Pesticides — How Research Has Succeeded and Failed to Translate Science into Policy: Endocrinological Effects on Wildlife

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Toxicological research became institutionalized in the United States in response to society's concern about cancer and acute mortality. Driven by risk assessment, research focused on the need for data development and the standardization of testing for regulatory and management purposes in a reactive mode. Although the research community has provided evidence for over 40 years that a number of pesticides and industrial chemicals have disruptive effects on the endocrine system, little attention was given to the evidence when determining the health hazards of synthetic chemicals because of the fixation on cancer. However, recent findings concerning the effects of a number of widespread chemicals on the reproductive success and fertility of wildlife and humans has led to the call for a proactive approach using investigative research (forensic science). Suggestions are presented to modernize the research agenda of public health institutions to meet society's needs to address the problems of exposure to endocrine, nervous, and immune system disruptors. — Environ Health Perspect 103(Suppl 6):81–86 (1995)

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Introduction

For over 40 years the research community provided evidence that a number of pesticides and industrial chemicals have disruptive effects on the endocrine system, especially during embryonic development. If the latter is true, why then has research not been able to translate this message into policy to prevent chemicals of this nature from entering commerce? This article will provide an argument that the blame cannot be placed solely on the research community; some must be placed on the current research agenda of the institutions dedicated to protect and restore human and wildlife health.

As toxicological research became institutionalized in response to society's concern about cancer and acute mortality following exposure to pesticides and industrial chemicals, it became driven by risk assessment. As a result, research focused on the need for testing (data development) and the standardization of testing (*1*). Protocols were established to determine the probability of a chemical causing cancer, acute mortality, visible birth defects, skin and eye irritation, and obvious neurotoxicological effects. Even though wildlife populations were recognized as harbingers of pesticide damage in humans as early as the 1960s (*2*), the science was ignored by those charged with protecting human health. The devastating effects of cancer so overwhelmed society that the insidious legacy of toxic chemicals being transferred to our children was overlooked at that time. Despite this, the fascination with cancer was successful in removing a number of the most egregious pesticides and industrial chemicals from the market and in preventing others from becoming introduced in commerce. And by restricting the production and use of these suspected carcinogens, seriously affected wildlife populations experienced some relief and rebounded (*3*).

It was not until the late 1980s, following an intense review and synthesis of the wildlife literature, that the importance of wildlife health end points as models for human health was again proposed (*4*). There was growing concern arising from the evidence that freshwater, marine, and terrestrial wildlife populations from widespread geographic regions were still experiencing reproductive problems. Outright mortality (acute toxicity) was not the case. Instead, adult animals appeared to be healthy, but their offspring were plagued with a suite of effects that suggested abnormal development of vital physiological systems. This led to early death among embryos and offspring or loss of fertility if they survived to adulthood. Such demographic shifts are the underlying reason for population instability.

Concern for what these findings might mean for humans prompted the gathering of 21 scientists from 17 disciplines at the Wingspread Conference Center, Racine, Wisconsin, in July 1991. The participants shared their knowledge relevant to "Chemically-Induced Alterations in Sexual Development: The Wildlife/Human Connection." After presentation of papers, the group issued a Consensus Statement (*5*) in which they were "...certain that a large number of man-made chemicals had been released into the environment that were capable of disrupting the endocrine systems of wildlife and humans," and that "...if the environmental load of man-made endocrine disruptors was not abated, widespread dysfunction at the population level would take place."

Among their conclusions they also stated that "it is urgent to move reproductive effects and functional teratogenicity to the forefront when evaluating health risks. The cancer paradigm is insufficient because chemicals can cause severe health effects other than cancer."

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They called for changes in testing to include "...hormonal activity *in vivo*," and..."integrated cooperative research...to develop both wildlife and laboratory models for extrapolating risks to humans."

In essence the group called for institutionalization of the essential forensic research (environmental detective work) that integrates multidisciplinary research in both the field and the laboratory to meet the challenge of a global environment dusted with man-made chemicals.

Under our present reactive, regulatory system, proof of causality is essential prior to action. Consequently, it is imperative to determine damage from pesticides in wildlife and/or humans in the environment, and to return to the laboratory and recreate this damage. Currently, no federal institution has the mandate to synthesize the literature available on the noncancer health effects of pesticides to determine potential damage and then undertake the necessary environmental detective work to determine if damage is occurring to wildlife or humans. Instead, the system has been locked into the traditional risk assessment strategy of testing pesticides on a chemical-by-chemical basis to determine allowable levels in the environment.

After 50 years of repeated warnings from scientists, the dominance of cancer as the effect of primary concern in assessing the risks of pesticides and other synthetic chemicals is being challenged by evidence of the effects of chemicals on the nervous, immune, endocrine, and reproductive systems of laboratory animals, wildlife, and humans (*6,7*). The disease state, or effect, in this case is measured by loss of function of one or more of these systems rather than by obvious physical deformities, outright mortality, or cancer. The bulk of the literature from this new effects research has focused primarily on the developmental toxicity of three industrial chemicals, PCBs, dioxins, and furans, and on only a few chlorinated pesticides such as DDT, its metabolites and analogs. As a result, little is known about the noncancer health effects of most pesticides and especially herbicides, the largest portion on a weight basis of pesticides currently in use in the United States (*8*).

The Wildlife Message

The scientific community has documented the endocrine disruptive effects of pesticides for almost 50 years, though little attention has been paid to the message. For example, in 1950, Burlington and Lindeman (*9*) first reported that DDT behaved like the female hormone, estrogen. DDT fed to newly hatched male chicks prevented them from growing combs and wattles and from reaching sexual maturity. Shugart (*10*) and Fox (*11*) later reported the occurrence of female–female pairing in colonial nesting birds carrying elevated levels of DDT and its metabolites and other organochlorine chemicals. Fry and coworkers (*12,13*) in the early 1980s reported that DDT, its metabolites and analogs—kelthane, dicofol, and methoxychlor—caused male birds to grow oviductal tissue and to be deprived of their dominant male behavioral characteristics in adulthood. Guillette (*14*) reported in 1994 that Lake Apopka, Florida, alligators and turtles were suffering from an estrogenlike effect, probably as a result of exposure to DDE, a metabolite of dicofol. The male alligators have shortened phalluses (penises), making them physically incapable of breeding successfully. Slider turtles sharing nesting mounds with the alligators become either females or intersex, a blend of both sexes. Functionally normal male turtles are not produced in the Lake Apopka nests. Except for DDT, the other pesticides—kelthane, dicofol, and methoxychlor—are still in production and use in the United States. Despite warnings from the research community, all the above pesticides, including DDT, are used on a global scale today.

Over the years researchers have reported a number of other reproductive problems among wildlife populations in the Northern Hemisphere that reflect disruption of the endocrine system (Table 1). Disruption was expressed as changes in functionality across species from terrestrial to marine animals. Often the effects were not recognized until they reached population proportions.

In most cases the responsibility for the above effects was not assigned to a single chemical for several reasons: *a*) because so many chemicals are present simultaneously in the environment, *b*) separating effects is impossible because many chemicals cause similar damage, and *c*) complementary laboratory research was not possible because of the high cost of organic chemical analyses.

Mechanisms of Action: Complicating the Risk Paradigm

Taking advantage of high technology (analytical chemistry, sophisticated microscopy, supercomputers, sensitive analytical assays), scientists are recording changes that take place at the molecular and cellular levels under both normal conditions in the presence of internally produced chemicals (hormones, neurotransmitters, growth factors, and inhibiting substances) and under abnormal conditions in the presence of toxic chemicals (pesticides and industrial chemicals) (*7*). Scientists have repeatedly documented the scrambling of normal hormonal signals by pesticides *in vivo* and *in vitro* (*15*). This mechanism-of-action approach has provided answers to how certain toxic chemicals affect various tissues, organs, and systems and how chemicals affect whole organisms. However, considering the number of chemicals widely released in the environment today, it is improbable the mechanisms of action of all the chemicals in use will be determined.

The results of extensive research on the effects of diethylstilbestrol (DES), a

Table 1. Environmental effects on the development of hormonally responsive tissue in wildlife.

Effect	Reference
Decreases	
Embryo hatchability	Mac et al. (*36*)
Embryo viability	Tillit et al. (*37*)
Chick survivorship	Kubiak et al. (*38*)
Fry survivorship	Walker and Peterson (*39*)
Egg size and numbers	McMaster et al. (*40*)
Numbers of animals reaching sexual maturity	Guillette (*14*), Leatherland (*41*)
Production of thyroid hormones	Fox (*11*), Leatherland (*41*), Leatherland et al. (*42*)
Production of estrogen	Munkittrick (*43*)
Production of testosterone	Munkittrick et al. (*44*), Subramanian et al. (*45*)
Production of retinols	Fox (*11*)
Immune-competency	Martineau et al. (*46*), Swart et al. (*47*)
Increases	
Size of thyroid	Moccia et al. (*48*)
Size of liver	Kubiak et al. (*38*)
Liver enzyme induction	Kubiak et al. (*38*)
Highly carboxylated porphyrins	Fox et al. (*49*)
Numbers of animals exhibiting sex reversal	Colborn and Clement (6), Guillette (*14*), Gibbs et al. (*50*), Davis and Bortone (*51*)
Spontaneous abortions	Reijnders (*52*)
Hermaphroditism	Guillette (*14*), DeGuise et al. (*53*)
Sex-associated birth defects[a]	
Asymmetrical brains	Henshel et al. (*54*)
Asymmetrical skulls	Zakharov and Yablokov (*55*)
Unusual behavior	Fox (*11*), Fry and Toone (*12*), Fry et al. (*13*)

[a]All crossed-bill, double-crested cormorants examined were phenotypic females ($n \geq 100$) (M Fry, personal communication); all crossed-bill bald eagle chicks discovered in 1993 were females ($n=3$) (T Kubiak, personal communication).

synthetic estrogenic pharmaceutical administered to several million women between 1948 and 1971, parallel effects reported in wildlife and humans as a result of exposure to PCBs, dioxin, and DDT (*16*). Many of the disruptive effects of DES have been documented in laboratory rat and mouse embryos and thus provide an excellent model for the effects of other estrogenlike compounds on humans and wildlife (*17*). The literature on DES, like that on PCBs, dioxins, and DDT, indicates that it affects developing organisms differently than mature organisms. Furthermore, the functional deficits in animals and humans as a result of exposure in the womb can occur at much lower concentrations than those required to illicit similar changes in adults (*18–20*). And most important, only one exposure, called a "hit," at a critical window of time during sexual differentiation can change the course of sexual development of the exposed individual (*18–20*).

It is during differentiation that construction of the vital physiological systems and programming of the pituitary/hypothalamic region of the brain takes place. It is also at this time that endocrine disruptors may be the most threatening, leading to endocrine, immune, and nervous systems that are architecturally unsound and hypothalami that do not respond to normal hormonal and neurotransmitter messages in the usual manner throughout life (*19*). The insidious nature of these effects makes the induced modifications difficult to discern, since in most cases they are expressed in the offspring of the individuals who were exposed, not in the exposed parents.

The endocrine system holds the key to fertility. For some sensitive populations the message is clear: avoidance and prevention are the only options for survival. Meanwhile, as decision makers wait for tolerance levels, dose–response curves, threshold levels, and unequivocal cause–effect linkages in order to regulate on a chemical-by-chemical basis, evidence that more and more synthetic chemicals are being passed from mother to offspring continues to surface (*21,22*). Top predator, long-lived wildlife populations are suffering declines. Evidence of human damage as the result of generational transfer of synthetic chemicals is accumulating.

Extrapolating to Humans

There is evidence that many man-made chemicals can invade the pristine environment of the womb (*23,24*). Defying the paradigm that the placenta is impenetrable to exogenous compounds, the chemicals readily cross the placenta and brain barrier as they are passed from the mother to her developing baby. In addition, in the case of estrogen-like compounds, if they do not bind to the estrogen-binding protein in human maternal blood that protects the fetus from a large part of maternally produced estrogen during gestation (*25*), their toxicity will be enhanced (*7*).

Using the laboratory animal as a model, the disruptive effects associated with exposure to developmental toxicants in the womb can range from mild to extreme, reflecting gradations of loss of potential. The effects are not necessarily expressed as a clinically relevant disease state. Furthermore, in many cases the effects are irreversible (*7,16*). There are an infinite number of windows of time during embryonic and the early postnatal period (*7,16*) when disruption can take place, each leading to potentially different changes in an individual's course of development and behavior. Response to exposure is unpredictable because the process of development is so delicate and complex. Consequently, a simple, standardized descriptor of damage can never be generated. For long-lived humans, the effects may never be traced to a specific exposure event because the effects can arise 20 years or more later—the disconnection between exposure and effect is too great. Ultimately, exposure of this nature leads to loss of potential at the individual level. At the population level, however, the effects could have vast social and economic impacts (*26*).

The full impact of exposure to chemicals on humans may just be coming to light. Because the effects are not expressed as physical disfigurements at birth, they do not appear in public health birth records. Often it is a generation or more before they are recognized. For example, loss of fertility that includes reduced sperm count associated with exposure to estrogens (*27*), shortened penises at puberty associated with exposure to PCBs and furans (*28*), cognitive and motor loss associated with exposure to PCBs (*29*), and aberrant immune responses associated with exposure to diethylstil-bestrol (*30,31*) have all been documented in humans to be a result of their exposure in the womb. None of the above were predictable at birth using current clinical examination procedures. And none are described as single diseases or syndromes associated with exposure to one chemical or a class of chemicals.

Human studies should consider the functional deficits reported in wildlife resulting from transgenerational exposure. Also, consideration should be given to the extent of constrained potential in children that includes behavioral, cognitive, social, immunological, and endocrinological end points. This is a daunting task because of the widespread use and distribution of pesticides and industrial chemicals.

Discussion

A veneer of long-lived, man-made chemicals now covers the earth from the Arctic to the Antarctic (*32*). Concentrations of these chemicals that include a number of organochlorine pesticides are now at levels associated with population declines of marine, freshwater, and terrestrial animals and with functional deficits in human offspring (*33*). It is impossible to predict the effect of the addition of a single new chemical to this veneer, let alone the addition of several hundred or more new chemicals a year that are introduced into commerce. It is doubtful that unequivocal cause-and-effect relationships will ever be made for the wildlife population declines and the human loss of potential mentioned above because so many chemicals are involved, many of which have never been identified analytically.

Unlike many of the developmental toxicants that are unintentionally produced, pesticides are produced and released to the environment intentionally. This provides opportunities to control further release of pesticidal compounds currently in use until they are proven safe and to prevent the release of new substitutes that may pose similar or greater threats. However, under the current regulatory system, to accomplish this, a case has to be made that the chemicals are, indeed, harmful. This can only be accomplished with quantitative evidence of damage. Unfortunately, the research agenda in the United States today is not organized to support science of this nature. Most of the current wildlife toxicology research comes as a result of serendipitous observations by scientists engaged in unrelated fields of studies or from reactive science to severe damage in areas heavily contaminated. Most human studies have also been reactions to concern over high-dose exposure.

Currently no government institution is dedicated solely to promoting innovative, multidisciplinary research on transgenerationally transmitted loss of function. This will require multilevel (gene to ecosystem)

research that addresses real-world pollution problems. Real-life exposure and effect studies should be encouraged using free-ranging wildlife as models for human exposure and effects. This will require extensive activities in the field, followed in the laboratory with replication of the damage found in the field, and should lead to identification of the most sensitive end point(s) (the lower limits of effect) on offspring using a multigenerational model.

To assure that the research agenda is modernized to meet society's current needs, a review process must be created for research proposals and it must be geared to support the cutting edge research necessary to keep ahead of the technologies producing new and more powerful pesticides. This must be a multidisciplinary review process separate from current practices in use in federal institutions today.

In addition to the institutionalization of ecotoxicological research, there are other research needs for

- Development of inexpensive, short-term screening techniques to test new and old products for endocrine, nervous, and immune system disruptive capacity;
- Acceleration of testing of banned and restricted products that still pose a threats to humans and wildlife because of their persistence and presence in human tissue;
- Industry to test all new products, their metabolites, intermediates, and by-products for *a*) multigenerational immune, endocrine, reproductive, and nervous system effects in at least three animal species and *b*) their environmental fate in all media; and
- Industry to provide the chemical analytical protocol to monitor its new products in the environment after they have been released.

In light of the new evidence about the endocrinological effects of PCBs, dioxins, furans, DDT and its analogs, and a growing list of pesticides and other chemicals used in commerce, it is prudent that society make a concerted effort to reexamine the endocrinological effects of *a*) all pesticides in use, *b*) any new pesticides that come on the market, and *c*) those that have been banned and restricted but still persist in the environment. Many of the latter chemicals have proved to be very persistent and are still present in the U.S. environment at dangerous levels (*34,35*). In addition, their use has not been discontinued overseas, and in some instances they are being used in greater intensities overseas than ever used in the United States.

Conclusion

Institutions will continue to fail to translate into policy the impacts of developmental toxicants on wildlife and humans if they remain locked in current modes of testing and continue to function in a reactionary manner. Testing must be broadened to include real-world experiences for both wildlife and humans. Until institutions shift to a preventive mode and incorporate these forensic studies in their agendas, little will change. It is also imperative that the cumulative results of the new testing be systematically reviewed and synthesized. And most important, the results of these syntheses must become accepted components of the decision-making process.

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