Contributions of Pesticide Residue Chemistry to Improving Food and Environmental Safety: Past and Present Accomplishments and Future Challenges

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ABSTRACT: The principles of modern pesticide residue chemistry were articulated in the 1950s. Early authors pointed out the advantages of systematizing and standardizing analytical methods for pesticides so that they could be widely practiced and the results could be reproduced from one laboratory to the next. The availability of improved methods has led to a much more complete understanding of pesticide behavior and fate in foods and the environment. Using methods based largely upon gas chromatography (GC) and high-performance liquid chromatography (HPLC) coupled increasingly with mass spectrometry (MS) and MS^n as the detection tool, residues can be measured at parts per billion levels and below in a variety of food and environmental matrices. Development of efficient extraction and cleanup methods, techniques such as ELISA, efficient sample preparation techniques such as QuEChERS, and automated laboratory and field instrumentation has also contributed to the tools available for use in modern pesticide residue analysis. As a result, great strides have been made in improving food and worker safety and in understanding environmental behavior and fate of pesticides. There are many challenges remaining in the field of pesticide residue chemistry that will continue to stimulate analytical chemists. New chemistries are emerging, often patterned on complex natural products. Analyzing for the parent chemicals and potentially multiple breakdown products will require analytical ingenuity. The development of more sensitive bioassays and knowledge of unintended side effects will challenge residue chemistry as well, as in the case of following the fate of environmental endocrine disruptors associated with some pesticides as well as nonpesticide contaminants from packaging materials and other familiar articles. Continued funding and other resources to ensure better training, international cooperation, and accelerated research and development activities will be a constant need in pesticide residue chemistry as it is for all areas of science that aim to mitigate or eliminate contaminants that can affect human and environmental health and safety.

KEYWORDS: pesticide residues, reproducibility, breakdown products, endocrine disrupters, analytical methods

■ INTRODUCTION

Synthetic pesticides have played a major role in food, feed, and fiber production as well as in public health and environmental quality for many years. By most accounts, this will continue to be the case for the foreseeable future (Figure 1),[1,2] although the types of pesticides used will trend from the more toxic and/or persistent chemical types to biorationals, low-dose materials with reduced risk to people and other nontarget organisms, and pest control agents that are based upon biotechnology as the world strives to adopt more sustainable, "green" technologies in the future.

Chemistry will continue to play a significant role in pest management including the use of synthetic chemistry to design new active ingredients and formulations, and analytical chemistry will assist in determining food safety, safety for farmworkers, consumers, and others in the food, feed, and fiber supply chains and in the protection and safety of the environment. Pesticide residue chemistry has evolved in response to these needs, particularly in the past 50-plus years since the discovery and widespread use of broad classes of chemical pest control agents — organochlorines, organophosphates, carbamates, pyrethroids, phenoxys, triazines, and many others.

In this paper, we will attempt to capture the notable contributions of pesticide residue chemistry in assuring the safe use of existing products and in furthering improvements in understanding and managing pest control agents in the future. The maturing of pesticide residue chemistry from largely art and practice to a science-based discipline accelerated as a result of work of early authorities such as Francis Gunther and Roger Blinn. They recognized that residue behavior would vary with each chemical and each foodstuff or matrix, hence the need for investigating each pesticide and matrix individually in the development of methods for quantitation. They also saw "real promise of systemization and standardization of efforts in new applications."[3] To paraphrase, the evolving art of residue determination should be accompanied by more emphasis on the underlying science so that methods might accommodate existing

and new pest control chemistries in fewer, more general analytical approaches.

This evolution from art to science-based residue methods has been well demonstrated in the development of techniques for detecting and measuring low concentration levels of pesticide residues (Figure 2).[4] In the 1940s and 1950s, techniques for residue determination largely relied on bioassay, gravimetric and titrimetric "wet" chemistry methods, colorimetry, and paper or (later) thin-layer chromatography. Achievable detection limits in food or environmental applications were, on average, between 1.0 and 0.1 ppm, and the selectivity was often based upon classes of chemicals (e.g., cholinesterase inhibition for organophosphates and carbamates) rather than specific compounds. Dating roughly from the 1960s and early 1970s, first gas and then modern liquid chromatography were adapted to residue determination. These techniques, when combined with the use of selective and/or sensitive detectors such as electron capture and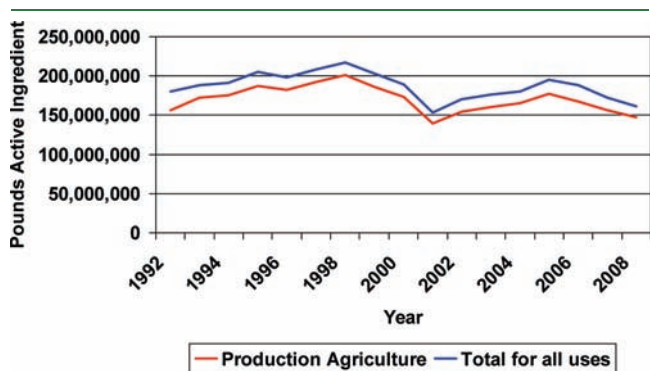 other ionization detectors for GC, and UV−visible spectrophotometric detectors for HPLC resulted in lower detection limits and improved selectivity.[5,6] For highly toxic chemicals that were relatively widely spread in food and environmental media, such as the polychlorinated dibenzodioxins and dibenzofurans, mass spectrometry coupled as the detection system to GC and HPLC became the method of choice, with much lower detection limits to ≤ 1 ppt in biological samples[7−12] and selectivity for each of the more toxic isomers and congeners. Mass spectrometry (MS)-based systems, including modifications such as tandem MS/MS or MS^n, time-of-flight (TOF), and inductively coupled plasma MS for inorganics have become the norm in pesticide residue determination as well as for other types of chemical contaminants in food and environmental samples. Pesticide residue chemists now often analyze for a variety of trace toxicants — persistent organic pollutants (POPs), heavy metals, and combustion byproducts — in addition to pesticides.

As the field evolved to high-performance chromatography, selective detection systems, and then MS-based techniques, the capital investment in instrumentation increased as well. But the advantages of GC- and LC-based methods, and specifically the ability to detect dozens or hundreds of individual analytes in a single run, resulted in decreasing costs per analysis, but with improved sensitivity and selectivity, and thus higher throughput and decreased turnaround time. These capabilities have justified the higher capital investment for initial purchase of the instruments in most commercial and regulatory laboratories.

Figure 1. Pounds of pesticide active ingredients used in California agriculture, 1992−2008. Source: California Department of Pesticide Regulation.[1,2]

■ FOOD SAFETY

With these advantages, residue chemists could process more samples in less time and do so with better accuracy and precision than ever before. Better characterization of the distribution of residues in groups of samples resulted in finding some of the more persistent and widely used chemicals in many types of common foods, including in foods consumed by sensitive
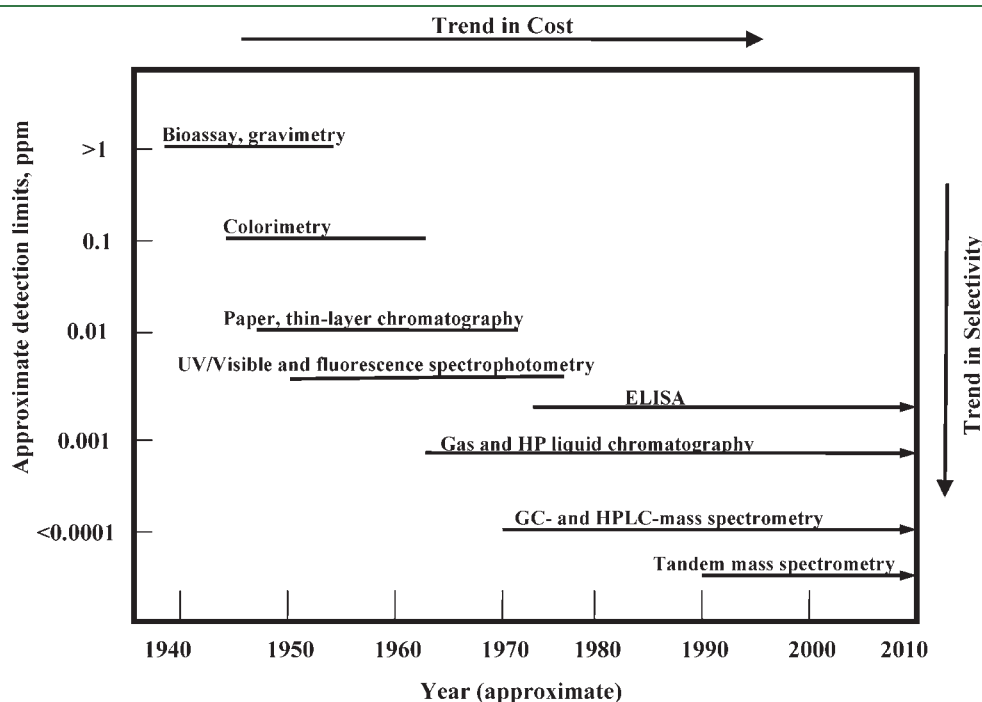

Figure 2. Development of chemical analytical methods over time. Adapted from Fong et al.[4]

Table 1. Food Monitoring in California, 2009 (Source: California Department of Pesticide Regulation)[15]

Marketplace Surveillance[a]	
pesticide residues	
no detectable residue	73.4%
within tolerance	24.2%
illegal residues[b]	2.4%
origin of samples	
domestic	57.4%
imported	41.6%
unknown	1%

[a] Includes wholesale and retail outlets, distribution centers, and farmer's markets. [b] Of the illegal residues, 12.3% were over tolerance and 87.7% contained pesticides not authorized for use on the commodity.

population subgroups such as infants and children.[13] This ability to determine aggregate and cumulative exposures for risk assessment provided the principles upon which the Food Quality Protection Act of 1996 in the United States was based.[14] Residue chemistry was the tool by which the widespread distribution of more toxic and in some cases bioaccumulated organochlorine, organophosphate, triazine, and other chemical classes of "legacy" pesticides introduced in the 1940s—1970s was characterized, leading to eventual banning of many chemicals and their replacement with less toxic, less persistent products. A good case can be made that food is now safer, at least in regard to exposures to residues of more toxic chemicals, as a result. Results from food monitoring programs in the United States and elsewhere bear this out: the rate or percent of pesticide residues in foods that exceed legal limits established by regulatory agencies, which are increasingly risk-driven, have decreased in large part because of the turnover in pesticide types to favor less toxic and/or persistent chemicals and by improvements in other areas such as application technology, which also benefited from the detailed information developed by pesticide residue chemists (Table 1).[15]

And yet there are still many safety issues associated with chemicals in foods, many of which lie outside the use of pesticides. Acrylamide is a case in point. Acrylamide is widespread in common foods, particularly in carbohydrate-rich foods that are prepared by high-temperature processing or cooking and are subject to Maillard browning reactions. Examples include potato chips, French-fried potatoes, crackers, and many other products.[16—18] The analytical procedures that led to the discovery and tracking of acrylamide in foods are those widely used in pesticide residue chemistry and, in some cases, residue chemists applied their expertise to determining acrylamide, and its precursors, and the effect of cooking/processing conditions to find conditions under which acrylamide levels could be minimized, again to the benefit of food safety.

There are other nonpesticide issues that could command greater analytical interest, including monomers, byproducts, and additives that may migrate from plastic articles and packaging into food[19] and food colorants, artificial flavors, metals, and other inorganics such as perchlorate, surfactants, oil spill-related chemicals, nanoparticles, and the toxins produced by pathogenic microorganisms and those present in fish (e.g., ciguatoxin in fin fish) and other aquatic human foods[20,21] (Figure 3). These are among the chemical types increasingly questioned by consumers and regulatory agencies. The "residue chemist of the future" must be adept at more than

pesticides analysis and willing to ply his/her trade where the problems of potentially harmful or illegal chemicals in foods may lead. Examples include the chemical "sleuthing" employed to track down melamine contamination in infant formula and domoic acid in seafood.[22—25] Future chemists will need to be prepared for such contingencies, including residues associated with the introduction of complex biorational chemicals to the pesticide and antibiotic markets, such as the avermectins (Figure 4). The ability to discriminate between enantiomers, to detect adducts and breakdown products and other "biomarkers" and the effect of these on animal and human metabolism (metabolomics) will define the successful residue chemist in the future.

Several such challenges that will drive residue chemistry in the future may be summarized as follows:

- changing nature of analyte chemistries, often patterned after complex natural products
- need for routine analysis for multiple residues in samples (including all classes of pesticides, as well as plasticizers, surfactants, polynuclear aromatic hydrocarbons, etc.)
- matrix composition effects
- need for lower detection limits resulting from more protective residue tolerances
- changing regulations and regulatory levels for chemicals (in food, water, air, etc.)

■ WORKER SAFETY

Residue chemistry has similarly led the way to improvements in worker safety, in part because improved methods have allowed researchers to better define when and how exposures occur. This in turn has led to better education of workers, better protective clothing (although there is still work to be done in this area), more frequent use of goggles, respirators, face shields, etc., and altered working habits that can help avoid exposures. As with food safety, changes in pesticide chemistry to favor reduced-risk chemicals and biorationals have helped as well. The lower incidence of occupational injury and illness, and particularly lowered fatality rates caused by occupational exposure to pesticides in California and the United States, reflects this improved safety record (Figure 5).[26]

Despite the decline in occupational pesticide illnesses, acute pesticide poisoning, especially among farmworkers, continues to be an important problem. Off-target pesticide drift, early re-entry, and use in conflict with the label have been identified as factors that contributed to exposure in more than half the occupational poisoning cases reported in the United States in 1998—2005.[27] Nonoccupational exposures present challenges as well, and each year there are examples of illnesses associated with exposures to pesticides that are improperly stored, especially in unlabeled containers, and with consumer products designed for home or garden use that are not used in accordance with label instructions.[28] Although acute occupational pesticide poisonings in developing countries are small in relation to overall reported poisoning and to occupational injuries in agricultural workers globally, they present important challenges and opportunities for contributions by pesticide chemists, along with regulators, educators and health practitioners, to worker health internationally.[29]

■ ENVIRONMENTAL SAFETY

Residue chemistry has also provided key information in the area of environmental safety[30] in such areas as

- understanding environmental fate processes for pesticides

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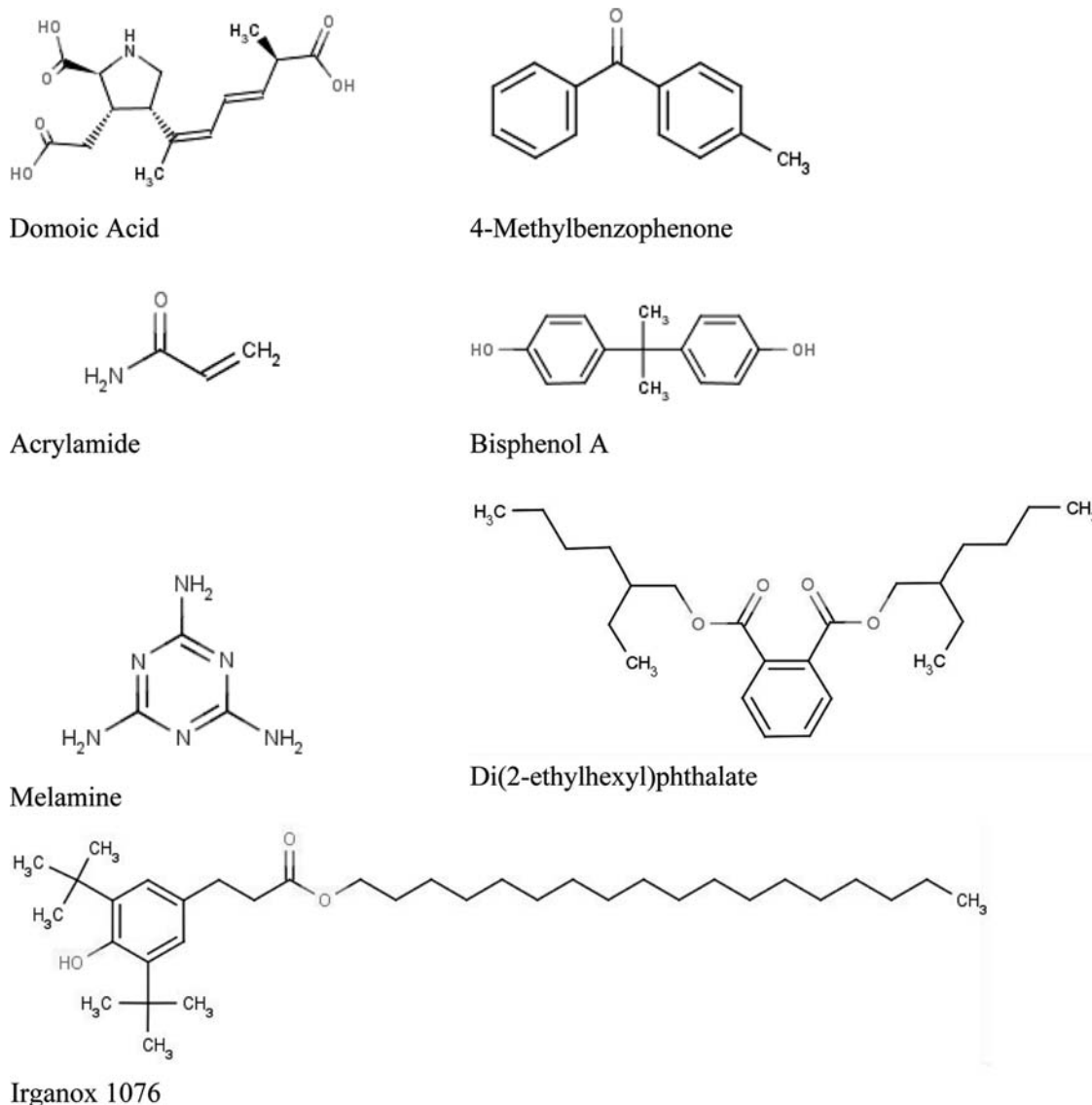dx.doi.org/10.1021/jf103902t |J. Agric. Food Chem. 2011, 59, 7536–7543

Figure 3. Food contaminants of recent concern. Structure source: National Library of Medicine, ChemID database.

- development of models and other screening tools for premarket evaluation of candidate pesticides
- avoiding contamination of water and air, particularly in and around populated areas, wildlife habitats, etc.

The ability of pesticides to become mobilized and thus widely distributed, through the atmosphere and surface and groundwater and in food chains, could only be roughly estimated until about 1970 when environmental processes affecting pesticides began to be delineated and addressed with research. Residue chemistry provided important data on occurrence, concentration levels, distribution and dissipation rates, and pathways.[31,32] Environmental fate and exposure models are now readily available, and many have been validated by experiments and/or field studies in which residue chemistry has played a key role in providing quantitative data upon which models are based and/or tested.

As an example, we were able to measure airborne pesticides, often many miles downwind from use areas, both during spraying when residues could drift off target and after spraying was completed and pesticides with appreciable vapor pressures could volatilize and be carried by wind currents.[33] Molinate, a

semivolatile herbicide applied to rice paddies, is a case in point.[34] The relatively high Henry's constant of dissolved molinate leads to a fairly constant rate of volatilization from flooded rice fields, such that the herbicide can be detected, both by the human nose and by trapping on XAD resin, several miles downwind of the rice-growing areas in California's Sacramento Valley, including on the rooftops of rural school buildings. There are now many reports of similar findings for other pesticides,[35] including intrusion into pristine foothill and high mountain areas in California[36] and elsewhere in the world.[37]

Volatilization and downwind air movement have been well documented for fumigants — volatile compounds by nature that are used to sterilize the soil before planting, to kill insects in stored grains, and to kill termites and other insects in structures. Examples of fumigants that have been studied in this regard are methyl bromide,[38] methyl isothiocyanate (formed from Metam Sodium in soil or water),[39] chloropicrin, and 1,3-dichloropropane. The release rate (flux) of these chemicals from soil to air generally follows their vapor pressures, that is, highest release rate for methyl bromide, lowest for MITC — all determined by residue chemistry
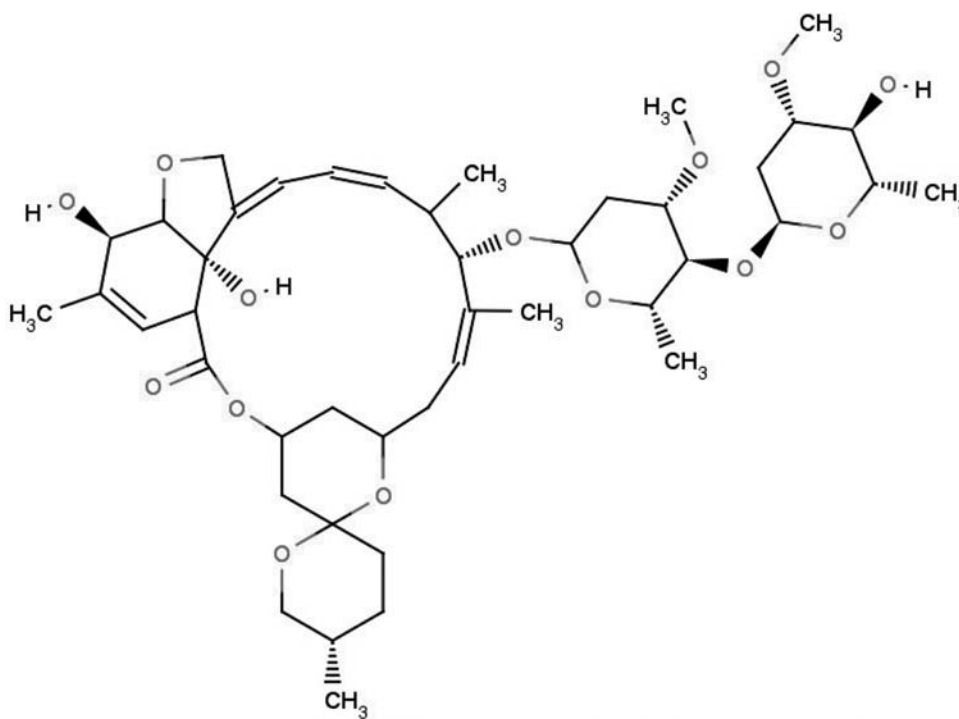
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Figure 4. Avermectin structure. Source: National Library of Medicine, ChemID database.
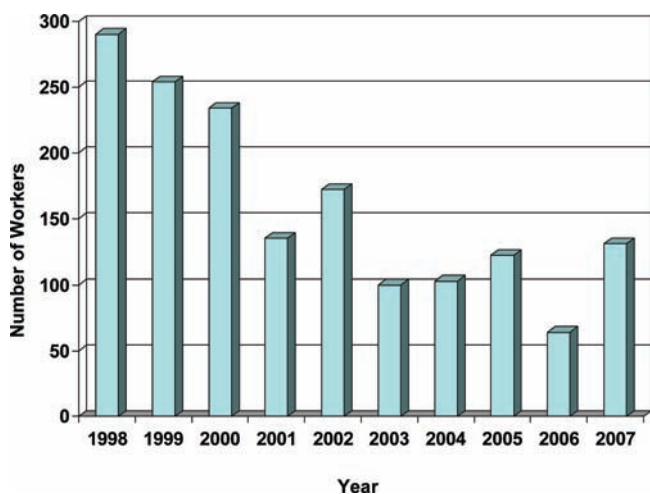

Figure 5. Numbers of workers per year with occupational acute pesticide-related illness. Source: California Department of Public Health.[26]

using the aerodynamic flux method[40−42] and various trapping techniques and postsampling analysis procedures.[43]

With the information developed by field experimentation and residue analysis, models have been developed to estimate emission rates from soil, water, surfaces, and other media, using fumigant physicochemical properties including vapor pressure and environmental conditions as inputs.[44,45] The measured or modeled release rates can then provide the source term for estimating downwind concentrations, where exposures might occur, by coupling with standard atmospheric dispersion models such as the Industrial Source Complex Short-term (ISCST) and CalPuff models. These models can be used to predict the movement of the plume of volatilized fumigant with distance, time since application, application rate, use of protective barriers to reduce rate of volatilization, varying wind directions and wind speeds, downwind topography, and soil and air temperature. It would be extremely expensive and time-consuming to run field studies under all likely scenarios of these variables, but simulations of downwind concentrations can be run for any time period or variety of wind patterns relatively rapidly using models. From a practical point of view, they allow regulators to make decisions on whether to allow a given application or to set buffer distances from application sites to homes, schools, playgrounds, farmworker work sites, etc., based upon estimated or modeled exposures.

This approach can also be used to estimate airshed or valley-wide concentrations of fumigants resulting from a single application or from multiple application sites. This approach was used to simulate methyl bromide levels in the Salinas Valley airshed resulting from fumigation of fields around the city of Salinas to 50 miles downwind near King City in the most southeasterly end of the valley.[38] The maximum air concentrations, either measured or modeled, can be compared with regulatory no observed adverse effect levels (NOAEL) or other health-based end points to estimate the effect on human health from a widespread practice such as field fumigation with methyl bromide to reduce nematode populations.

The point is that residue chemistry plays a vital role in the development and validation of models. Residue chemists who combine their expertise with that of modelers can make huge impacts on regulatory policy and on human and environmental safety.

Residue chemistry is also a vital part of the teamwork needed to track down and mitigate adverse effects of pesticide drift to wildlife. Wilson et al. described a series of experiments to determine exposures of red-tailed hawks to airborne residues of chemicals used in orchards as dormant season sprays, to kill overwintering pests.[46,47] Residue analysis was performed on hawk feathers, talons, and excreta (for diagnostic metabolites) and in the field air during normal atmospheric conditions and

also during heavy fogs.[48] The results implicated ethyl parathion, and its conversion product and activated form ethyl paraoxon, among about six pesticides used as dormant spray active ingredients, as the chemical responsible for observed mortality and morbidity among hawks in the general region of dormant spraying. A critical piece of information was the exact replication of the cholinesterase inhibition dose–response for fogwater collected from the orchard vicinity and for pure ethyl paraoxon standard.

The combination and comparison of residue analytical results with relevant biological end points to determine the biological relevance, if any, of their chemical findings represents another area for future focus. Long-term, low-level exposures are particularly difficult to evaluate in terms of their biological significance, representing a current frontier as residue chemistry provides findings of residues at ever lower concentration levels.

Another continuing challenge for residue chemistry is to produce data on multiple analytes that may occur, or co-occur, in foods, environmental media, and wildlife. Early multiresidue methods, such as the Mills FDA procedure for pesticides in fatty tissue,[49] were time-consuming, heavily reliant on wet chemistry (column chromatography, derivatization, etc.), and consequently slow and wasteful of solvent and reagents. A relatively recent approach that has been readily adopted by residue chemists worldwide is the QuEChERS method developed by Anastassiades, Lehotay, and colleagues.[50,51] In this Quick, Easy, Cheap, Effective, Rugged and Safe approach, a subsample is extracted with acetonitrile, mixed with a combination of readily available salts, agitated, and centrifuged, and an aliquot is injected directly on GC or LC. We need more such developments in the sample preparation area, or ideally no sample preparation at all, to increase throughput and reduce costs of analysis.

How we envision or accomplish methods with no sample preparation is yet to be determined. One approach is the use of in situ methods such as near-infrared spectrophotometry. As presently practiced, near-IR and many of the other in situ spectrometric methods lack the sensitivity needed for parts per million and lower detection and quantitation, but adaptation of atmospheric ionization mass spectrometry to determining the composition of air particulate matter[52,53] shows what can be done, with MS- or antibody-based methods or other emerging techniques documented increasingly in the pages of *Analytical Chemistry* and other references waiting to find applications in pesticide residue chemistry. Thus, another challenge for residue chemistry is to team up with those doing basic method discovery and development research and adapt the latest techniques to residue chemistry.

Fortunately, the human talent in pesticide residue chemistry, which includes scientists in academia, federal and state agencies, chemical companies, and independent contract analytical laboratories (Table 2), has been quite outstanding, as well illustrated by the quality of work presented at the Florida Pesticide Residue Workshop[54] and professional societies such as ACS and IUPAC.[55] Attracting talented scientists to residue chemistry is made possible by public funding to IR-4 and to FDA, CDFA, and other federal and state agencies and the availability of competitive funding from USDA, states, and industry sources. This funding is in constant jeopardy and will require support from all concerned about food, worker, and environmental safety. Programs that support graduate students, either directly or indirectly, should receive high priority to ensure a continuing supply of talent to the ranks of pesticide chemistry.

Table 2. Some Principal Agencies and Other Organizations in the United States That Conduct Pesticide Residue Analysis

federal
Environmental Protection Agency
Food and Drug Administration
Department of Agriculture
    Food Safety and Inspection Service
    Agricultural Research Service
    Agricultural Marketing Service
Fish and Wildlife Service
Geological Survey

state
California Department of Pesticide Regulation
California Department of Agriculture
California Department of Fish and Game
Florida Department of Agriculture
Texas, Oregon, Washington, New York, Massachusetts, Hawaii, Colorado, Maryland, Michigan, Minnesota, Montana, Ohio, and Wisconsin Departments of Agriculture, Environment, or Health

universities
IR-4[a]
Cornell University
University of California, Davis
University of Florida
Michigan State University
others

industry
National Food Processors Association
food companies
chemical companies
commercial laboratories

[a] The IR-4 Project (Interregional Research Project 4), begun in 1963, has contributed to the field of residue chemistry, serving as a major resource for minor food crop and ornamental growers by developing research data to support new EPA tolerances and labeled product uses.

■ SUMMARY

Residue chemistry will continue to perform its vital roles of safeguarding people and the environment from harmful residues. Areas that will challenge and help to improve residue chemistry in the future may include the following:

- apply the principles and techniques of residue chemistry to detecting residues of contaminants in addition to pesticides, such as acrylamide, melamine, microbial agents and their toxic metabolites, plasticizers and related compounds, and artificial colorants and flavors
- continue to be at the forefront of adapting new technologies to improve the detection and measurement of pesticide residues, such as has occurred with the use of stereoselective chromatographic methods for resolving enantiomers,[56] and adaptation of SPME and related techniques as exemplified by QuEChERS[50,51]
- utilize methods that can not only detect and measure but also indicate the biological relevance of residues, such as adapting new advances in proteomics, metabolomics, and

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other "omics" techniques that are based in molecular biology; here and now examples lie in the use of restriction fragment length polymorphism (RFLP) methods for detecting adulterants in foods.[57,58]

- build on the example of QuEChERS and other rapid methods to develop methods that require little or no sample preparation and, particularly, those that can be used in situ and/or in the field

- encourage the development of models that can accurately and quickly estimate residue loads on the basis of readily available inputs and conduct experiments to validate these models

- develop multiresidue methods that accommodate large numbers of pesticides and also residues of environmental concern as part of the same basic methodology

In all areas and applications of residue analysis, sampling (obtaining, preserving, and preparing a representative and valid sample for analysis) of commodities or segments of the environment, or people or other organisms, is often the operation which limits utility of the analytical information.[59] Better training of those charged with developing protocols and conducting sampling would significantly improve the quality of residue data. In situ methods might play a role by allowing for combining distributions from larger numbers of representatives of the population in a given analysis.

The outlook for pesticide residue chemistry and related contaminant analytical fields is extremely promising given the successes of the past in improving food, worker, and environmental safety. It will depend in the future on the availability of new and emerging technologies, a talent base that is distributed worldwide, and cultivation of funding and other resources devoted to contaminant analysis.

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