

G R A D I E N T  
**TRENDS**

R i s k S c i e n c e & A p p l i c a t i o n

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Letter to our Readers

January 2002

Dear Colleague,

Evolution of Pesticide Science

*The numerous technical and regulatory changes that have characterized the history of pesticide use have led to more responsible management of these materials.*

Regulation of pesticides in the U.S. spans nearly a century and has evolved from an initial focus on trade, to environmental concerns, and then later concerns for public health. This evolution has been paralleled by changes in the science by which pesticides are evaluated, and the types of commonly used pesticides and pesticide management practices.

*...it must be recognized that the U.S. is not experiencing an epidemic of pesticide-related maladies.*

Pesticide regulation began in 1910 with the Insecticide Act, which addressed accuracy in container labeling, and expanded in 1947 with the passage of the Federal Insecticide, Fungicide, and Rodenticide Act

(FIFRA). FIFRA required pesticide manufacturers to register their product with the U.S. Department of Agriculture (USDA) prior to sale or interstate transfer. Not until 1954, with an amendment to the Federal Food, Drug, and Cosmetic Act (FFDCA), did pesticide regulation begin to go beyond commerce to address issues of public health and the environment. The FFDCA Amendment provided the basis for establishment of tolerance limits for pesticides on agricultural commodities and food crops. The 1958 FFDCA Amendment, the Delaney Clause, prohibited carcinogenic additives in food items at levels greater than in the original agricultural commodity. Spurred on by the publication in 1962 of Rachel Carson's "Silent Spring," potential environmental impacts of pesticides came to the forefront as reflected in FIFRA 1964, which allowed for the suspension of registration of pesticides determined to be unsafe. The U.S. EPA was given authority for pesticide regulation in 1970, continuing the shift in focus towards environmental concerns. FIFRA 1972 represented a further

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Pesticides have been around for a long time, and the benefits, such as the eradication of malaria in parts of the world as a result of the use of DDT, are well known. Risks, however, are also present: the ecological harm wrought by DDT, or the suspicion that malathion can cause cancer. New syndromes, such as Multiple Chemical Sensitivity, have been blamed in part on pesticides. Pesticide use has also been hotly debated on the East Coast over the last two years as more and more communities spray for control of mosquitoes bearing the West Nile Virus during the summer months. This issue of *Trends* examines these issues and others surrounding the use of pesticides.

Contributors to this issue include Dr. Barbara Beck, Gradient Principal and internationally recognized expert in toxicology, Mr. Richard Blanchet, who specializes in ecological risk assessment, and Ms. Sunessa Schettler and Dr. Mara Seeley, risk assessors with specialties in public health. Joining them is Steven Russell, Senior Legal Counsel with the American Chemistry Council, who contributes his thoughts on responsible chemicals management.

We hope you will find this issue of *Trends* thought provoking and helpful as you grapple with these issues in your own community.

Yours truly,



Neil Shifrin, Ph.D.  
 President

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# Evolution of Pesticide Science

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change by requiring pesticide manufacturers to conduct defined scientific studies aimed at demonstrating that use of a pesticide would not cause “unreasonable adverse effects on human health or the environment.” FIFRA 1972 also addressed pesticide management practices, for example by prohibiting use of a pesticide in any manner inconsistent with its label. As time passed, the EPA continued to emphasize risk reduction, for example, through establishment of policies to speed up the registration of “safer” pesticides. The Food Quality Protection Act (FQPA) of 1996 addressed issues of risk and risk reduction (rather than benefits of pesticides) by establishing a single standard for pesticide residues in all foods, by requiring the EPA to consider both dietary and nondietary exposures to pesticides, by addressing risks to infants and children as distinct sub-populations, and by requiring consideration of endocrine-disrupting effects of pesticides.

Similar to regulatory changes, the types of pesticides used over time have evolved, from inorganic arsenicals to the post World War II introduction of synthetic organic pesticides, one of the first of which was dichlorodiphenyl-trichloroethane (DDT). DDT was a boon to mosquito control and clearly a much less acutely toxic insecticide to humans than the arsenicals it replaced. Adverse effects of DDT on wildlife populations led to the introduction of organophosphates (OPs), a class of pesticides that is much less environmentally persistent and less subject to biomagnification than DDT. While OPs are more toxicologically potent than DDT with respect to human health, occupational and accidental mortality from pesticide poisoning did not increase with this use. In fact, pesticide-related mortality has generally declined in the U.S. over time, a consequence of the improvements in pesticide management practices as well as changes in pesticide formulations.

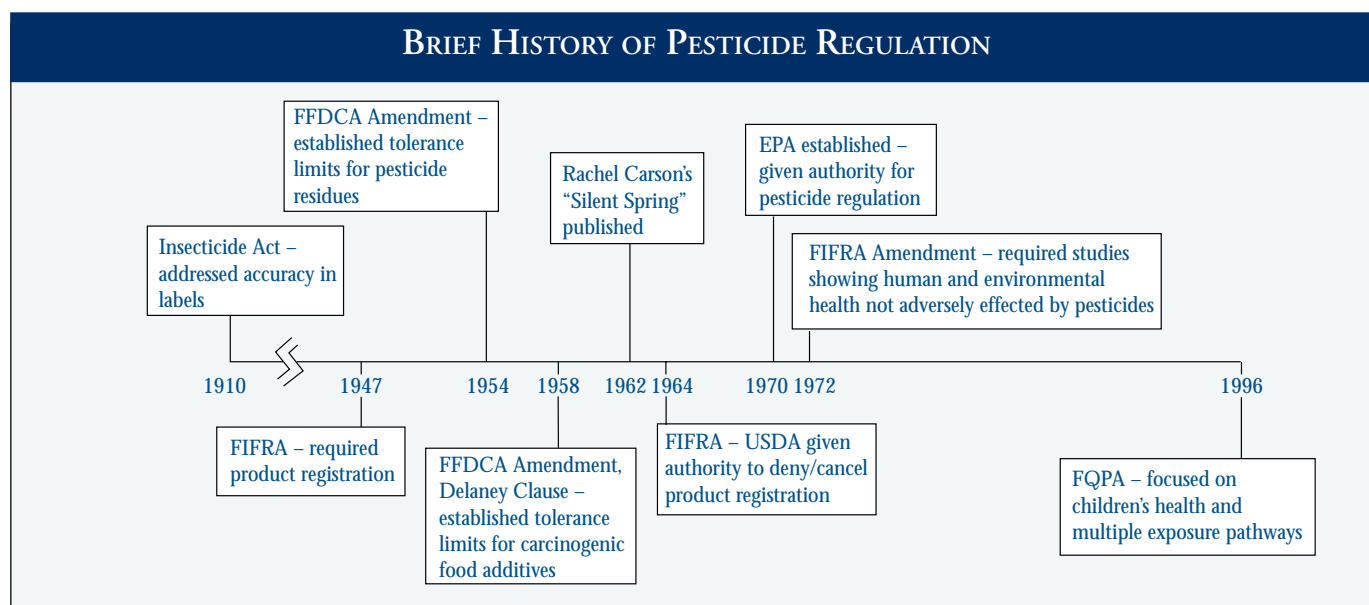
Similarly, the science of pesticide toxicology continues to evolve with new emphasis on overall risk. The FQPA requires that the EPA perform aggregate exposure assessments of dietary pesticides (*i.e.* exposures *via* multiple routes for a single pesticide) and cumulative risk assessments for pesticides that operate *via* the same mechanism of action. These requirements have necessitated improvements in analytical and laboratory tools to estimate pesticide body burdens. In addition, scientists are intensifying efforts to develop a mechanistic understanding of a particular pesticide’s mode of action. The FQPA requirement that children’s risks be considered in particular (and the controversial 10X “safety factor” for protection of children) has spawned additional testing requirements for developmental effects of pesticides as well as development of new techniques to assess children’s exposure (*e.g.* videotape studies of children’s activities).

These broader statutory and agency emphases on risk and risk reduction of pesticides are laudable. Still, it must be recognized that the U.S. is not experiencing an epidemic of pesticide-related maladies. In fact, the frequency and magnitude of adverse effects of pesticides in the U.S. has diminished over the past decades, while benefits of wise use of pesticides, *e.g.* more efficient food production, continue to accrue. This is likely the result of a growing awareness that any chemical, pesticidal or otherwise, can have its benefits realized if its risks are responsibly managed.

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## For Additional Information:

Ragsdale, N.N. and J.N. Seiber, eds. 1999. Pesticides: Managing Risks and Optimizing Benefits. American Chemical Society. Washington, D.C.



# Risks vs. Benefits of Pesticide Use

*The balance between the risks and benefits of pesticide use is a delicate one, as history has shown us.*

As societies attempt to harvest necessary materials from nature, such as food, fiber, and lumber, one fact emerges: human beings find themselves in competition with other species

**Synthetic pesticides became the symbols of progress during the postwar years and provided an unprecedented level of control over environmental risks.**

for the same things. As populations explode on a global scale, more pressure has been placed on available resources for producing the articles necessary for day-to-day existence.

Contrary to some schools of thought, the use of pesticides is not an ecological sin. When their use is approached from the sound base of ecological principles, chemical pesticides provide dependable and valuable tools (Luckman and Metcalf, 1982). The benefits associated with pesticide use are best illustrated by lives saved, increased crop yields, and economic growth. Synthetic pesticides became the symbols of progress during the postwar years and provided an unprecedented level of control over environmental risks.

However, these beneficial results soon led to overuse and misuse of pesticides. Over the last decades, experts have pieced together evidence suggesting that pesticides and their effects were more difficult to control than had been anticipated. The first serious surprise was the rapid evolution of insect resistance to pesticides, which created a demand for new products. Second, pesticide residues often persisted longer and traveled farther in the environment than initially expected. Third, residues accumulated in plant, animal, and human tissues (Wargo, 1996).

An excellent example of the risks and benefits of pesticide use can be found in the case of dichlorodiphenyl-trichloroethane (DDT). The discovery of the insecticidal properties of DDT, by the Swiss scientist Paul Muller in 1939, began the modern chemical industrial revolution and was a turning point in both public health and agricultural history. Among insect-borne diseases, malaria has been the most deadly in modern history, killing from 100 to 300 million people and infecting and debilitating hundreds of millions of others during the 20<sup>th</sup> century alone (Wargo, 1996). DDT use during World War II showed immediate success in controlling typhus, malaria, and yellow fever, demonstrating the new control humans could exercise over disease.

When the World Health Organization (WHO) was established in 1945, it relied primarily on DDT to control mosquito-borne diseases, especially malaria. The results of the WHO efforts were extraordinary. By 1970, malaria had been

eliminated from Europe, North America, major portions of Central and South America, most of the Caribbean Island nations, the former Soviet Union, Japan, Singapore, Korea, Taiwan, Australia, and some Middle Eastern states. An area inhabited by more than 725 million people that was malarious in 1950, was by 1970 virtually free from the disease. In addition to lives saved, agricultural production rose and general public health improved as other insect-borne diseases such as plague were also reduced (Spielman and D'Antonio, 2001).

However, these benefits were not realized without a cost. Growing mosquito-resistance to DDT necessitated the use of higher application rates, and the development and use of related chlorinated compounds. DDT and its analogs were ultimately associated with environmental effects, most notably the decline of certain avian species due to the compound's effects on egg shell integrity.

Although malaria continues to destroy human lives, it is reasonable to suppose that many millions of people escaped death because the use of DDT enabled them to get through their vulnerable childhood years without infection. Today, we face new insect-borne diseases, such as West Nile Fever, and the pesticide risk-benefit debate once again has new urgency. Today, as in years past, the use of pesticides holds substantial promise in

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## BENEFITS AND RISKS ASSOCIATED WITH PESTICIDE USE

### Benefits

- Prevents loss in yield in agricultural systems
- Rapid action to prevent damages
- Convenient, effective
- Control of disease transmission
- Improved public health
- Decreased number of human deaths associated with insect-borne diseases

### Risks

- Persistence
- Environmental contamination
- Increased death in non-human species
- Development of pesticide resistance
- Resurgence of treated populations
- Residues in food, feed, and tissues

# Examining Multiple Chemical Sensitivity

*Attempts to positively associate the panoply of MCS symptoms with environmental chemical exposures have been largely unsuccessful.*

Multiple Chemical Sensitivity (MCS) is a diagnosis assigned to individuals reporting symptoms involving multiple organs, in association with exposure to very low levels of environmental chemicals. The symptoms described in individuals with MCS are non-specific, and most frequently involve the central nervous system, the respiratory tract, or the gastrointestinal system. A key feature of MCS is that the symptoms, such as headaches, fatigue, memory loss, joint discomfort, and sleep disturbances, are largely subjective. Another key feature of

*In spite of the numerous reports over the years of individuals with MCS, no scientifically defensible mechanisms to explain the association between MCS and low-level environmental exposures have emerged.*

MCS is that symptoms can be elicited by exposure levels several orders of magnitude below levels known to cause adverse health effects in individuals without MCS. Furthermore, these symptoms appear to have no relationship to known

effects for the chemicals in question.

An extensive list of chemicals has been noted to cause MCS. These chemicals are diverse, both in terms of chemical structure, as well as mechanism of toxicological action. Pesticides, such as chlordane and chlorpyrifos, are among the more common chemicals associated with MCS.

Providing an explanation for MCS presents a conundrum for toxicologists. A key tenet of toxicology is that for every non-carcinogenic chemical, no matter how hazardous, there is a safe level. However, for MCS, there is no apparent safe level, or threshold. Another observation in toxicology is that effects are typically specific for one, or only a few organ systems, rather than the multiple organ systems involved in MCS. Additionally, while there may be differences between individuals in the magnitude of a response, there usually is not a difference regarding the nature of the response, as is observed with MCS.

In spite of the numerous reports over the years of individuals with MCS, no scientifically defensible mechanisms to explain the association between MCS and low-level environmental exposures have emerged. Although various theories have been advanced, they are either not supported by currently available data, or have not been tested. For example, some researchers have suggested there is an immunological basis to MCS. However, several well-conducted epidemiology studies have not detected significant differences in a variety of tests diagnostic for immunological function between individuals with and without MCS. Other researchers have suggested that

psychological factors may partly explain MCS, based on the observation that many individuals with MCS also report symptoms of depression before and after the onset of their MCS. Although a higher rate of psychiatric disorders is the most consistent finding for individuals with MCS across studies, these studies have largely been cross-sectional, and thus are not useful to establish causation. Furthermore, the association between psychological factors and MCS is not observed in all individuals with MCS. Thus far, there are no consistent differences, for a variety of diagnostic tests of physiological function, that could explain what distinguishes individuals with MCS from other similarly exposed individuals.

Although people with MCS often report a link between their symptoms and exposure to pesticides, there are no scientific studies linking pesticide exposure with MCS. Future studies may provide the necessary evidence to link environmental exposure with the variety of symptoms reported in individuals with MCS. However, to date, this evidence is lacking. In the absence of convincing evidence causally linking environmental exposures with MCS symptoms, low-levels of exposure to environmental chemicals, such as pesticides, cannot be clearly implicated as the culprit for MCS.

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#### For Additional Information:

Fiedler, H. and N. Kipen. 1997. Chemical sensitivity: the scientific literature. *Env. Health Perspectives*. 105(S2):409-415.

Gots, R.E. 1996. Multiple chemical sensitivities: distinguishing between psychogenic and toxicodynamic. *Reg. Tox. and Pharm.* 24:S8-S15.

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#### BY THE WAY...

The EPA, in developing reference dose (RfD) guidance, has not found it necessary to use the 10X safety factor for children, if appropriate care has been taken in determining the uncertainty/variability factors.

Source: U.S. EPA RfD Technical Panel. "A Review of the Reference Dose and Reference Concentration Processes. Internal Review Draft." August 2001.

## What's New at Gradient

### Dr. Mara Seeley becomes Diplomate of the American Board of Toxicology

Congratulations to Gradient's Dr. Mara Seeley, who recently passed the American Board of Toxicology exam.

### Dr. Barbara Beck Appointed to Society of Toxicology Program Committee

The Program Committee is responsible for the planning and organization of the scientific program of the Annual Meetings. Dr. Beck's appointment runs from May 2001 to April 2004.

### Dr. Barbara Beck Testifies Before Congress

Dr. Barbara Beck recently gave congressional testimony before the subcommittee on Environment, Technology, and Standards on "Arsenic in Drinking Water: An Update on the Science, Benefits, and Cost to the Subcommittee on Environment, Technology, and Standards."

### Recent and Upcoming Presentations

Nashville, TN. March 17-21, 2002. Lorenz R. Rhomberg. "Quantifying Uncertainty in Human Reproductive Risk Projected from Rat Inhalation Studies on Ethylene Oxide: A Framework Based on Data-Based Statistical Distributions of Extrapolation Factors," presentation at the Society of Toxicology's 41<sup>st</sup> Annual Meeting.

Nashville, TN. March 17-21, 2002. Mara Seeley, S. Schettler, C.Liu, R.J. Blanchet, and T.S. Bowers. "Assessing Potential Cancer Risks Associated with Insecticides Used to Control the Mosquito-Borne West Nile Virus: Use of the Margin of Exposure Approach," presentation at the Society of Toxicology's 41<sup>st</sup> Annual Meeting.

### Recent Articles

Bowers, T.S. and R.L. Mattuck. 2001. Further comparisons of empirical and epidemiological data with predictions of the Integrated Exposure Uptake Biokinetic model for lead in children. *Human and Ecological Risk Assessment*. 7(6):1699-1713.

Brand, K.P., P.J. Catalon, J.K. Hammitt, L.R. Rhomberg, and J.S. Evans. 2001. Limitations to empirical extrapolation studies: The case of BMD ratios. *Risk Analysis* 21(4):625-639.

Evans, J.S., L.R. Rhomberg, P.L. Williams, A.M. Wilson, and S.J.S. Baird. 2001. Reproductive and developmental risks from ethylene oxide: A probabilistic characterization of possible regulatory thresholds. *Risk Analysis* 21(4):697-717.

Beck, B.D., R.L. Mattuck, T.S. Bowers, J.T. Cohen, and E. O'Flaherty. 2001. The development of a stochastic physiologically-based pharmacokinetic model for lead. *The Science of the Total Environment*. 274:15-19.

Long, C.M., H.H. Suh, L. Kobzik, P.J. Catalano, Y. Ning, and P. Koutrakis. 2001. A pilot investigation of the relative toxicity of indoor and outdoor fine particles: in-vitro effects of endotoxin and other particulate properties. *Environmental Health Perspectives* 109:1019-1026.

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Seeley, M.R., L.E. Tonner-Navarro, B.D. Beck, R. Deskin, V.J. Feron, G. Johanson, and H.M. Bolt. 2001. Procedures for health risk assessment in Europe. *Regulatory Toxicology and Pharmacology*. (34):153-169.

To request copies of articles or presentations, please contact us at [trends@gradientcorp.com](mailto:trends@gradientcorp.com) or telephone Alison F. Barlow at (617) 395-5000.

## Risks vs. Benefits of Pesticide Use

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the control of disease. However, the potential risks associated with their use should be a part of any risk-benefit decision to use them.

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### References:

- Luckman, W.H. and R.L. Metcalf. 1982. Chapter 1: The Pest Management Concept. In: Introduction to Insect Pest Management. 2<sup>nd</sup> Edition. Metcalf, R.L. and W.H. Luckman (Eds). John Wiley and Sons. New York. pp 1-32.
- Spielman, A. and M. D'Antonio. 2001. Mosquito: A Natural History of our Most Persistent and Deadly Foe. Hyperion. New York.
- Wargo, J. 1996. Our Children's Toxic Legacy. Yale University Press. New Haven, Connecticut.

# Guest Editorial: Grandpa Knew Best

*Chemical safety is best ensured through a variety of mechanisms.*

Grandpa thought everyone needed a really big tool box. He used to say, "If all you have is a hammer, everything starts looking like a nail." He was right, and not just about home repair.

If you ask a lobbyist how to be sure that a product is safe for its intended use, he will probably urge better regulation. Ask an engineer, and she will check blueprints, run information through models, and review test data. Someone in marketing might say that product performance and customer satisfaction are the most important drivers. Lawyers, of course, will advise that the threat of product liability decisions prevent risky products from coming to market. Environmental organizations think that making information publicly available can be a catalyst for change, improvement and safer products.

*...few CEOs are willing to "bet the company" on a product that presents even a potential unreasonable risk.*

Each perspective is different, and each is correct. The safety of chemical products is a shared responsibility which requires the participation – and perspectives – of many. Given the number of chemicals in commerce, no single approach can possibly do the job. In fact, there are at least four mechanisms in place to promote chemical safety.

First is the Toxic Substances Control Act (TSCA) – the principle legal mechanism to control basic industrial chemicals. It gives the EPA broad authority to order testing and data submission, to limit or ban the use or manufacture of a chemical, and to regulate the introduction of new chemicals into the market. TSCA is risk-based, so the EPA must weigh the potential costs and benefits of proposed regulatory actions. Scientific uncertainties and complex technical issues can make

this process difficult. Multiply that difficulty by thousands of chemicals, and it is clear why some regulators have expressed preferences for more simple (but less accurate) hazard-based approaches.

Fortunately, chemical safety does not rest on TSCA alone. Practical safety considerations play a major role. Does the product perform properly? Can the customer use it safely and easily, without special equipment or training? Can the product be safely made and shipped to the customer? In the consolidated and ultra-competitive chemicals marketplace today, even a potential "no" to any of these questions can doom a product.

Third, like it or not, the fear of a mammoth product liability judgment also plays a significant role in chemical safety. With jury verdicts routinely costing companies millions, and even hundreds of millions of dollars, few CEOs are willing to "bet the company" on a product that presents even a potential unreasonable risk.

Voluntary industry programs provide a critical fourth leg in chemical safety. Responsible Care's® ten guiding principles cover chemicals in the workplace, disposal, distribution, testing and chemical assessment, as well as agreements to set and publicly measure progress against performance goals. More recent efforts by American Chemistry Council members to invest in mechanistic research and provide the public with test data on thousands of high production volume chemicals demonstrate a commitment not just to understand chemical hazards, but to be proactive in disclosing potential risks.

Managing chemical risks is a constant, complex task. It requires cooperation, patience, and a dedication to science. Fortunately, if any one tool doesn't do the job, we've got a big tool box.

Steven Russell, Esq.  
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American Chemistry Council

## In the next issue:

*Overview: Indoor Air Quality*

*Time/Activity Patterns and Exposure*

*Health Effects of Molds*

*Guest Editorial: Indoor Liability Issues*

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