologically inactive. The U.S. Environmental Protection Agency (U.S. EPA) recognizes that the statutory nomenclature for pesticides under FIFRA engenders public misunderstanding stating, "… many consumers have a misleading impression of the term 'inert ingredient' believing it to mean water or other harmless ingredients" (U.S. EPA 1997). In fact, an inert

ingredient "… may have biological activity of its own, it may be toxic to humans, and it may be chemically active" (U.S. EPA 2002). The arbitrary distinction between active and inert ingredients is well illustrated by the more than 500 inert ingredients that, according to U.S. EPA (2006a), have been or are currently used as active ingredients.

A significant proportion of typical pesticide formulations are inert ingredients. A survey of over 200 common household products in retail stores in Oregon found that these products contained on average 86% inert ingredients (NCAP 2006a). Similar results were found in surveys of products for sale in New York (Surgan and Gershon 2000, reporting surveys in 1990, 1997 and 1999). Agricultural products also contain a significant proportion of inert ingredients. A review of over 100 agricultural products found that they contained an average of more than 50% inert ingredients (NCAP 2006b).

Inert ingredients serve a variety of functions in pesticide formulations, acting as solvents, surfactants, or preservatives, among many other functions (U.S. EPA 2002, 2005a). Products with the same active ingredient may be described as granular, flowable, emulsifiable, or wettable based on the inert ingredients in the formulation (NPTN 1999). A single product may contain a number of inert ingredients, each with a different purpose in the formulation (U.S. EPA 2005a).

Independent assessment of the hazards of pesticide formulations is stymied by the lack of public access to product-specific information about inert ingredients. FIFRA requires that active ingredients be identified on product labels, but makes no such requirement for inert ingredients. The only products for which complete identification of inert ingredients is required are minimum risk, FIFRA-exempt products (40 Code of Federal Regulations §158.25). As a result, inert

ingredients are rarely identified on the product label. In 1999, only 10% of more than 100 commonly available pesticide products sold in retail stores in New York identified any of the inert ingredients on the label. None of these labels identified all of the inert ingredients in the products (Surgan and Gershon 2000).

Pesticide manufacturers claim that some inert ingredient information is protected as confidential business information (NCAP v. Browner 1996). In addition, inert ingredients are protected as confidential by many governments (OECD 1998). Our experience is that the current process for identifying ingredients involves substantial bureaucratic delay and, in some instances, litigation. There is a clear need for more public disclosure of the identity of all ingredients of pesticide products.

Inadequate Assessment of the Hazards of Pesticide Formulations

The U.S. EPA has identified almost 3,000 substances, with widely varying toxicity, that are used as inert ingredients in the U.S. (U.S. EPA 2004). For example, paper is used as an inert ingredient, but so are toxic chemicals like naphthalene and xylene (U.S. EPA 2004). The U.S. EPA estimates that about 50 percent of all inert ingredients are at least moderately risky (U.S. EPA 2002). Given the toxicity of inert ingredients and their widespread use in pesticide products, formulations should be fully assessed when pesticides are registered with the U.S. EPA. This, however, is not currently the case. Of the 20 toxicology tests required (or conditionally required) to register a pesticide in the U.S., only seven short-term acute toxicity tests use the pesticide formulation; the rest are done with only the active ingredient. The medium- and long-term toxicity tests that explore endpoints of significant concern (cancer,

reproductive problems, and genetic damage, for example) are conducted with the active ingredient alone. The requirements for other types of tests are similar. Only half of the required (or conditionally required) tests of environmental fate use the formulated product, as do only a quarter of the tests for effects on wildlife and non-target plants (40 Code of Federal Regulations §§158.290, 158.340, 158.490, and 158.540). As a result, many potential long-term effects of pesticide formulations are not assessed as part of the registration process. Testing requirements are similar in many other countries (OECD 1994).

Research indicates that some inert ingredients in pesticide formulations can have a significant impact on the human health and environmental impacts of these products. Examples are detailed below. These studies demonstrate that reliance upon tests conducted with active ingredients alone as the basis for the evaluation of the health and environmental impacts of pesticide formulations is inadequate.

Inert Ingredients Can Increase Toxicity of Pesticide Formulations

Numerous studies indicate that inert ingredients may enhance the toxicity of pesticide formulations to the nervous system, the cardiovascular system, mitochondria, genetic material, and hormone systems.

A household formulation of the insecticide bifenthrin reduced the viability of rodent nerve cell cultures while bifenthrin did not. Both the formulation and the active ingredient reduced the outgrowth of neuritis in vitro, but the effects of the formulation were more severe (Tran et al. 2006). These observations suggest that the inert ingredients would enhance developmental neurotoxic effects of bifenthrin.

Inert ingredients can also be toxic to the cardiovascular system. An herbicidal formulation of glufosinate caused a decrease in blood pressure and changes in heart rate of rats, in vivo. Glufosinate alone had no effects on either parameter. Similar results were obtained in vitro (Koyama et al. 1997).

Inert ingredients also increased in vitro inhibition of mitochondrial oxidative activity by three herbicides. The concentration of active ingredient required to reduce mitochondrial activity by 50 percent was 136 times higher for a formulation containing only 2,4-D and picloram than the concentration of those ingredients required when the inert ingredients were also included (Oakes and Pollack 1999). Results were similar with a formulation containing 2,4-D and 2,4,5-T (Oakes and Pollack 2000). A glyphosate formulation caused a significant reduction in the activity of rat liver mitochondrial respiratory complexes in vitro, but glyphosate alone had no effect (Peixoto 2005).

Pesticide formulations have proven to be more potent genotoxins than active ingredients alone in a variety of test systems. In vitro treatment of human lymphocytes with glyphosate and a glyphosate formulation resulted in a significantly higher rate of induction of sister chromatid exchange by the formulated product. Both the formulation and glyphosate increased micronucleus formation in mouse bone marrow; the increase was "more pronounced" with the formulation (Bolognesi et al. 1997). An herbicidal formulation containing atrazine increased DNA damage in human lymphocytes, while atrazine alone did not (Zeljezic et al. 2006).

Inert ingredients may enhance the reproductive toxicity of active ingredients. Both the herbicide glyphosate and a glyphosate formulation were toxic to human placenta cell cultures.

However, the formulation was significantly more toxic than glyphosate alone; the median lethal dose for the formulation was half that of the active ingredient (Richard et al. 2005).

Several reports demonstrate disruption of endocrine function by inert ingredients. A glyphosate-containing herbicide formulation inhibited progesterone production in vitro in mouse Leydig cells, but glyphosate did not (Walsh et al., 2000). A glyphosate formulation inhibited the activity of human placenta cell aromatase, which converts androgens into estrogens. Again, glyphosate alone did not inhibit the activity of this enzyme (Richard et al. 2005). Two 2,4-D formulations caused estrogen-like proliferation of MCF-7 breast cancer cells in vitro while 2,4-D did not (Lin and Garry 2000).

Inert Ingredients Can Increase Exposure to Pesticide Formulations

Inert and active ingredients can interact to diminish the protective efficacy of both clothing and skin, reduce the efficacy of washing, and increase persistence and off-target movement of pesticides.

Dermal exposure is the most common exposure route for people who handle or apply pesticides. Some inert ingredients can increase dermal absorption or penetration of the active ingredient. In a comparison of the penetration of three formulated herbicidal products through hairless mouse skin with their respective active ingredients, dermal penetration of the formulations was 3 to 30 times greater than the penetration of the active ingredients alone (Brand and Mueller 2002). Similar results were obtained in studies of absorption of the insecticide lindane and the wood preservative pentachlorophenol through human and porcine skin, respectively (Dick et al. 1997a and 1997b, Baynes et al. 2002). In all three studies, solvents used

as inert ingredients increased the dermal absorption of the active ingredient. A surfactant used as an inert ingredient increased absorption of the insecticide carbaryl through porcine skin (Baynes and Riviere 1998).

Pesticide labels often instruct users to wear protective gloves or clothing to reduce the potential for exposure to toxic ingredients. The efficacy of protective clothing, however, may be diminished by inert ingredients in the formulation; as a result, pesticide workers may be unable to make a fully informed decision. For example, solvents used as "inerts" in a formulation of the herbicide 2,4-D act as cosolvents to increase the permeation of the active ingredients through nitrile gloves (Harville and Que Hee 1989). Similar cosolvent effects occurred when a formulation of the herbicide MCPA was tested on four glove materials (Purdam et al. 2001).

Inert ingredients can also reduce the protective efficacy of work clothing which is washed and re-used, thereby enhancing exposure to pesticides. Some inert ingredients adversely affected laundry removal of the insecticide methyl parathion from clothing. The emulsifiable concentrate formulation was more difficult to remove than a wettable powder and an encapsulated formulation (Laughlin et al. 1985). Similar results were obtained in a comparison of emulsifiable concentrate and wettable powder formulations of the insecticides cyfluthrin and cypermethrin (Laughlin et al. 1991).

It is not surprising that some inert ingredients can increase persistence of pesticides in the environment, as that could be the reason for their inclusion in the formulation. But increasing persistence also results in more potential for human and other non-target exposure. The persistence of the insecticide chlorpyrifos in soil, foliage, and fruit varied significantly among

formulations containing different inert ingredients. A microencapsulated formulation was most persistent (Montemurro et al. 2002).

Inert ingredients can also affect the distribution and behavior of active ingredients in the environment, in some instances enhancing run-off, leaching and volatilization. Herbicide run-off from nursery containers varied between granular and sprayable formulations (Wilson et al., 1995). The concentration of the insecticide imidacloprid in run-off from turf treated with a granular formulation was twice as high as the concentration following treatment with a wettable powder formulation (Ambrust and Peeler 2002).

Inert ingredients can even affect volatilization of active ingredients, contributing to airborne migration and inhalation exposures. Volatilization of the insecticide azadirachtin varied among formulations; volatilization was greater from a wettable powder formulation than from three emulsifiable concentration formulations (Sundaram 1997).

Inert Ingredients Can Increase Ecotoxicity of Pesticide Formulations

The severity of varied toxic effects of pesticide active ingredients in non-target plants, animals, and microorganisms can be enhanced by the inert ingredients with which they are formulated.

Adverse impacts of pesticides on non-target plants can be mediated by inert ingredients in the formulation. For example, a phytotoxic compound is formed by thermal degradation of a fungicidal benomyl formulation containing starch as an inert ingredient. That degradation is facilitated by the starch, a source of water for the reaction (Tang and Song 1996). An inert ingredient in a permethrin-based insecticide product reduced frost tolerance of spruce (*Picea*

abies) seedlings (Kohmann 1999). Inert ingredients may also compound interactions between active ingredients. The herbicides glyphosate and glufosinate-ammonium were synergistically phytotoxic with the herbicide metsulfuron-methyl, and this synergy was more pronounced for formulations than for active ingredients alone (Kudsk and Mathiassen 2004).

Inert ingredients can increase avian toxicity of some pesticide formulations. Treatment of chick embryos with a 2,4-D formulation resulted in a significantly higher frequency of sister chromatid exchanges than did treatment with 2,4-D alone (Arias 2003).

Toxic effects of some pesticide formulations on fish can be increased by the inert ingredients. One of the most commonly known examples is glyphosate; some formulations are 10 to 100 times more acutely toxic to fish than is the active ingredient alone (U.S. EPA 1993). A formulation of the fungicide vinclozolin, but not vinclozolin alone, caused fish (*Oryzias latipes*) to develop intersex gonads (Kiparissis 2003). Exposure of captive salmon (*Salmo salar* L.) to environmentally relevant levels of the inert surfactant 4-nonylphenol reduced the growth of smolts (Arsenault et al. 2004), suggesting that exposure to a formulation containing 4-nonylphenol might explain the decline of some wild salmon populations.

Similarly, amphibians may be adversely affected by inert ingredients. Two formulations of the insecticide chlorpyrifos were more neurotoxic in vitro to frogs and caused more damage (swelling) to mitochondria than chlorpyrifos alone (Swann et al. 1996). Exposure of *Rana pipiens* tadpoles to environmentally relevant concentrations of glyphosate formulations reduced size at metamorphosis, increased time to metamorphosis, increased the frequency of tail damage,

and increased the frequency of abnormal gonads. Glyphosate alone did not have these effects (Howe et al. 2004).

Pesticide formulations can be strikingly more toxic to microorganisms than their active ingredients alone. A glyphosate formulation was 100 times more toxic to ciliated protozoans than glyphosate (Everett and Dickerson 2003). A formulation of the insecticide propetamphos was 100 times more toxic to the microbial flora in sediments than propetamphos (Garcia-Ortega et al. 2006).

Discussion

There is a substantial and growing body of research demonstrating the inadequacy of reliance upon testing the active ingredient alone when assessing the exposure to pesticides, their toxic effects, and their behavior in the environment. Inert ingredients are often biologically or chemically active and can affect each of these parameters. Demonstrations of important impacts of inert ingredients have not been limited to particular classes of pesticides, types of formulations, or toxicity endpoints. Instead, it appears that the effects of inert ingredients may be both common and far-reaching.

It is often unclear if inert ingredients are directly responsible for certain toxic effects or if those effects are attributable to interactions between inert and active ingredients. Because inert ingredients are rarely identified, studies comparing the effects of the active ingredient, the inert ingredients, and the formulation are not common. Such three-way comparisons were done in seven cited studies; this literature suggests that the situation is complex. In four instances interactions between active and inert ingredients were important (Oakes and Pollack 2000, Tang

and Song 1996, Arias 2003, and Swann et al 1996); three studies demonstrated that the increased toxicity was primarily due to the inert ingredients (Zeljezic et al 2006, Koyama et al 1997, and Oakes and Pollack 1999).

Similarly, full assessment of exposure to pesticide formulations is impeded by the lack of information about the concentration of individual inert ingredients. Only five of the cited studies provided this information. Label disclosure of all ingredients with percent composition would facilitate these much-needed studies.

Consistent with our growing awareness of the complexities of the toxicity of mixtures, it is no surprise that pesticide formulations act differently than active ingredients alone. As early as 1988, the National Research Council concluded: “Mixtures that are of particular concern include chemicals generated in fire, hazardous wastes, pesticides, drinking water, fuels and fuel combustion products,” adding that “toxicological studies of mixtures are essential for estimating human risks” (NRC 1988).

More recently, the Agency for Toxic Substances and Disease Registry identified chemical mixtures as one of six priority areas in public health research (De Rosa et al. 2004). In Europe and Japan, a recent survey found “a growing interest among toxicologists and regulators in the toxicology and risk assessment of chemical mixtures" (Feron et al. 2002). A review of ecotoxicology tools identified mixtures as one of the top three challenges in assessing environmental contamination (Eggen and Segner 2003).

Current testing requirements for pesticides are inadequate to fully assess the health and environmental effects of these mixtures. To remedy this situation, all pesticide ingredients

should be identified on product labels and pesticide registration should be based on full assessments of formulations as they are sold and used. Requirements that manufacturers develop analytical methods for active ingredients should be expanded to include inert ingredients. Furthermore, evaluations of pesticides required under the U.S. National Environmental Policy Act, the Endangered Species Act, analogous state laws, and similar laws in other countries consider all impacts of formulations, not just those of active ingredients. Programs to track pesticide use should include both active and inert ingredients, as should monitoring of pesticides in humans and the environment. Researchers could then use this information to set priorities.

In 1994, the American Medical Association urged the U.S. Congress, government agencies, and other organizations to "support all efforts to list both active and inert ingredients on pesticide container labels and material safety data sheets" (American Medical Association Council on Scientific Affairs 1997). Health and environmental researchers worldwide should support such efforts. Independent investigation is stymied by the secrecy which shrouds the inert ingredients in pesticide products.

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