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CHANGES IN PESTICIDE USE AND DIETARY RISK IN THE USA SINCE THE PASSAGE OF THE FOOD QUALITY PROTECTION ACT (FQPA) IN 1996

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CHANGES IN PESTICIDE USE AND DIETARY RISK IN THE USA SINCE THE PASSAGE OF THE FOOD QUALITY PROTECTION ACT (FQPA) IN 1996

By

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ABSTRACT

CHANGES IN PESTICIDE USE AND DIETARY RISK IN THE USA SINCE THE PASSAGE OF THE FOOD QUALITY PROTECTION ACT IN 1996

By

Faye Regina Aquino Viray

The enactment of the Food Quality Protection Act (FQPA) in 1996 resulted in major changes in the registration of pesticides. These included increased safety for infants and children, the reregistration of older pesticides including the use of aggregate and cumulative exposure assessments, and the expedited registration of reduced-risk (RR) pesticides. Special regulatory focus has been on three groups of pesticides: the neurotoxic organophosphate (OP) and carbamate (NMC) insecticides, and the B2 carcinogenic fungicides. Despite the pressure to substitute RR pesticides for these older, toxicologically suspect compounds, there has been little public analysis of changes in the pesticide use and residue levels or of changes in dietary risk resulting from FQPA. This study aims to assess these changes. The data were obtained from publicly-available databases, i.e. the USDA's Pesticide Data Program, the California Department of Pesticide Regulation, the CropLife Foundation, and the FDA's Total Diet Study.

The use and food residue detects of individual OPs showed a strong declining trend with an approximately 50% overall decline for the group from 1994 to 2006. The use of NMCs also declined approximately 70% from 1994 to 2006, but their residue detection trends were variable and did not clearly correspond to the decline in use. The use of the B2 fungicides declined less (10-20%) and there was no overall decrease in residue detects for most of these compounds. The RR insecticides and fungicides showed a steady increase over this time such that they are now central in pest management

programs for fruits and vegetables but the residue data are too limited to establish a trend. It was estimated that approximately 50% (33-60%) of the RR pesticides were registered by USDA's IR-4 program. In some cases, residue detections were unexpectedly high and greater than those for the older compounds. Since the RR pesticides are applied at much lower rates than the older compounds, their adoption has resulted in lower levels of chemical use in fruit and vegetable production. This decreased environmental load, coupled with the improved toxicological profiles of the RR compounds, implies an increase in environmental and worker safety as well as a reduction in dietary risk.

The replacement of the B2 carcinogenic fungicide, iprodione, by the IR-4 registered RR compound, fludioxonil for use on stone fruits, was selected as a case study to illustrate changes in dietary risk after FQPA. Both the DEEM and Lifeline exposure assessment programs were used. The exposures were compared to the reference doses (RfDs). The percentage of the RfDs estimated for fludioxonil were lower than those for iprodione in both acute and chronic exposures, and the iprodione risks declined significantly after the passage of FQPA. These risks were highest for the 1-2 year old age group and declined rapidly thereafter with age. However, the largest contribution to food safety was through the reduction in carcinogenic risk due to reduced levels of exposure to iprodione and the lack of carcinogenicity of fludioxonil. A comparison of these risks at different tiers of analysis showed that both the acute and chronic dietary risks generally decreased from the lower to higher tiers (tier 1>tier 2>tier 3) which is expected since the input parameters become more realistic at higher tiers of analysis. Finally, a comparison of the DEEM and LifeLine programs in these analyses revealed comparable results despite considerable differences in their approaches to estimating dietary exposures.

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-Faye

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LIST OF ABBREVIATIONS

aPAD	Acute Population Adjusted Dose
aRfD	Acute Reference Dose
AMS	Agricultural Marketing Service
AZM	Azinphos-methyl
BEAD	Biological and Economic Analysis Division
CA-DPR	California Department of Pesticide Regulation
CAG	Cumulative Assessment Group
CARES	Cumulative and Aggregate Risk Evaluation System
CLF	CropLife Foundation
CMG	Common Mechanism Group
cRfD	Chronic Reference Dose
CSFII	Continuing Surveys of Food Intake by Individuals
CSREES	Cooperative State Research, Education, Extension Service
DEEM	Dietary Exposure and Evaluation Model
DRI	Dietary Risk Index
EBDC	ethylenebisdithiocarbamate
EDSP	Endocrine Disruption Screening Program
EDSTAC	Endocrine Disruptor Screening and Testing Committee
EPA	Environmental Protection Agency
ETU	ethylthiourea
FDA	Food and Drug Administration
FEPCA	Federal Environment Pesticide Control Act

FFDCA	Federal Food, Drug and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
FT	Field Trial
GAO	General Accounting Office
HCB	hexachlorobenzene
HFT	Highest Field Trial
ILSI	International Life Sciences Institute
IR-4	Interregional Research Project No. 4
IRED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of Detection
MF	Modifying Factor
MOE	Margin of Exposure
MRM	Multiresidue method
NAPIAP	National Agricultural Pesticide Impact Assessment Program
NAS	National Academy of Sciences
NASS	National Agricultural Statistics Services
NCFAP	National Center for Food and Agricultural Policy
NCHS	National Center for Health Statistics
NDs	Non-detects
NHANES	National Health and Nutrition Examination Surveys

NMCs	*N*-methylcarbamates
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Adverse Effect Level
NRC	National Research Council
OIG	Office of Inspector General
OP(s)	Organophosphate(s)
OPP	Office of Pesticide Program
PCT	Percent Crop Treated
PDP	Pesticide Data Program
ppm	Parts per million
PUMS	Public Use Micro Data Sample
RAC	Raw Agricultural Commodity
RED	Reregistration Eligibility Decision
RfD	Reference Dose
RPF	Relative Potency Factor
SAES	State Agricultural Experiment Stations
SAP	Scientific Advisory Panel
SDWA	Safe Drinking Water Act
TDS	Total Diet Study
UF	Uncertainty Factor
USDA	United States Department of Agriculture
WPS	Worker Protection Standard

CHAPTER 1
INTRODUCTION

1.1 Pesticide Regulation Before the Food Quality Protection Act (FQPA)

Pesticides in the United States are regulated under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA). The Environmental Protection Agency (EPA) registers pesticide uses under the FIFRA and sets pesticide tolerances in food under the FFDCA. The Food and Drug Administration (FDA) enforces the tolerances for most foods, and the tolerances for meat, poultry and some egg products are implemented by the U.S. Department of Agriculture (USDA). Regulation dates back to 1910 when the Federal Insecticide Act was passed "to ensure the quality of pesticide chemicals purchased by consumers" in response "to concerns from the U.S. Department of Agriculture (USDA) and farm groups about the sale of fraudulent or substandard pesticide products, which was common at that time" (Toth 1996). In 1947 the FIFRA was enacted and extended the coverage to include herbicides and rodenticides. Under the FIFRA, tolerances were set for pesticide residues in food. It required registration of all pesticide products with the USDA before they were sold within or outside the U.S. The standards for labeling the products were set and labeling was also required. The EPA was created in 1970 and was charged to administer the FIFRA. The FIFRA was amended in 1959 and in 1964 but the most significant changes took effect in 1972 under the Federal Environmental Pesticide Control Act (FEPCA). The changes included (Toth 1996):

1. Requirement that all pesticides (including those sold interstate) be registered with EPA and classified by the agency for *general* or *restricted use*.

2. Certification was required for persons applying *restricted* use pesticides.
3. Set a new registration standard for pesticides, allowing the registration of a pesticide only if it could be determined that the pesticide would not cause *unreasonable adverse effects.*

With this law, the emphasis on pesticide regulation in the U.S. moved from quality assurance and adequate labeling of pesticide products to the protection of public health and the environment from their potential hazards (Toth 1996). The FIFRA was further revised and amended from 1975 to 1981 to improve the registration process of pesticides and "provide for consideration of the agricultural benefits of pesticides in regulatory decision made by the EPA" according to Toth (1996), and the pesticides registered before August 1975 were reviewed as a consequence of the amendments. In 1988, FIFRA was further amended "to establish a 9-year schedule for completion of the reregistration of pesticide active ingredients registered before November 1984 and to impose substantial fees on registrants to cover much of the costs of the registration". This led to voluntary cancellations of thousands of registrations by registrants due to obsolescence, costs and data requirements; only a few were suspended or canceled by the EPA. Worker safety also became a concern and led to the revision of the Worker Protection Standard (WPS) for agricultural pesticides which took effect in 1992. It required modification of labels to include the use of personal protective equipment, restriction of re-entry intervals of workers to pesticide-treated areas, and notification of workers about treated areas.

The Federal Food and Drugs Act, or Pure Food Law, enacted in 1906 was intended for public protection from adulterated or misbranded food but it did not include

pesticide residues. The Food and Drug Administration (FDA) was authorized to enforce the tolerances for chemicals to protect public health when the FFDCA was passed in 1938. The Miller Amendment to the FFDCA required tolerances be set for all pesticides and further required any raw agricultural commodity to be condemned as adulterated if it contained a pesticide residue above the tolerance level established by the FDA (Toth 1996). Food additives were also covered in the 1958 amendment through the Food Additives Amendment. This implied that processed foods containing pesticide residues that exceeded tolerance levels were considered "adulterated and subject to seizure similar to raw agricultural commodities" according to Toth (1996). The amendment also included the Delaney Clause which called for a zero tolerance for any food additive (including pesticides) that might cause cancer.

1.2 Driving Forces for the Enactment of the FQPA in 1996

The Food Quality Protection Act (FQPA) amended both the FIFRA and the FFDCA, and one of the major driving forces of the enactment of the FQPA was the huge backlog at the EPA when it started the review of pesticide registrations in 1975. During the period of 1976 to 1988, the EPA's review or reregistration of older pesticides was proceeding at a much slower pace than originally anticipated by the EPA or Congress (Toth 1996). This underlined the need to have a more rapid reregistration process. Concerns about the risk and safety of farm workers and applicators were also major drivers for the changes in the pesticide regulation. The Delaney Clause was highly criticized in some quarters and was also a reason for the FQPA. Its concept of zero carcinogenic risk inhibits the flexibility of a regulatory agency to make tolerance decisions based on the latest risk models because it means that even the most trivial risk cannot be allowed and it also "creates a false expectation that a processed food will not

have any cancer-causing substances in it" (Vogt 1995). Vogt (1995) further commented that since the Delaney Clause sets a standard only for carcinogenic residues that concentrate in processed foods, the same pesticide chemical must meet inconsistent requirements (zero-risk versus risk-benefit balancing) depending on whether it is found in/on processed or raw food. This is often referred to as the "Delaney Paradox". The Delaney Clause also limited the introduction of lower-risk pesticides that could replace older and potentially more hazardous compounds also according to Vogt (1996). The National Academy of Sciences (NAS) was tasked by the EPA to "review the conflicting standards and basis for tolerance setting" in 1984. In the 1987 analysis report, *Regulating Pesticides in Food: The Delaney Paradox* by the NAS/National Research Council (NRC) it was concluded that pregnant women, infants and children faced unique risks from pesticide exposure, and that existing EPA risk assessment procedures were not taking these unique risks into account (Landrigan and Benbrook 2006). The increased emphasis on protecting the health of infants and children led to the creation and refinement of the U.S. Department of Agriculture's Pesticide Data Program (PDP) and to major EPA research initiatives.

Endocrine disruption became a critical focus and was also a contributor to the passage of the FQPA. It has led to the development of the Endocrine Disruptor Screening Program (EDSP) by the EPA, when the FQPA and the Safe Drinking Water Act (SDWA) were amended in 1996. The program required the EPA to "develop a screening program, using appropriate validated test systems and other scientifically relevant information to determine whether certain substances may have an effect in humans that is similar to an

effect produced by a naturally occurring estrogen or other endocrine effect as the EPA may designate" (U.S.EPA 2007b).

1.3 Major Regulatory Changes Imposed by the FQPA

The passage of the FQPA was a turning point in the regulation of pesticides and led to several major changes:

- Amendments to the FFDCA provided special provision for the more sensitive population, i.e. infants and children (FQPA 1996) and an additional 10-fold safety factor when establishing acceptable levels of exposure was required "to further protect infants and children unless reliable information in the database indicates that it can be reduced or removed" (U.S.EPA 2007c).

- The focus of regulating pesticides switched from balancing risks and benefits to a greater emphasis on public health and the environment. The Delaney Clause was removed when the FFDCA was amended and the FQPA enacted in 1996. The FQPA eliminated the distinction between raw-food and processed-food tolerances so that all pesticide residues are regulated under an amended FFDCA section 408 that requires all tolerances be "safe", ensuring a "reasonable certainty of no harm" from pesticides (NRC 2000) and established a single health-based standard. Although the switch has been significant, in practice benefit considerations are still important.

- Tolerances were required for the issuance of emergency exemptions. Section 18 of the FIFRA authorizes EPA to permit state and federal agencies to allow the unregistered use of a pesticide for a limited time if EPA determines that emergency pest conditions exist and no registered pesticide would be effective (NRC 2000) and tolerances were now required for pesticides under the emergency exemption. This is a very significant aspect of the FQPA and the NRC (2000) noted that this "had the most

profound effect on the ability of the agency to meet its deadlines, and it is responsible in part for the reduced number of new uses and new active ingredients".

- Tolerance reassessment and reregistration of pesticides were required by the FQPA. Under the FQPA, there was increased provision for the assessment and quantification of the risks from pesticides. The FQPA required reevaluation of all tolerances set before August 1996 within ten years. Pesticides containing any active ingredient registered before November 1, 1984 were required to be reregistered and a periodical review every 15 years was also mandated for the reregistered pesticides.

- Aggregate exposure assessment was developed by the EPA as part of the reregistration process. It considers all routes such as dietary, drinking water, and non-occupational exposures to a single chemical for risk assessment purposes.

- Cumulative exposure assessment was also developed by the EPA. It requires assessing the cumulative risk from exposure to pesticides and other substances that have of a "common mechanism of toxicity" (EPA, 2002). The FQPA also requires consideration of endocrine disruption effects for tolerance reassessment and risk evaluation (U.S.EPA 2007c). An environmental endocrine disruptor is defined as an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (U.S.EPA 1997). This called for the EPA to develop the Endocrine Disruptor Screening Program (EDSP) that is responsible for testing and screening for possible endocrine disruptors. As of late 2008, the EDSP program had yet to be finalized by EPA.

- FQPA required the development of a minor use program in the EPA and provided that special considerations be afforded to minor use actions (U.S.EPA, 2007b).
- FQPA mandated and required EPA to expedite the approval of reduced-risk pesticides.

1.4 EPA's Response to the FQPA

The main requirement of the FQPA since its enactment in 1996 is to accomplish the review and reassessment of tolerances of pesticides within ten years according to the new standards. By August 2006, EPA had completed over 99% of the 9,721 tolerance reassessments required by FQPA. Three thousand two hundred tolerances were recommended for revocation and 1,200 tolerances were modified and the safety of 5,237 tolerances was confirmed. Nearly 4,400 out of 17,592 individual pesticide end-use product registrations have been cancelled (U.S.EPA 2006a). Also, the addition of the extra ten-fold factor for children's safety is now a standard in dietary risk assessment. Another outcome of the FQPA is the impact assessment from aggregate exposure from food, residential and non-residential sources that EPA requires for reregistration of pesticides and the introduction of cumulative risk assessments for pesticides having a common mechanism of toxicity. The EPA completed the cumulative risk assessments of the organophosphate and the carbamate pesticide groups in 2006 and 2007, respectively.

The primary issue dealt with during the development of the cumulative exposure assessment method was the consideration of what constitutes a common mechanism of toxicity. A common mechanism of toxicity group consists of chemicals for which scientifically reliable data demonstrate that the same toxic effect occurs in or at the same organ or tissue by essentially the same sequence of major biochemical events (U.S.EPA 2007a). The EPA worked with the International Life Sciences Institute (ILSI) and

participated in workshops to discuss this issue in relation to the organophosphates. Consequently, the common mechanism of toxicity of the carbamates, chloracetanilides, thiocarbamates and dithiocarbamates was also considered. A series of consultation and deliberations in developing the method included hazard and dose-response assessment, endpoint selection, and probabilistic approach issues and the use of advanced computer risk assessment models such as LifeLine and the Dietary Exposure and Evaluation Model (DEEM). Probabilistic analysis involves the use of a statistical technique (e.g. Monte Carlo analysis) to quantify both the distribution of exposures to pesticide residues and the probability or chance of exposure to any particular residue level (U.S.EPA 2000).

Worker safety and exposure also became a concern and led to the establishment of guidelines specifically addressing worker exposure by the EPA. The Worker Protection Standard (WPS) is a federal regulation designed to protect agricultural workers (people involved in the production of agricultural plants) and pesticide handlers (people mixing, loading, or applying pesticides, or doing other tasks involving direct contact with pesticides) (U.S.EPA 2005). The 2005 WPS contains "requirements for pesticide safety training, notification of pesticide applications, use of personal protective equipment, restricted reentry intervals following pesticide application, decontamination of supplies, and emergency medical assistance".

The Endocrine Disruptor Screening Program (EDSP) was created by the EPA in 1998 due to increasing concerns and evidence that some chemicals affect the endocrine system. In June 2007 EPA published the EDSP draft list of initial active ingredients and pesticide inerts to be considered for screening. The inadequacy of conventional testing methods to determine if a substance would interact with a specific component of the

endocrine system and whether additional testing is needed by the EPA to fully assess and characterize the effects on both humans and animals were some of the issues considered by the EPA in the creation of the EDSP (U.S.EPA-EDSP 2000). It went through series of consultations and deliberations and started with the formation of the Endocrine Disruptor Screening and Testing Committee (EDSTAC) in 1996 "to provide advice and counsel to EPA on a strategy to screen and test chemicals and pesticides that may be the cause of endocrine disruption in humans, fish and wildlife" (U.S.EPA 1996). The issues that were discussed included developing a selection and prioritization process for chemicals and pesticides for screening; development of a process for identifying new and existing screening tests and mechanisms for validation; the availability of validated screening tests for early application; and processes and criteria for deciding when additional tests, beyond screening tests, are needed and how many of these additional tests will be validated (U.S.EPA 1996). A tiered method for screening and testing for chemicals that might have hormonal effects was also deliberated on and was included in the EDPS's report to Congress in 2000. The tier 1 screening included identification of substances which have the potential to interact with the endocrine system and tier 2 would confirm that potential and characterize the effects (U.S.EPA-EDSP 2000).

The reassessment and reregistration process of older pesticides paved the way for exploring the use of safer, reduced-risk compounds as replacements for the older pesticides such as organophosphates (OPs), carbamates and B2 (probable human) carcinogens thought to be particularly likely to cause harmful effects. The Office of Pesticide Program (OPP) of the EPA initiated the Conventional Reduced-Risk Program to "expedite the review and regulatory decision-making process of conventional

pesticides that pose less risk to human health and the environment than existing conventional alternatives" (U.S.EPA 2006b). The program's goal is to rapidly register commercially viable alternatives to riskier conventional pesticides such as neurotoxins, carcinogens, reproductive and developmental toxicants, and groundwater contaminants (U.S.EPA 2006b). The EPA (2006b) considers a pesticide use as reduced-risk if it meets some or all of the following criteria:

- Low impact on human health
- Low toxicity to non-target organisms (birds, fish and plants)
- Low potential for groundwater contamination
- Lower use rates
- Low pest resistance potential, and
- Compatibility with Integrated Pest Management

However, reduced-risk pesticides do not necessarily lack all potential to cause harm. They are defined relative to a specific existing compound. The EPA's decision on the reduced-risk pesticides is made at the use level for a pesticide/use combination and "is based on comparison between the proposed use of the pesticide and existing alternative currently registered on that use site" (U.S.EPA 2006b).

1.5 The IR-4 Project

Minor (specialty) crops generally do not give enough incentive to manufacturers to support the costs of the registration of pesticides. Consequently, the State Agricultural Experiment Stations (SAES) established the Interregional Research Project No. 4 (IR-4) in 1963 "to facilitate regulatory clearances for crop protection chemicals on specialty or minor food crops as well as minor uses on major crops (corn, soybean, cotton, small grains, etc.) with funding from USDA" (IR-4 2006a). These minor or specialty crops

include many fruits and vegetables, nuts, herbs, spices, and ornamental and nursery plants. They are planted in low acreage but are high value crops and account for more than $43 billion in annual production and occupy 12 million acres of farmland although they are grown on low acreage farms (Miller 2007) from which twenty-six states across the U.S. derive more than 50% of their agricultural crop sales (IR-4 2006b).

The IR-4 conducts controlled field trials with application of pesticides to crops of interest followed by analysis of the residues. Petitions with a requested tolerance or other clearance are then submitted to the EPA and when approved, the new use is added to the pesticide label and the use becomes legal. The minor use program of the EPA was created as mandated by the FQPA and required the EPA to address minor use registrations, reregistrations and policy issues. The U.S. EPA (U.S.EPA Undated), defines "minor use" as the use of a pesticide on an animal, on a commercial agricultural crop or site, or for the protection of public health where—

(1) the total United States acreage of the crop is less than 300,000 acres, as determined by the Secretary of Agriculture; or

(2) the Administrator, in consultation with the Secretary of Agriculture, determines that, based on information provided by an applicant for registration or a registrant, the use does not provide sufficient economic incentive to support the initial registration or continuing registration of a pesticide for use and—

a. there are insufficient efficacious alternative registered pesticides available for use; or

b. the alternatives to the pesticide use pose greater risk to the environment or human health; or

c. the minor use pesticide plays or will play a significant part in managing pest resistance; or

d. the minor use pesticide plays or will play a significant part in an integrated pest management program.

The IR-4 program has been very active in promoting the registration of reduced-risk pesticide uses after the FQPA in collaboration with EPA's Conventional Reduced-Risk Program. Since the IR-4 was established, it has achieved more than 10,000 pest control clearances on food crops (including biopesticide uses) and more than 10,000 clearances on ornamental crops (Miller 2007). Since 2000, over 80% of IR-4's research effort has involved new pest management technologies with biopesticides and lower risk chemistries (IR-4 2005).

1.6 Need for Evaluation of Changes and Impacts Since the Passage of the FQPA

So far there has been little publicly-available analysis of the changes in pesticide usage after the FQPA or of the effects this may have had on pesticide residues in the U.S. diet and the attendant changes in dietary risk. In 2006 the EPA issued a report on its accomplishments since the enactment of the FQPA. Among the achievements claimed by the EPA were (U.S.EPA 2006a): the establishment of the extra ten-fold children's safety factor, timely reassessments (at that time they had completed 99% of the reregistration requirements), refinement of the pesticide risk assessment process, development of the aggregate and cumulative exposure assessment methods, more collaboration with the public for exchange of information, creation of advisory committees to ensure stakeholder consultation, establishment of a public participation process, and a pesticide

web site to enhance the transparency of the public process. In spite of the tremendous achievements by the EPA, there was no evaluation and measurement of how pesticide use and the dietary risks have changed since the FQPA was passed.

The U.S. EPA-Office of the Inspector General (OIG) reviewed and evaluated the activities of the EPA related to the implementation of the FQPA and released their report in 2006. The primary goal of the OIG was "to evaluate the effectiveness of EPA's Office of Pesticide Programs (OPP) in measuring the overall impact of FQPA implementation activities" (U.S.EPA-OIG 2006a). The evaluation included reviews of internal documents and reports, inputs from internal program staffs and internal and external stakeholders, "other research on potential human health indicators related to pesticide exposures, dietary risk and reductions in risk due to EPA action" and "analysis of publicly available toxicological and residue data supporting EPA dietary risk assessments to assess the impact of FQPA on dietary pesticide risks from 1994 through 2003" (U.S.EPA-OIG 2006a). According to the report, the EPA-OIG "found that OPP has primarily measured its success and the impact of FQPA by adherence to its reregistration schedule rather than by reductions in risk to children's health". They concluded that the "EPA can measure the impact of FQPA on children's health more efficiently through the examination of pesticide exposure data, and changes in usage patterns, substitutions and import trends" (U.S.EPA-OIG 2006a). The OIG further recommended that "OPP work to move away from primarily using outputs as performance measures, and implement a suite of output and outcome measures to assess the human health and environmental impacts of its works". The OIG, through a contractor, developed and recommended a novel approach, the Dietary Risk Index (DRI), to measure the impact of FQPA. This is a basic unit of

measure proposed for use in tracking pesticide dietary risk (U.S.EPA-OIG 2006b). In response, the OPP questioned the validity of the index because "it makes no distinction among the potential adverse effects prevented by OPP action" which cannot be simply summed to develop an overall risk estimate, and has to be further reviewed more thoroughly (U.S.EPA-OIG 2006a). It is not clear that OPP has pursued this approach further.

California through its Department of Pesticide Regulation (CA-DPR) became the first and only state to initiate the requirement for full reporting of all pesticide use in agriculture in 1990. It required growers and commercial pest control operators to report monthly pesticide use. The records are collected, processed and stored in the CA-DPR use database and are made available to the public. The database is beneficial for assessing pesticide use in the areas of risk assessment, worker health and safety, water quality and pest management among others. The CA-DPR annually publishes the Statewide Summary of Pesticide Use Report Data which includes a brief narrative overview and a breakdown of the pounds and acreage of pesticide use. One volume is indexed by chemical and the second indexed by commodity. Data are studied and analyzed and the agency issues annual analyses of pesticide use trends. The CA-DPR on-line report for 2006 showed a continued decline in pounds of organophosphate and carbamates used with approximately 17M pounds in 1995 declining to 7M pounds in 2006 (CA-DPR 2006, 2007b). However, the use of chemicals known to cause cancer varied but remained almost unchanged overall from 1995 to 2006. The noticeable decrease in use of the organophosphates and carbamates shows the impact of the FQPA. California also collects

and maintains an extensive pesticide residue database for produce in California that is available and accessible to the public.

The registration and adoption of newer and safer pesticides have increased as a result of the FQPA. The NRC (2000) cited current patterns of use of modern pesticides that are considered reduced-risk chemicals based on the biennial report of the EPA Office of Pesticide Programs (U.S.EPA 1999). The report showed that the proportion of pesticide active ingredients that are considered to be safer than conventional pesticides, i.e. biological chemicals and reduced-risk conventional chemicals, has steadily increased from 1994 to 1999 as shown in Figure 1.1. The CA-DPR reported that pesticide use statistics in 2006 showed continued progress toward safer, less toxic pest management and an overall decline in the use of pesticides by nearly six million pounds from 2005 to 2006 (CA-DPR 2007a). The use of lower risk pesticides increased from 2004 to 2005 with 630,000 pounds applied (60% increase) and 2.4 million acres treated (39% increase).

There has only been very limited analysis of changes in pesticide residue levels in foods since the passage of the FQPA. An analysis of selected organophosphate pesticide residues in produce using data from the USDA-PDP from 1994 through 2004 was conducted by Punzi (Punzi 2005) and was presented during the Florida Pesticide Residue Workshop and Foodborne Pathogen Analysis Workshop in 2005. A simple graphical method was used "to allow examination of the relatively large amount of data without the use of statistical tools so that, at a glance (i.e., using eyeball statistics), a trend could be

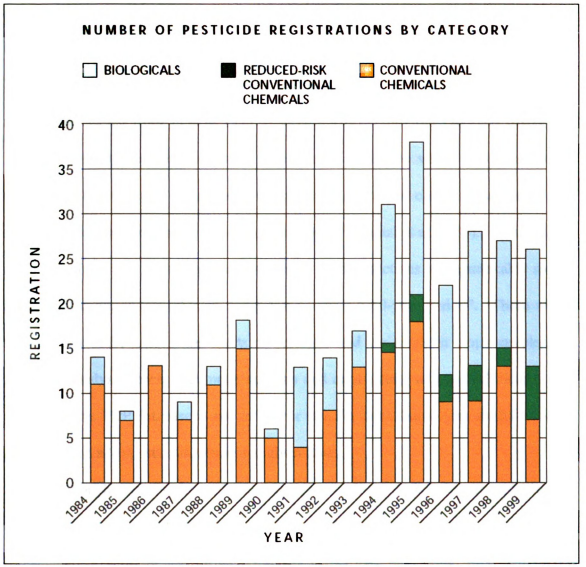

Figure 1.1. Registration of active ingredients considered to be safer chemicals (U.S.EPA 1999).

immediately apparent even to those unaccustomed to examining residue testing data" (Punzi 2005). Several pesticide-commodity pairs were studied for residue trends. The chlorpyrifos residues in apples showed decreased percent detections from 25% in 1999 to less than 1% in 2002. This is consistent with the regulatory action of the EPA in 2000 when it started phasing out uses of chlorpyrifos on fruits and only pre-bloom application was allowed in apples (Punzi 2005). In the same study, clear trends for the increase in the detection rates of phosmet was reported and was correlated to the decrease in detection

rate of methyl parathion "presumably due to the cancellation of the latter" according to Punzi (2005). In a summary report on the residue data collected by the USDA-PDP, Punzi et al. (2005) showed a slight decrease in detection rates with time although the annual rates varied from 71% in 1993 to 42% in 2003. From 1997 to 2003 (except for 1999 and 2002), the detection rates were steady at 55±2% which was "noteworthy considering that different groups of commodities are analyzed each year and not all the same pesticides are measured on each commodity" (Punzi et al. 2005). Punzi (2005) concluded that "the percentage of samples with detections was remarkably similar for several commodities over, in some cases, nearly a 10-year period". These results indicate that differences in the limits of detection and variations in crops sampled and pesticides analyzed each year make analysis and establishing of trends difficult. This shows that the PDP database is not set up for trend analysis but is very useful for other purposes such as exposure assessment at given times.

Although there are some limited reports on the changes in the use and residue levels of pesticides since the enactment of the FQPA, the dietary risks have not been investigated, except for the EPA-OIG report (U.S.EPA-OIG 2006a, b) which used a novel and questionable method. Measuring the dietary risks of the old pesticides and evaluating how it has changed are means to assess the effectiveness of the FQPA and, given adequate data sources, can be undertaken by using computer programs developed to handle risk assessments under the FQPA, such as the Cumulative and Aggregate Risk Evaluation System (CARES), Dietary Exposure and Evaluation Model (DEEM) and LifeLine computer programs. These programs use the probabilistic approach wherein the entire range of consumption and residue values is used "to estimate the distribution of

exposure for the population of concern and the probability of exposure at any particular level and allows for a more realistic estimate of exposure" (U.S.EPA 2000). The development of these programs resulted from the new requirements of the FQPA which presented many technical challenges to EPA. The competing programs all address these challenges but in somewhat different ways and all are used by regulators.

From the above review, it is apparent that surprisingly little has been published on the impact of the manifold changes in pesticide regulation implemented by the FQPA on pesticide use patterns, the adoption of reduced-risk pesticides, the levels of pesticide residues in the diet, and on changes in dietary risk with particular reference to infants and children. It is equally clear that there is a need for additional studies on these topics. A further area worthy of study is to assess how the IR-4 program has contributed to these changes in minor crop production, pesticide use, and dietary risk, particularly in the registration of reduced-risk pesticides. These pesticides have become increasingly important since the restrictions and cancellation of uses of a number of the old compounds as a result of the FQPA.

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CHAPTER 2
PESTICIDE USE TRENDS

In 1996 the FQPA set in motion major regulatory changes on the registration and use of pesticides. The initial focus was on the more toxic older compounds such as the insecticidal organophosphates (OPs) and the *N*-methylcarbamates (NMCs). Reregistration was required for all pesticides containing any active ingredient that was first registered before November 1984 (FIFRA 2004). The FQPA also requires aggregate and cumulative risk assessments as part of the reregistration process. Aggregate risk assessment is associated with the combination of all pathways and exposures to a single chemical while the cumulative risk assessment combines exposures to different chemicals having a common mechanism of toxicity. The cumulative risk assessments of the OPs and the NMCs, which are the most widely used groups of insecticides, were completed in 2006 and 2007, respectively (OP preliminary cumulative risk assessment released in 2001). The cumulative risk assessments used the relative potency factor (RPF) approach which is a method for determining the combined risk associated with exposure to the OPs or the NMCs and is calculated as the "ratio of the toxic potency of a given chemical to that of the index chemical" (U.S.EPA 2006d, 2007g). Brain cholinesterase inhibition was selected as the toxicity endpoint with methamidophos and oxamyl as the index chemicals used for the cumulative risk assessments of the OPs and the NMCs, respectively. After a number of regulatory actions to reduce uses and restrict exposure, the EPA concluded that "the results of the OP cumulative risk assessment support a reasonable certainty of no harm finding as required by the FQPA" (U.S.EPA 2006d) and the "cumulative risks from food, water, and residential exposure to NMCs do not exceed the Agency's level of

concern" (U.S.EPA 2007g). The regulatory consequences of the FQPA are additional restrictions and cancellations of uses and tolerances set for many important pesticides found to have the potential for unacceptable detrimental effects to humans.

The B2 carcinogenic fungicides (the B2s, classified as probable human carcinogens) were also among the priority pesticides to be evaluated under the FQPA. Chlorothalonil, captan, maneb, iprodione and mancozeb are some of these B2 fungicides that are very important in disease management (Ragsdale 2000). The EPA is also focusing on evaluating available data for the pyrethroid pesticides to determine if this group calls for a cumulative assessment. The EPA will employ various measurements and modeling tools, studies and data analysis "to identify and quantify critical routes and pathways of exposure for the pyrethroids pesticides and to assess population estimates of aggregate and cumulative pyrethroids exposure" (U.S.EPA 2007e).

Subsequent to the passage of FQPA, in 1997 the EPA established a priority system for reviews of "new chemicals, new uses, experimental use permits and registration amendments, requiring the review of scientific data" as follows (Tinsworth 2000):

- Methyl bromide alternatives
- Reduced-risk candidates
- U.S. Department of Agriculture-EPA identified potentially vulnerable crops
- Minor use priorities
- Non-minor use priorities; and
- Pesticides that addressed trade irritants.

The OP replacements were placed next to methyl bromide alternatives in 1998 when the EPA revised the list. This was due to the EPA's risk concerns presented by OP products that were on the market at that time both for individual OP compounds and as a group of compounds that may have a common mechanism of toxicity (Tinsworth 2000).

Despite the extensive regulatory actions intended to change use patterns and reduce pesticide risk since 1997, few studies have been published to show the effect of the regulatory actions on the use of pesticides and virtually none are available in the refereed literature. The California Department of Pesticide Regulation (CA-DPR) releases annual reports containing comprehensive data on the pounds of individual active ingredients (a.i.) applied for agricultural and non-agricultural uses, and the total acres treated with pesticides by commodity. Composite data are provided for several classes of compounds, e.g. usage of reproductive toxins, carcinogens, organophosphates, carbamates, groundwater and toxic air contaminants, oils, biopesticides and fumigants. The CA-DPR also reports the general use trends of these pesticides. In a study conducted by Epstein and Bassein (2003), California Pesticide Use Reports were utilized to study the use of pesticides for the production of fruits, vegetables and nuts in California form 1993 to 2000. The study showed "no trend towards decreased or increased usage of the pesticides on "risk" lists that are used to control vegetable and fruit diseases in the field" (Epstein and Bassein 2003). On the other hand, the report by the U.S. General Accounting Office (GAO) (U.S.GAO 2001) indicated that the "riskiest subset of pesticides" including organophosphates, carbamates and possible carcinogens decreased by 14% from 455M pounds of active ingredient in 1992 to about 390M pounds in 2000. The CA-DPR 2006 report (CA-DPR 2007a) shows continued decline of the

anticholinesterases (OPs and NMCs) from 1997 to 2006 for both agricultural and non-agricultural applications.

National usage reports have also been released by Gianessi and Silvers (2000) and Gianessi and Reigner (2006a, b). Gianessi and Silvers (2000) compared pesticide usage based on the data collected by the National Center for Food and Agricultural Policy (NCFAP) from 1992 to 1997. The NCFAP trend study focused on active ingredients that have undergone noticeable changes in the usage patterns between 1992 and 1997 at the national aggregate level, as estimated in the NCFAP national pesticide use database (Gianessi and Silvers 2000). The NCFAP pesticide use report released in 2006 showed an aggregate decrease in fungicide use by 17M pounds and a reduction of 61M pounds in herbicide use between 1997 and 2002 (Gianessi and Reigner 2006b). This study complements the limited information available on how the use of pesticides has changed over time. There are virtually no publications on this topic in the refereed scientific literature.

2.1 Pesticide Use Databases

Several pesticide usage databases are publicly and electronically available. Among the agencies that maintain pesticide use databases are the USDA National Agricultural Statistics Services (NASS), the CropLife Foundation (CLF) and the California Department of Pesticide Regulation (CA-DPR). In addition, proprietary databases are produced, most notably the Doane AgroTrak and the Buckley Reports. However, there is no comprehensive publicly available national database on pesticide usage. These databases vary in a number of ways and have different advantages and disadvantages for use analysis. The CA-DPR use database has a comprehensive

collection of data and has annual use data available while the CLF and NASS both cover national use of pesticides. Although the CA-DPR database represents California only, the state is "the largest and most diverse agricultural producer in the United States and produces more than half of the country's fruits, vegetables and nuts and uses approximately 22% of the total agricultural pesticides in the nation" (U.S.GAO 2001). The CLF has a collection of data from various sources including NASS, individual state reports, USDA crop profiles and the CA-DPR annual reports. However, the CLF reports are released only every five years and the use data are not specific for any particular year. The Doane AgroTrak and the Buckley Report may have the most complete and comprehensive national statistics of pesticide use but the major disadvantage is their proprietary nature and very expensive acquisition cost.

2.1.1 *California Department of Pesticide Regulation (CA-DPR)*

California is the only state that requires full reporting of all pesticide use. The pesticide use reporting program is internationally recognized as the most comprehensive of its kind in which more than 2.5 million records of chemical applications are annually collected and processed by the CA-DPR. The pesticide use reporting process starts before the purchase and use of a pesticide with the property owners (or pesticide applicators) obtaining an identification number from the county where any pest control work is to be performed. Site identification numbers are obtained by growers from the County Agricultural Commissioner for each location and crop/commodity where pest control activities are to be undertaken. The identification number is recorded on the restricted material permit or other approved form. Geographic information, operator identification or permit number, name and address and field location are among the information

required for agricultural application reports. Non-agricultural applications require less information which includes pesticide product name and manufacturer product registration number, and amount used among others. The staff at the County Agricultural Commissioner's office reviews the reports for accuracy and they are entered into a county database and transferred monthly to the CA-DPR. The CA-DPR uses the data for risk assessment, for safety and protection of the health of workers, protection of endangered species, and air and water and assessments of pest management alternatives.

2.1.2 *CropLife Foundation (CLF)*

The CLF releases national pesticide use reports every five years and there have been three national summary reports issued dated 1992, 1997 and 2002. The pesticide use database is not specific for any particular year. The first report was released in 1995 by the National Center for Food and Agricultural Policy (NCFAP) compiled from state-level usage database that quantified the use of each active ingredient by crop and state (Gianessi and Reigner 2006a). The report on pesticide usage was based on crop acreage for 1992 and usage patterns for 1990-1993 and the 1995 NCFAP report is referred to as the 1992 report; the 1997 report represents 1995-1998 usage patterns and crop acreage data for 2007; and the 2002 report represents 2002 acreage data and use surveys from 1999 through 2004. State and crop pesticide use data from publicly available reports are organized into a national database of pesticide use in U.S. crop production. The CLF use database is a collection of usage data from various sources. Gianessi and Reigner (2006b) listed the following sources of information:

- Surveys conducted by the National Agricultural Statistics Service (NASS)

- Reports for individual states and selected crop by USDA's Cooperative State Research, Education and Extension Service (CSREES) and national pesticide benefit assessments conducted by USDA's National Agricultural Pesticide Impact Assessment Program (NAPIAP)
- USDA Crop Profile reports
- State of California Department of Pesticide Regulation Annual Reports
- Assignments. In cases where usage profiles for a crop in a state were not available from the above sources, usage estimates were assigned by assuming that a state's pesticide use profile for an active ingredient/crop combination is similar to that of a nearby state. Use coefficients (% acres treated and average annual rate) from known states were applied to the corresponding crop acreage based upon *Census of Agriculture* acreage planted figures in the unknown states.

A survey of extension service specialists for pesticide use profile information is conducted by CLF for states and crops not covered completely by the available surveys and reports.

2.1.3 *National Agricultural Statistics Service (NASS)*

The NASS publishes reports on agricultural chemical use every year, covering selected vegetables and fruits in alternate years, starting in 1990 for vegetables and 1991 for fruits. Use data are from surveys funded by the U.S. Department of Agriculture Pesticide Data Program (USDA-PDP). Chemical use information on targeted vegetable and fruit crops from various states is collected by NASS to support the evaluation of food safety and water quality issues by USDA-PDP. NASS provides online access to the

Agricultural Chemical Use Database from which a variety of useful information can be obtained. This information includes acreage of commodity planted, percent acres treated, active ingredient (a.i.)/acre/treatment/, average number of treatments, a.i./acre and total a.i. used. The database contain vast amount of pesticide use data, but the parameters reported are limited with only the data for the minimum, maximum and average uses accessible. The actual data are not reported which make trend data reporting less accurate. There are also limitations due to discontinuities in the crop coverage with time.

2.1.4 *Doane AgroTrak*

Doane AgroTrak provides data on agrochemical use and is the major source of information for the U.S. EPA Biological and Economic Analysis Division (BEAD), but it is not a publicly available database and can only be used internally by the subsciber. Doane is proprietary to a purchaser at a cost of $500,000 per year (Holm 2005). The report covers 58 crops with 40 variables in principal states and it maintains confidentiality of the sample size to the paying clients.

2.1.5 *Buckley Report*

The Buckley report covers 31 crops and is also available only to clients on a proprietary basis. It develops its surveys through 72 field/crop consultants who collect data from growers, agriculture consultants, extension agents, dealers, co-op advisors and food processors. The Buckley Report summarizes data on the state level for the following variables: active ingredient, brand name, formulation, cost, acres treated, volume used, target pests and the product group markets. The Buckley cotton insecticide report costs $36,500 while the specialty crop report is $75,000. The EPA has purchased the Buckley Report in the past but does not do so currently (Holm 2005).

2.2 The IR-4 Program

The IR-4 program is funded by the USDA to develop pesticide registrations and clearance for use on minor and specialty crops. These crops include many fruit, vegetable and nut crops. Minor crops are defined by EPA as those being grown on less than 300,000 acres nationally. Approximately half the registration petitions submitted annually to EPA originate with IR-4. Since the passage of FQPA the program has focused most of its attention on facilitating the registration of reduced-risk and OP replacement pesticides and since 2000, 70-80% of its studies have been on these new compounds (IR-4 2006). However the extent to which this program has contributed to the availability and use of these safer materials has not been evaluated.

2.3 Objectives

The objectives of this section of the study are to assess the following in the U.S. since the enactment of the FQPA in 1996:

1. Changes in the use levels of selected higher risk pesticides (anticholinesterase insecticides and B2 carcinogenic fungicides) in fruit, vegetable and nut production.
2. Changes in the use of safer (reduced-risk) compounds as replacements in these aspects of agriculture.
3. The contributions of the IR-4 program to the enhanced availability of reduced-risk pesticides for minor and specialty crop uses.

2.4 Methods

2.4.1 *Selection of Pesticides*

The preliminary selection of the conventional pesticides and pesticide groups was conducted based on human health concerns and toxicological endpoints. These groups were the organophosphates (OPs) and *N*-methylcarbamates (NMCs) (anticholinesterases), and the B2 carcinogens (Appendix A) that have been the major focus of regulatory attention by the EPA following the passage of the FQPA. Fungicides and insecticides that have been classified as reduced-risk were selected as well and were mostly those that have been registered since the passage of the FQPA. These have been the primary focus of efforts for registration for specialty crops, including many fruits, vegetable and nut crops, by IR-4.

The selection of pesticides from each group was narrowed down to those listed in Table 2.1. The selection was based on high usage and major health concerns. The use (pounds applied and acres treated) for these pesticides were plotted and the trends were analyzed.

2.4.2 *Pesticide Toxicity*

The toxicological properties including the FQPA factor (additional safety factor) for the OPs, NMCs, B2 carcinogens, and the reduced-risk pesticides were compiled and shown in Appendix B. The reduced-risk pesticides and the B2 fungicides have low acute oral toxicities but the B2s have some developmental and neurotoxicity concerns. The OPs (except for acephate and diazinon) and the NMCs are of high acute oral toxicity. However, there is some level of toxicity to aquatic and/or terrestrial organisms for both the conventional and reduced-risk pesticides. Azinphos-methyl, chlorpyrifos,

Table 2.1. Selected pesticides for use and residue trends analyses

B2 Carcinogens	OPs	NMCs	Reduced-risk Fungicides	Reduced-risk Insecticides
1.captan	1. acephate	1. aldicarb	1. azoxystrobin	1. acetamiprid
2.chloro-thalonil	2. azinphos-methyl	2. carbofuran	2. cyprodinil	2. bifenazate
3.iprodione	3. chlorpy-rifos	3. carbaryl	3. fenhexamid	3. buprofezin
4.mancozeb	4. diazinon	4. methomyl	4. fludioxonil	4. imida-cloprid
5.maneb	5. dimethoate	5. oxamyl	5. mefenoxam	5. indoxacarb
	6. disulfoton		6. trifloxy-strobin	6. methoxy-fenozide
	7. fenamiphos			7. pymet-rozine
	8. fonofos			8. pyriproxi-fen
	9. methamid-ophos			9. spinosad
	10. methida-thion			10. tebufen-ozide
	11. methyl parathion			11. thiameth-oxam

disulfoton and methamidophos have been reported to cause worker exposure concerns. The FQPA factors used for the reassessment of the pesticides ranged from 1X to 5X except for methyl parathion and chlorpyrifos with 10X. Some of the pesticides are included in the Endocrine Disruptor Screening Program (EDSP) draft list which "presents the draft list of the first group of chemicals that will be screened for the EPA's EDSP" (U.S.EPA 2007c). These pesticides include B2s (captan, cholorothalonil and iprodione), the OPs (acephate, azinphos-methyl, chlorpyrifos, diazinon, dimethoate, disulfoton, methamidophos, methidathion, methyl parathion) and the NMCs (aldicarb, carbaryl, carbofuran, methomyl and oxamyl), and the reduced-risk insecticide imidacloprid. Based on the toxicological properties of the various pesticides, the reduced-risk pesticides have significantly fewer toxicity concerns, either acute or chronic, compared to the conventional pesticides.

The organophosphate (OP) group was the EPA's first priority group reviewed under the Food Quality Protection Act (U.S.EPA 2007b). The OPs are of great concern due to their potential neurotoxicity caused by the inhibition of cholinesterase in both the central and peripheral nervous systems (Mileson *et al.*, 1998 cited by (U.S.EPA 2006d)). The toxicological properties of the individual OP pesticides are shown in Appendix B.

The *N*-methylcarbamate (NMC) pesticides are also cholinesterase inhibitors, but are classified as a separate group from the OPs. The NMCs were concluded to have a common mechanism of toxicity in 2001 by the U.S. EPA. The Common Mechanism Group (CMG) was established "based on the shared structural characteristics and similarity and their shared ability to inhibit acetylcholinesterase (AChE)" (U.S.EPA 2005a). In 2004 the EPA assigned ten carbamate pesticides as members of the Cumulative Assessment Group (CAG) that included aldicarb, carbaryl, carbofuran, oxamyl and methomyl. Appendix B shows the toxicological properties of these pesticides.

Carcinogenic chemicals have been classified in several different ways by EPA. The 1986 classification consisted of the following categories (U.S.EPA 2007a):

- Category A: Human carcinogen
- Category B: Probable human carcinogen
    - B1: agents for which there is limited evidence of carcinogenicity from epidemiologic studies
    - B2: agents for which there is sufficient evidence from animal studies and for which there is inadequate evidence or no data from epidemiologic studies

- Group C: Possible human carcinogen
- Group D: Not classifiable as to human carcinogenicity
- Group E: Evidence of non-carcinogenicity for humans

In 1996 the "Proposed Guidelines for Carcinogenic Risk Assessment" was released by the EPA and provided the following revision of the carcinogenicity classification (U.S.EPA 2007a):

- Known/Likely: available tumor data effects and other key data are adequate to convincingly demonstrate carcinogenic potentials for humans.
- Cannot be determined: data are not adequate to convincingly demonstrate carcinogenic potentials for humans.
- Not likely: no basis for human hazard concern

The most recent carcinogenic classification of chemicals is from the 2005 Guidelines for Carcinogen Risk Assessment. They are referred to as descriptors and consist of the following categories (U.S.EPA 2007a):

- Carcinogenic to humans
- Likely to be carcinogenic to humans
- Suggestive of evidence of carcinogenic potential
- Inadequate information to assess carcinogenic potential
- Not likely to be carcinogenic to humans
- Multiple descriptors: more than one descriptor can be used when an agent's effects differ by dose or exposure route.

In this study, the carcinogenic fungicides considered were based on the 1986 classification and thus are referred to as the B2 carcinogens or the B2s (agents for which

there is sufficient evidence from animal studies and for which there is inadequate evidence or no data from epidemiologic studies). These fungicides include captan, chlorothalonil, iprodione, mancozeb and maneb and the toxicological properties are shown in Appendix B.

Captan is a member of the *N*-trihalomethylthio group of compounds and metabolizes to the highly reactive species thiophosgene that causes much of its observed toxicity (U.S.EPA 1999c). The irritant properties of captan can be attributed to thiophosgene and "may be responsible for the intestinal tumors in mice, although the exact mode if action is unclear". The U.S. EPA has established dietary, occupational and residential acute and chronic toxicological endpoints for captan.

Chlorothalonil has been classified by the EPA as "likely" to be a human carcinogen. It contains an impurity, hexacholorbenzene (HCB), which has also been classified by the EPA as B2 carcinogen based on data that show significant increases in tumor incidences in hamsters and rats (U.S.EPA 1999d). The acute and chronic NOEL and the RfD were established for chlorothalonil and HCB.

Iprodione was classified as a B2 carcinogen by EPA based on evidence of tumors in both sexes of mice (liver) and in the male rat (Leydig cell). A No Observed Effect Level (NOEL) and Reference Dose (RfD) were established based on combined chronic toxicity and carcinogenicity in rats. Iprodione is also associated with endocrine disruption according to the EPA but "the extent of these effects and the mode of action are not yet fully understood" (U.S.EPA 1998e). Neurodevelopmental studies are also lacking for this compound.

Mancozeb, a dithiocarbamate fungicide, targets the thyroid organ through its metabolite, ethylenethiourea (ETU). Thyroid toxicity was manifested as alterations in thyroid hormones, increased thyroid weight, and microscopic thyroid lesions and thyroid tumors (U.S.EPA 2005b). Neurotoxicity is also a concern for mancozeb exposure due to the developmental effects observed after dosing with mancozeb or ETU. The No Observed Adverse Effect Levels (NOAELs) and the Lowest Observed Adverse Effect Levels (LOAELs) have been established for mancozeb to address these concerns. There have also been concerns regarding endocrine effects of mancozeb based on available human health and ecological effects data according to the EPA (U.S.EPA 2005b).

The carcinogenic potential of the related dithiocarbamate fungicide, maneb, is also considered to be due to its B2 carcinogen metabolite, ETU. The cancer risk of maneb has been assessed "by estimating exposure to maneb-derived ETU and using the ETU potency factor" and in 1999 the EPA concluded that cancer risk for maneb and the other EBDC fungicides should continue to be evaluated this way (U.S.EPA 2005c). Maneb also showed possible thyroid effects which may "indicate potential endocrine disruption" based on ecological and human health effects data (U.S.EPA 2005c).

2.4.3 *Survey and Evaluation of Pesticide Use Databases*

The pesticide use databases were surveyed and evaluated for comprehensiveness and continuity of data from 1992 to 2006. The databases evaluated were the CA-DPR, the NASS and the CLF. Doane AgroTrak and the Buckley Report were also considered but their expensive purchase cost was the limiting factor preventing their use. The CA-DPR has the most complete and comprehensive use data and reports and the CLF database has a nationwide coverage of pesticide use and thus both were selected as the main sources of

use data for trend analysis. The NASS database does not have the actual usage data publicly available (i.e. only the minimum, maximum and average data are reported) and these are not accurate to use in trend analysis.

2.4.4 *Pesticide Groups Use Trend Analysis*

The overall use trends for conventional pesticide groups (OPs, NMCs, and B2 carcinogens) were compared based on the cumulative acres treated and pounds applied for fruits, vegetables and nut crops. The total acres treated and pounds applied, and percent change in use were calculated and compared for the years 1994 and 2006 based on the CA-DPR data and for 1992 and 2002 based on the CLF data.

2.4.5 *Individual Pesticide Use Trend Analysis*

The total pounds applied and total acres treated data from 1992 to 2006 for fruits, vegetables and nut crops for the individual OP, NMC, and B2 carcinogenic pesticides were compiled from the CA-DPR and the CLF pesticide use databases. The reduced-risk pesticides were classified as to low, medium or high use (acres treated) based on the 2006 CA-DPR data. Changes in use trends were analyzed and were correlated with the regulatory history of the pesticides. The reason for the changes in use was assessed based on the regulatory history and the expert opinion of people knowledgeable in the pesticide selected.

2.4.6 *Environmental Load and Application Rate*

The environmental load (lbs/acre) was calculated from the ratio of the total pounds applied and the total acres treated. The application rate is the ratio of the total pounds of the pesticides applied and the total number of applications per year. Both were

calculated for the insecticides (OPs, NMCs and reduced-risk) and the fungicides (B2s and reduced-risk) based on the CA-DPR pesticide use data from 1992 to 2006.

2.5 Results and Discussion

2.5.1 *Pesticide Groups*

The percent change in acres treated and pounds applied of the B2, OP and NMC pesticide groups based on the CA-DPR (California) and the CLF (national) data are shown in Table 2.2. The two databases provide reasonably similar results. The NMCs had the most significant decrease in use (74% (CA-DPR) and 72% (CLF) in pounds applied and 60% (CA-DPR) and 65% (CLF) in acres treated), but a considerable decrease in acreage and application amounts of the OPs was also evident. The B2 fungicides showed much less change with 21% and 11% decreases in pounds applied. The CA-DPR data show a decrease of 17% in acres treated for this group, but the acreage treated with B2s increased by 29% based on the CLF data. This is not necessarily surprising since the two databases differ in geographical range and in the timeframes for data collection. Concerns about the neurotoxic effects of the NMCs have led to several reassessments and additional risk assessments of these compounds and were included in the carbamate cumulative risk assessment. According to the CA-DPR the pounds of carbamates applied "continued to decline as they have for nearly every year since 1995" (CA-DPR 2005).

Table 2.2. Percent change in the use of the B2 carcinogen, OP and NMC pesticide groups

Pesticide Groups	Percent change			
	CA-DPR (1994-2006)		CLF (1992-2002)	
	Pounds applied	Acres treated	Pounds applied	Acres treated
Organophosphate	-47.6	-46.9	-57.4	-76.9
N-methylcarbamate	-74.0	-60.1	-71.5	-65.0
B2 Carcinogen	-21.2	-17.1	-11.2	29.3

The use of the OPs decreased by 48% in pounds applied and 47% in acres treated based on the CA-DPR data while the CLF data showed 57% and 77% decline in pounds

applied and in acres treated, respectively. This is due to the major regulatory changes brought about by the enactment of the FQPA that required reassessments of old pesticides and additional requirements for aggregate and cumulative risk assessments. Worker exposure and occupational concerns were also major contributing factors to the decline in use of the OPs. Although regulatory activity has been a primary reason for decreased use of the anticholinesterases and increased use of the reduced-risk pesticides, pesticide use decisions are complex and additional reasons for this switch in individual situations could be because:

- some older pesticides were discontinued because of business decisions by the chemical pesticide industry
- there were changes in cropping systems and pest pressures
- some older pesticides became less competitive because of the improved properties and convenience of replacement compounds e.g. improved systemic properties and increased use as seed treatments rather than foliar sprays, as well as greater compatibility with pest management programs
- some older pesticides became less effective as the target pests developed resistance
- the alternating use of different pesticide classes has increased as a resistance management strategy

Trends in use of the OPs, NMCs, and the reduced-risk insecticide groups are shown in Figure 2.1. Based on the CA-DPR data, there is an apparent continuously increasing trend in both acres treated and pounds applied with the reduced-risk insecticides while the OPs and the NMCs declined quite regularly from 1996 to 2006.

The reduced-risk insecticides acres treated started to exceed that of the NMCs in 1997 and the OPs in 2002 and the pounds applied almost equaled that of the NMCs in 2006. The trend in acres treated and pounds applied with the B2 fungicides is not as clear as for the insecticides (Figure 2.2). The acres treated increased from ~1M in 1992 to ~3.5M in 2000 but then declined to a constant level from 2001 with ~1.7 M in 2006. The increase in the acres treated (~3.6M) for the B2s in 2000 is mostly from iprodione. The pounds applied increased from ~1M in 1992 to ~5M in 1998 but declined to ~2.5M in 2006. On the other hand, the use of the reduced-risk fungicides continuously increased from <0.5M acres in 1997 to ~1.5M acres in 2006 and almost equaled the acres treated with the B2s. The pounds applied increased from ~50,000 pounds in 1992 to ~350,000 pounds in 2006.

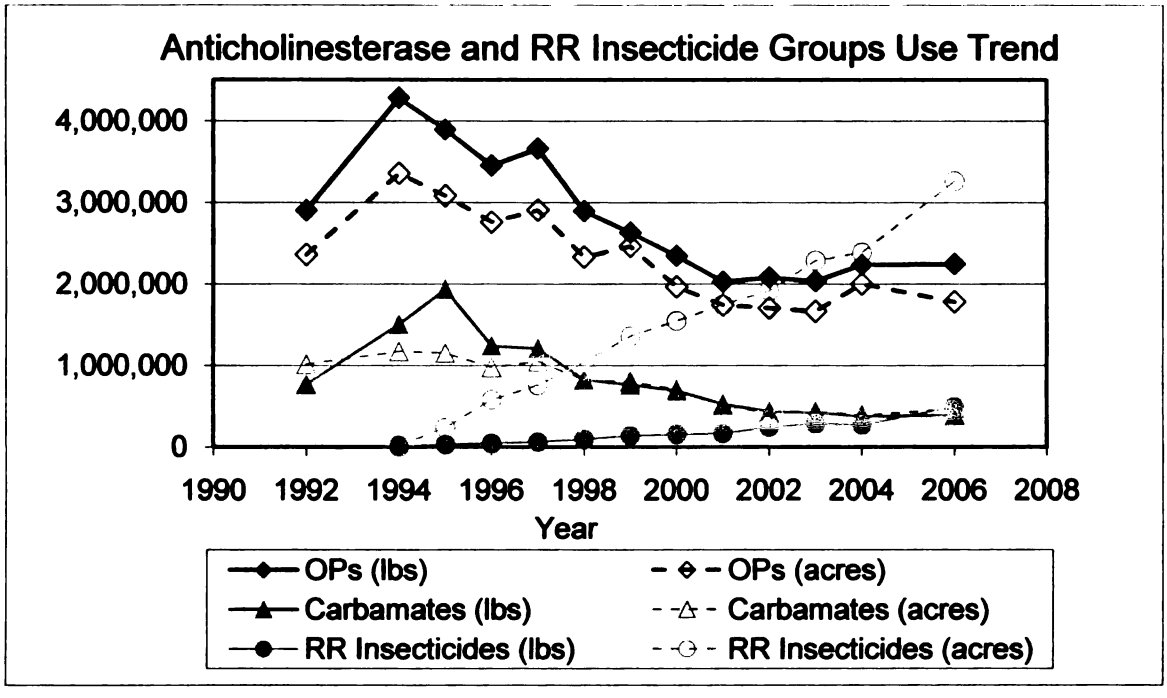

Figure 2.1. Acreage treated and pounds applied of the OPs, NMCs and reduced-risk insecticide groups.

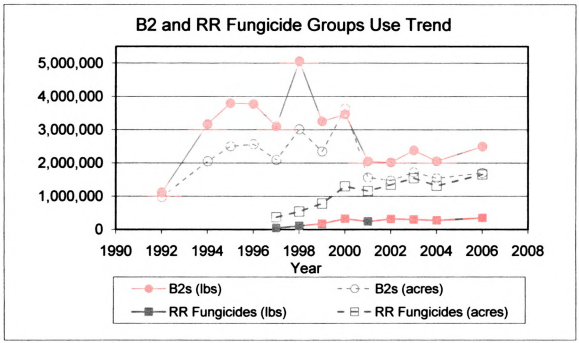

Figure 2.2. Acreage treated and pounds applied of the B2 carcinogenic and the reduced-risk fungicide groups.

A regular increase in the use of reduced-risk pesticides from their first use in 1995 to 1.7 million pounds in 2005 is also evident from a summary graph for all reduced-risk compounds and uses combined that was developed by CA-DPR (CA-DPR 2006). Similarly, summary data documenting the continued decline in total anticholinesterase insecticide use, with an overall decrease of about 50% from 1994 through 2006, were recently provided by CA-DPR (CA-DPR 2007a).

2.5.2 *Individual Pesticides*

2.5.2.1 *B2 Carcinogenic Fungicides*

Iprodione

Iprodione was first registered as a fungicide in the U.S. in 1979 with major uses on agricultural crops, ornamentals, turfgrass and for residential ornamental applications. In 1998 the use of iprodione for postharvest pathogen control on stone fruits was cancelled (Adaskaveg et al. 2005), preharvest uses were restricted, and the removal of all

residential uses followed due to cancer and occupational risk concerns (U.S.EPA 1998d). Figure 2.3 shows the trend in the CA-DPR and the CLF use data for iprodione. Among the B2s considered in this study, the CLF use data are greater than that of the CA-DPR except for iprodione. This implies that most of the agricultural uses of iprodione could have come from California. However, the CA-DPR data show an unexpected peak of increased acres treated for iprodione in 2000 due mostly to uses on nectarines (~500,000 acres), peaches (~550,000 acres) and plums (~500,000 acres). Apart from this peak, after the 1998 use restrictions, use fell by about 50%.

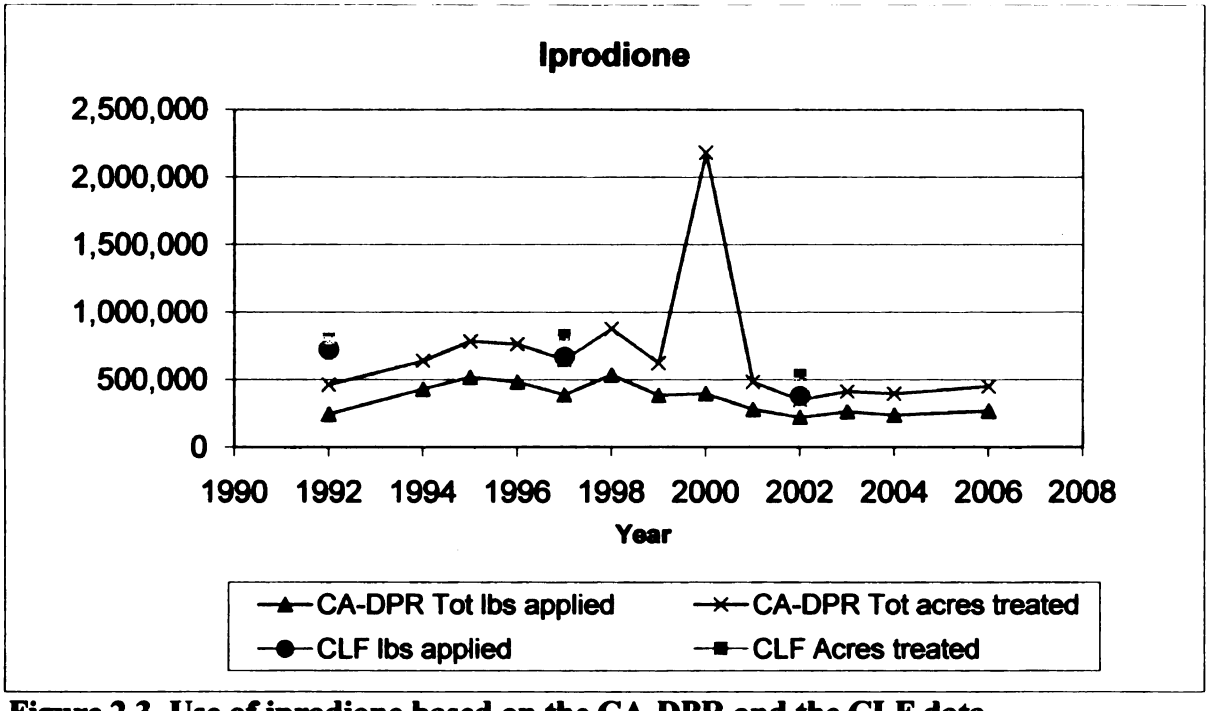

Figure 2.3. Use of iprodione based on the CA-DPR and the CLF data.

Mancozeb

Mancozeb was first registered in 1948 for use on food and ornamental crops to prevent harvested crops from deterioration in storage and transport (U.S.EPA 2005b). Other uses include seed treatments and horticultural applications. Registration standards were issued in April 1987 but a Special Review of mancozeb and other ethylenebisdithiocarbamates (EBDCs) identified the pesticide group and its metabolite as

a developmental toxicant and a probable human carcinogen. The EPA canceled all uses of mancozeb and other EBDC products on several crops including nectarines, peaches, and spinach in 1992 because "the dietary risks of EBDCs exceeded the benefits for the canceled food/feed uses" (U.S.EPA 2005b). Requirements for personal protective equipment for workers using EBDCs were also established by the EPA. The CLF and the CA-DPR data show similar use trends for mancozeb (Figure 2.4). Based on the CA-DPR data there has been relatively constant pounds applied and acres treated from 1994 to 1997 but this has been variable and has decreased since then. There were significant increases in 1998 and 2006. Increased acres treated and pounds applied in 1998 were due to the increased use on grapes (~138K lbs), onions (>100K lbs) and potatoes (>100K lbs) and in 2006 the major increased uses were on onions and on grapes.

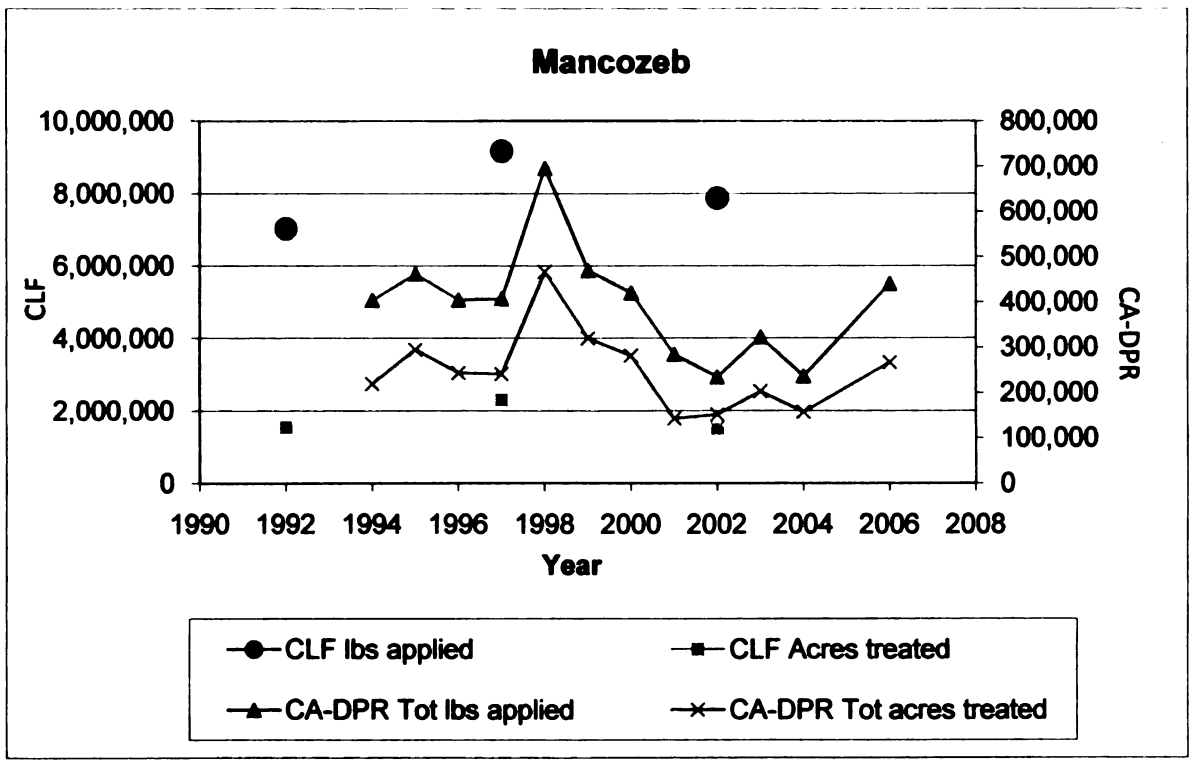

Figure 2.4.Use of mancozeb based on the CA-DPR and the CLF data.

Maneb

Maneb was first registered in the U.S. in 1962 for food and ornamental crop uses and belongs to the EBDC pesticide group. In 1987 the EPA expressed health concerns for its metabolite, ethylenethiourea (ETU), including carcinogenic, developmental, and thyroid effects. In 1992, the EPA cancelled various maneb uses when the EPA "concluded that the dietary risks of EBDCs exceed the benefits" for some feed/food uses (U.S.EPA 2005c). In 2005, the EPA (U.S.EPA 2005c) reported that uses of maneb on sweet corn, grapes, apples and fig were not eligible for reregistration and these were voluntarily canceled by the registrants. National use (Figure 2.5) data show an overall decline in the use of maneb but the CA-DPR data does not show any significant decrease.

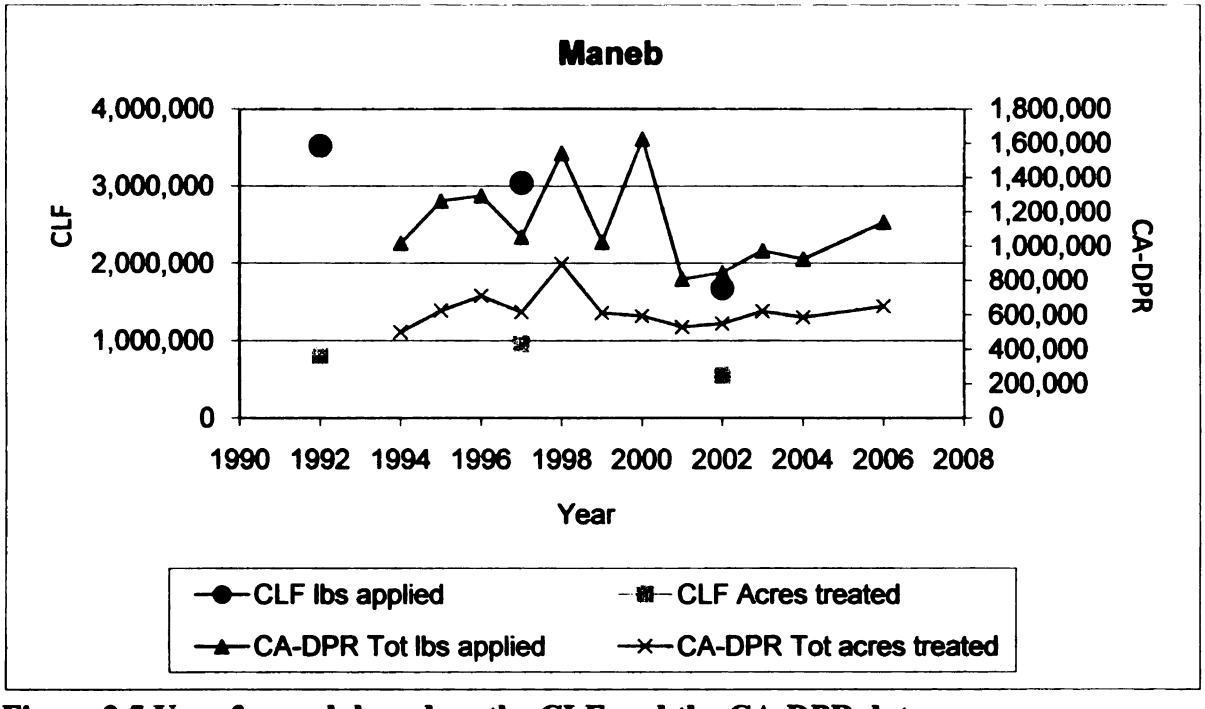

Figure 2.5.Use of maneb based on the CLF and the CA-DPR data.

Captan

In 1951, captan was first registered for the control of fungal diseases in fruit crops. It is registered for use on terrestrial and greenhouse food crops, seed treatments

and ornamental sites as well as non-food indoor uses but various uses of captan were cancelled and several tolerances were revoked in 1993 and 1999. The Reregistration Eligibility Decision (RED) for captan was issued in 1999 and it retained its previous classification as a B2 carcinogen (U.S.EPA 2004a). In 2004, a re-evaluation of the cancer risk assessment for captan was requested by the Captan Task Force and it was concluded that captan is not "likely to be a human carcinogen nor pose cancer risks of concern when used in accordance with approved product labels" (U.S.EPA 2004a) based on the weight-of-evidence approach. However, as a compound with a probable threshold for carcinogenic action, it is likely to cause cancer in humans following prolonged, high level-oral exposures (Wilkinson et al. 2004). No significant change in the overall use trend of captan is evident based on the CA-DPR and the CLF data (Appendix C) but there was a noticeable increase in pounds applied in 1998 based on the CA-DPR data due to high usage on almonds (~1.1M lbs) in that year. The cancer reclassification of captan is a probable explanation for the continued use of captan as well as its low susceptibility to resistance due to its multiple modes of action and broad spectrum control of fungi, and its low cost.

Chlorothalonil

Chlorothalonil was first registered for food use on potatoes in 1970 and is used mainly on food crops and for outdoor residential applications. In 1987, the EPA classified chlorothalonil as a B2 carcinogen. It contains an impurity, hexachlorobenzene (HCB) that is also classified as a B2 carcinogen based on data that show significant increases in tumor incidences in hamsters and rats (U.S.EPA 1999d). In 1997, evaluation of the weight-of-evidence was conducted by the EPA with reference to the carcinogenic

potential of chlorothalonil and supported a classification of chlorothalonil as 'likely' to be a human carcinogen by all routes of exposure (U.S.EPA 1999d). Tolerances have been established for combined residues of chlorothalonil and its impurity. Acute and chronic NOELs and RfDs have also been set for chlorothalonil, HCB and its metabolite. The use of chlorothalonil has been comparatively constant with a slow decline since 1997 as shown in Appendix C. The decline may be attributed to its continued classification as a B2 carcinogen even after its reevaluation but clorothalonil too has advantages of cost, low resistance potential and broad spectrum efficacy that help to maintain its use.

2.5.2.2 *N-methylcarbamates*

Aldicarb

The first use of aldicarb was registered in 1970 and is currently registered for use on many agricultural crops. In 1981 aldicarb was classified as a restricted use pesticide and subjected to Special Review in 1984. The sale and use of aldicarb on potatoes was voluntarily suspended in 1990 due to detection of tolerance-exceeding residues in individual potatoes (Angier et al. 2006). Consequently, the registrant agreed to cancel other uses to reduce dietary risks but these were later reinstated in Florida, Idaho, Washington and Oregon after new application methods demonstrated significantly lower residues in potatoes (U.S.EPA 2007f). However, the EPA (2007f) still has aldicarb under the Special Review process "because of risks of ground water contamination". Aldicarb shows a decreasing trend in use from 1992 to 2006 as shown in Figure 2.6. Total pounds applied decreased by 66% based on the CLF data (1992-2002) and 91% based on the CA-DPR data between 1994 and 2006. Aldicarb has a very high acute toxicity and a record of causing human poisoning, and the EPA noted that there are "human health risks of

concern associated with the current registered uses of aldicarb from drinking water exposure, and potential environmental risks of concern to birds, mammals and fish" (U.S.EPA 2007f) which account for the decline in the use of aldicarb. In 2007 the EPA determined that products containing aldicarb "unless labeled and used as specified (in the aldicarb reregistration eligibility document), would present risks inconsistent with FIFRA and FFDCA" (U.S.EPA 2007f).

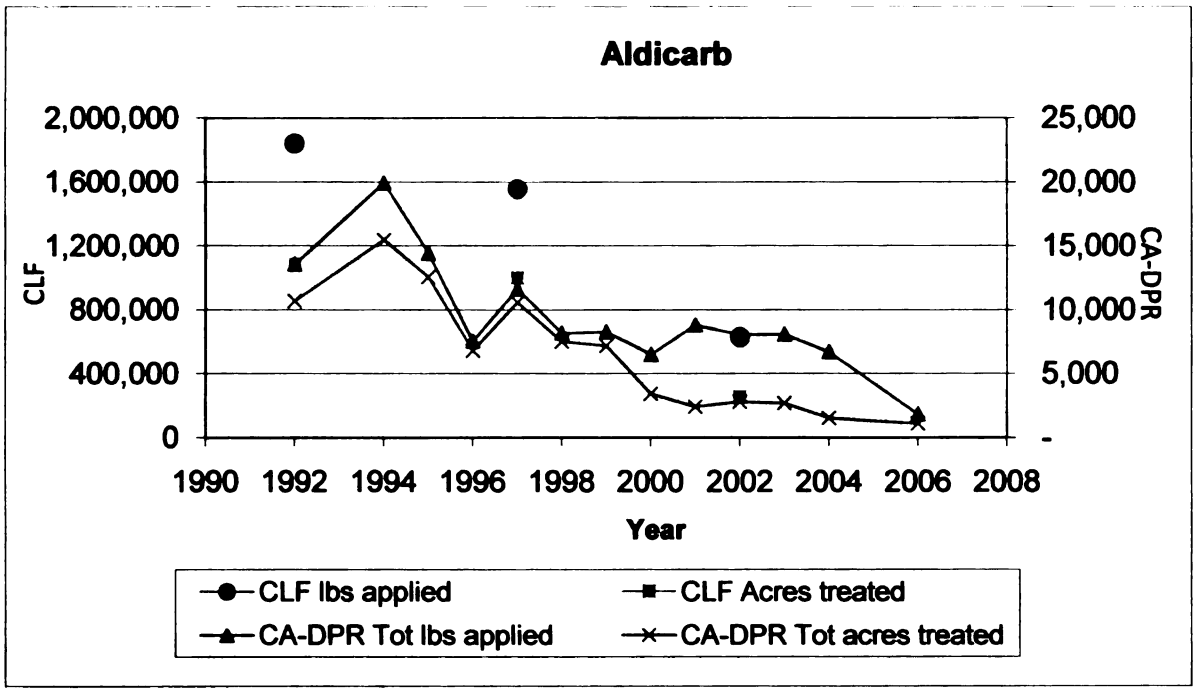

Figure 2.6.Use of aldicarb based on the CA-DPR and the CLF data.

Carbaryl

Carbaryl was first registered in 1959 for use on cotton but its applications have increased to include many food uses. Its use came under scrutiny in the 1980s when health risks became a concern. In 1988, the Registration Standard issued in 1984 was revised and included terms and conditions for its continued registration (U.S.EPA 2003b). In 2001, the EPA identified a common mechanism of toxicity for the *N*-methylcarbamates (NMCs) that included carbaryl. The Interim Reregistration Eligibility Decision (IRED) for carbaryl was released in 2003 which addressed potential health and

ecological risks and included rate reductions and revocations of tolerances for several uses including stone fruits and citrus (U.S.EPA 2003b, 2007g). Data Call-Ins were issued by the EPA in 2005 that required submission of more data on toxicology, worker exposure monitoring and environmental fate for carbaryl. This resulted in voluntary cancellations of the products by many of the registrants. According to the EPA "approximately 80% of all of the carbaryl end-use products registered at the time of the 2003 IRED have since been canceled through this process or other voluntary cancellations" (U.S.EPA 2008a). Carbaryl shows an overall decline in use trend as shown in Figure 2.7 except for a spike in 1995 when the elevated use was due to increased use of carbaryl on oranges based on the CA-DPR data. These use trends clearly correspond to the regulation of the use of carbaryl.

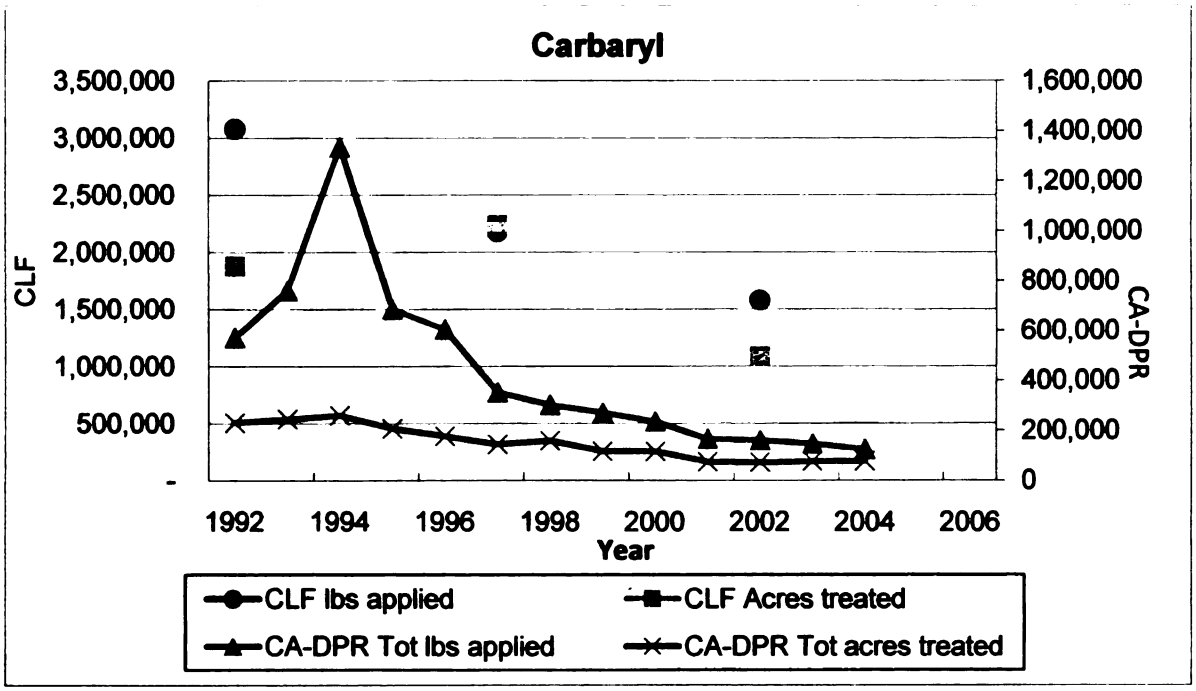

Figure 2.7.Use of carbaryl based on the CA-DPR and the CLF data.

Carbofuran

Carbofuran was first registered in the U.S. in 1969 to control soil and foliar pest on different field, fruit and vegetable crops. In the 1990s, changes were made in the labels of carbofuran (e.g. reduced application rates) by the registrants due to ecological and drinking water risks. Since 1994 the sales of granular carbofuran were limited to 2,500 lbs per year in the U.S., for use only on certain crops (U.S.EPA 2006b). Based on the ecological and human health risk assessments related to carbofuran uses, the EPA "had determined that all uses of carbofuran do not meet the standard for continued registration under FIFRA" (U.S.EPA 2006b). In keeping with this regulatory activity, Figure 2.8 shows use trends from the CLF where the pounds applied decreased by 81% from about 3.3M pounds in 1992 to 625,000 pounds 2002, and from the CA-DPR database showing a 93% decline from 96,000 pounds in 1994 to only 6,700 pounds in 2006.

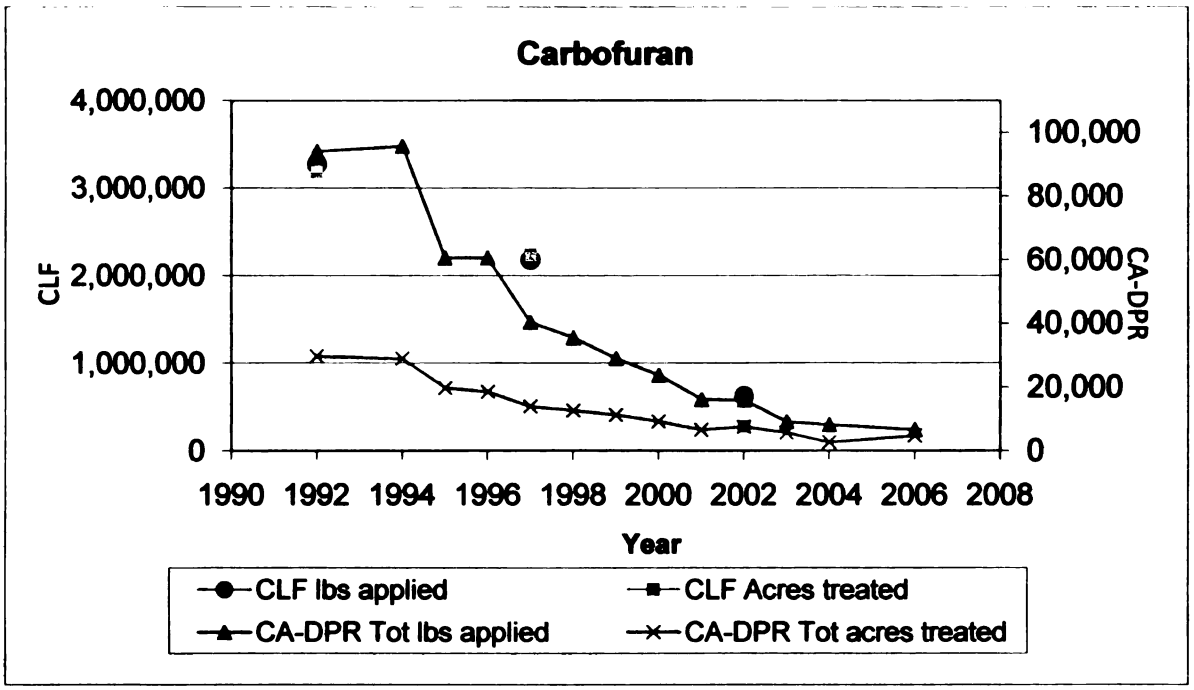

Figure 2.8.Use of carbofuran based on the CA-DPR and CLF data.

Methomyl

Methomyl was first used as an insecticide in commercial plantings of chrysanthemums and was registered by E. I. Dupont de Nemours and Co. in 1968. Its current registered uses include agricultural, industrial and commercial applications. In 1978 it was classified as restricted use pesticide, and a registration standard, modified tolerances and labels were issued in 1989. Greenhouse and ornamental uses were voluntarily cancelled in 1998. The EPA maintained the restricted use classification based on its acute toxicity and use patterns (U.S.EPA 1998f). Between 1994 and 2006, the pounds of methomyl applied decreased by 75% and acres treated by 71% based on the CLF data; and by 55% and 49% in pounds applied and acres treated, respectively, based on the CA-DPR data (Figure 2.9). A significant decrease in the use of methomyl is evident after the enactment of the FQPA as a result of the voluntary cancellations and its classification as a restricted use compound.

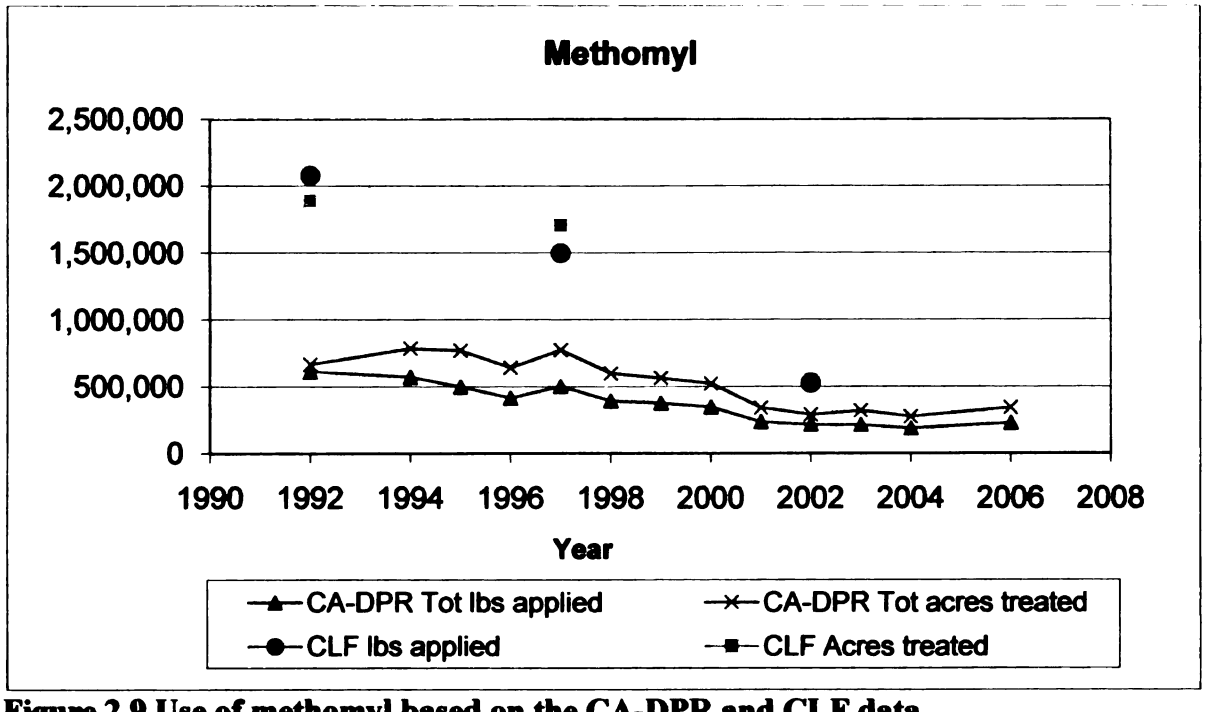

Figure 2.9.Use of methomyl based on the CA-DPR and CLF data.

Oxamyl

E.I. DuPont de Nemours, Inc. first used oxamyl on ornamentals, tobacco, and on non-bearing fruit in 1974 and more uses have been added since then (U.S.EPA 2000d). Oxamyl is registered for use on terrestrial food and feed crops. The first Registration Standard was issued in 1987 and was updated in 1991. In 2002, the EPA revoked several oxamyl uses because they were no longer considered as feed items (U.S.EPA 2002a). The EPA concluded that minimal risks were associated with oxamyl except for dietary intake by children 1-6 years old which EPA believed was "due to an overestimation of exposure and consequently risk because of the rapid reversibility of oxamyl induced cholinesterase inhibition was not accounted for" (U.S.EPA 2000d). The use of oxamyl shows a moderate overall decreasing trend as shown in Appendix C. However, the CLF data shows an increase in pounds applied in 2002 compared to 1992. Based on the CA-DPR data, usage decreased by 43% in pounds applied and 56% in acres treated from 1994 compared to 2006. The USDA reports that growers are using lower rates (0.46 to 0.62 lb ai/A) and applying the pesticide less frequently (about twice per year compared with the allowable 12 times) (U.S.EPA 2000d).

2.5.2.3 *Organophosphates*

Azinphos-methyl (AZM)

Azinphos-methyl was first registered as an insecticide in the U.S. in 1959. The major uses of AZM include applications on fruits and vegetables and on nursery plants. The Worker Risk Strategy, a process which looked at over 80 chemicals that had any reported worker incidents in California was initiated by the EPA in 1992 and AZM was ranked 5th among the 28 chemicals required for the development of additional incident

data. In 1993 the use of AZM on sugarcane was limited to prescriptive use only in Louisiana and required prior approval of the state for all applications due to large fish kills (U.S.EPA 2001b). This use was subsequently cancelled voluntarily by all AZM registrants in 1999. In 1998, the California Department of Pesticide Regulation (CA-DPR) and the EPA took actions to protect agricultural workers. The CA-DPR issued a 120-day emergency regulation to protect workers exposed to AZM use on grapes and on most tree crops. The EPA took this action to the national level and worked with the CA-DPR to establish interim mitigation measures that were fully implemented for the 1999 growing season. Further, the EPA granted use cancellations requested by the registrants of AZM (U.S.EPA 2000b) and in 2000, the EPA revoked and modified some tolerances for AZM in and on various crops (U.S.EPA 2000a). More cancellations of AZM uses were implemented in 2005 and in November 2006, the EPA issued a final decision to phase out all remaining uses of AZM by September 30, 2012 (U.S.EPA 2006a). The use of AZM follows this regulatory activity closely and has continuously declined from 1996 to 2006 as shown in Figure 2.10. The CLF data show about a 47% decrease in pounds applied and 50% in acres treated while there is a 91% decrease for both based on the CA-DPR data.

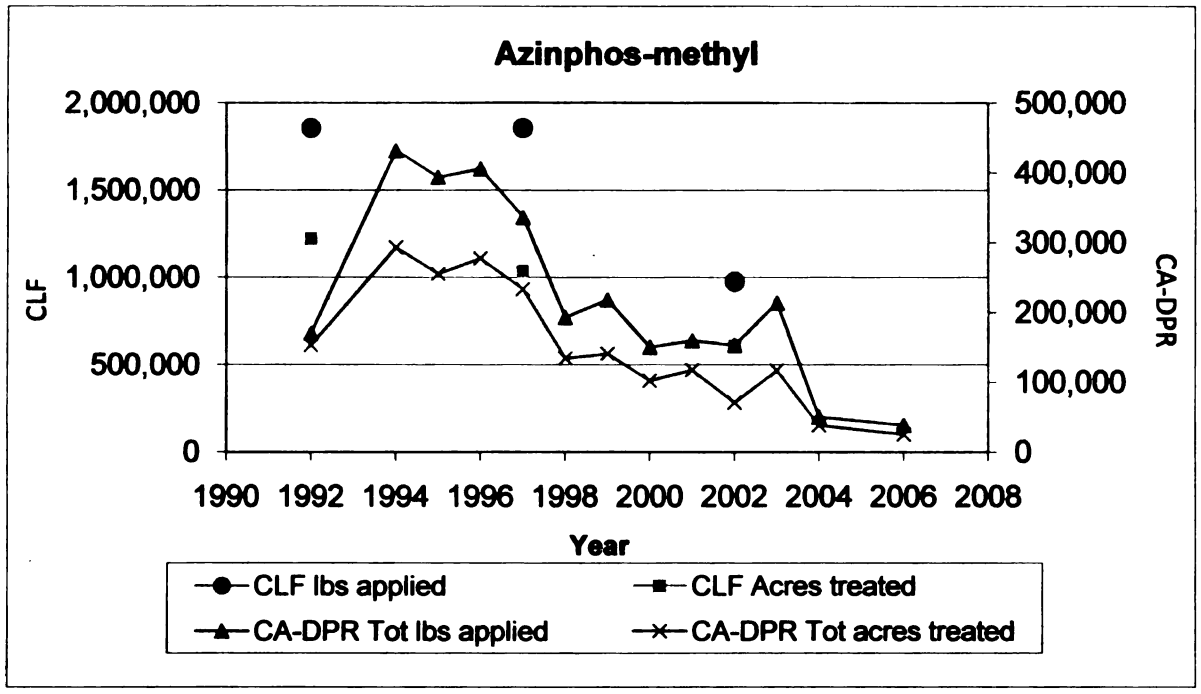

Figure 2.10.Use of azinphos-methyl based on the CA-DPR and the CLF data.

Chlorpyrifos

Chlorpyrifos was first registered in 1965 for use on foliage and soil-borne insect pests on food and feed crops. In 1996 tolerances were revised for residues of chlorpyrifos in or on several raw agricultural commodities by establishing time-limited tolerances as permanent tolerances (U.S.EPA 1996a). Various indoor uses of chlorpyrifos were eliminated in 1997 to reduce indoor exposure of children and other sensitive groups. In 2000, nearly all residential uses were phased out following an agreement between the registrants and the EPA (U.S.EPA 2002d). In July 2002 several tolerances for chlorpyrifos were revoked because they were no longer needed or were associated with food uses that were no longer registered in the U.S. (U.S.EPA 2002a). Figure 2.11 shows the decline in the use of chlorpyrifos over time based on the CLF data. This amounted to 56% fewer pounds applied and 88% fewer acres treated, which was probably due to the preliminary risk assessment by the EPA that "showed acute dietary risks from food exceeded the acute population adjusted dose (aPAD) for infants, all children, and nursing

females of child-bearing age (13-50 years old) (U.S.EPA 2002d). The EPA also recorded the registrants' agreement to eliminate use on tomatoes and restrict use on apples to address excessive risks. On the other hand, the CA-DPR data show a different pattern where use decreased from 1997 to 2003 but has increased again since then. This is primarily due to a large increase in use on almonds but increased use on walnuts and oranges also contributed to this late rise.

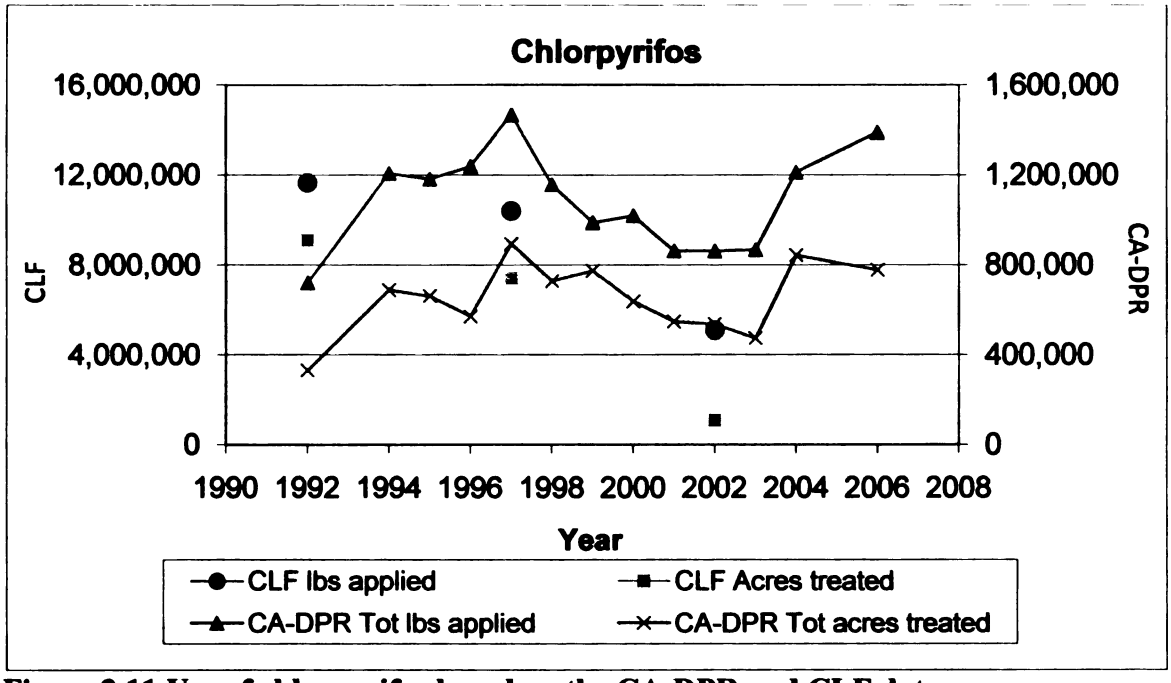

Figure 2.11.Use of chlorpyrifos based on the CA-DPR and CLF data.

Diazinon

Diazinon was first registered in the U.S. in 1956 as an insecticide, acaricide and nematicide for fruits, vegetables, and forage and feed crops. In 2001 EPA approved requested product cancellations and amendments to terminate all indoor uses after negotiations with the technical registrants due to the findings of the EPA that diazinon, as currently registered, was an exposure risk, especially to children (U.S.EPA 2001a). Other agricultural uses were also cancelled in 2001 except for spinach, strawberries and tomatoes due to a nationwide need for the application of diazinon on these crops

(U.S.EPA 2001a). More cancellations of agricultural uses followed from 2001 to 2003. The EPA's Interim Reregistration Eligibility Decision (IRED) human health risk assessment for diazinon in 2004 indicated residential and occupational risk concerns but acute and chronic food risks were below the level of concern (U.S.EPA 2004c). Generally, diazinon shows a moderate but regular decreasing use trend since 1994 (Figure 2.12) based on the CA-DPR data. The CLF data showed the same trend from 1992 to 1997 but with a slight increase in pounds applied in 2002.

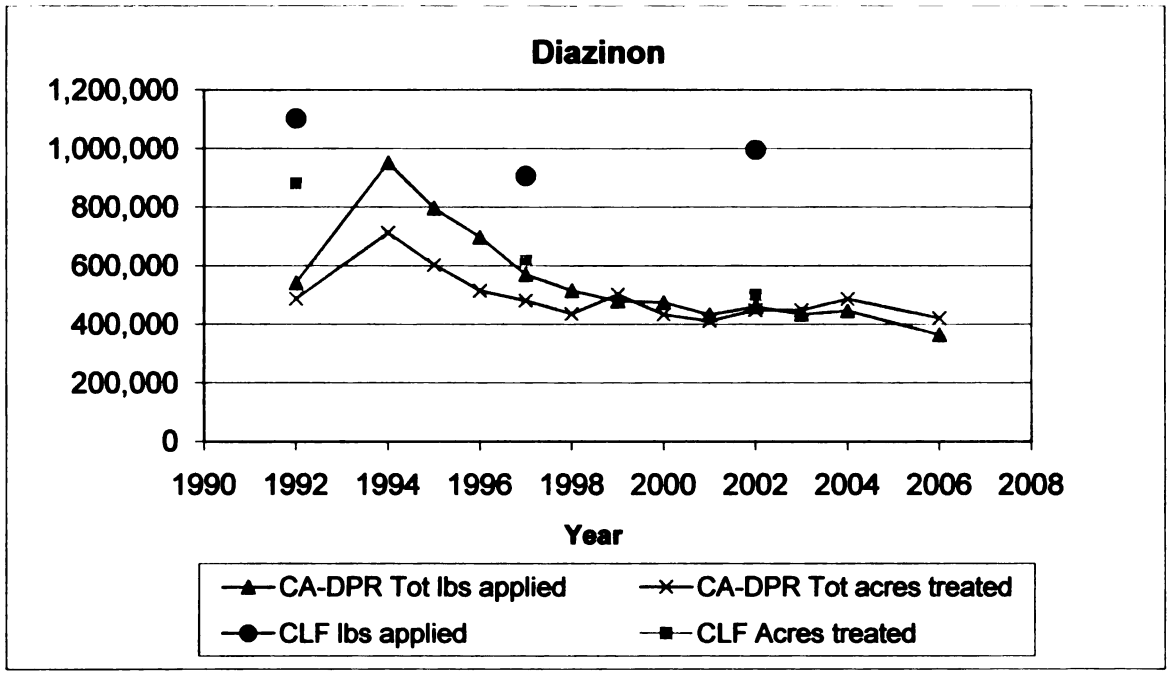

Figure 2.12.Use of diazinon based on the CA-DPR and the CLF data.

Dimethoate

Dimethoate was first registered and used in the U.S. in 1962. It has been used on both food and non-food products as well as in a variety of non-agricultural applications. In 2000 all non-agricultural and residential uses of dimethoate were cancelled (U.S.EPA 2006c) and more use cancellations on various crops followed in 2004 (U.S.EPA 2004b). Further uses were cancelled in 2005 including those on seven crops (apples, broccoli

raab, cabbage, collards, grapes, head lettuce, and spinach) that were identified as significant dietary risk contributors along with four crops for which there were no field trial data to support tolerances (fennel, lespedeza, tomatillo, and trefoil) (U.S.EPA 2006c). Since its peak in the early 1990s, it appears that the use of dimethoate has declined regularly with an overall decline of greater than 50% by 2006 based on both databases (Figure 2.13).

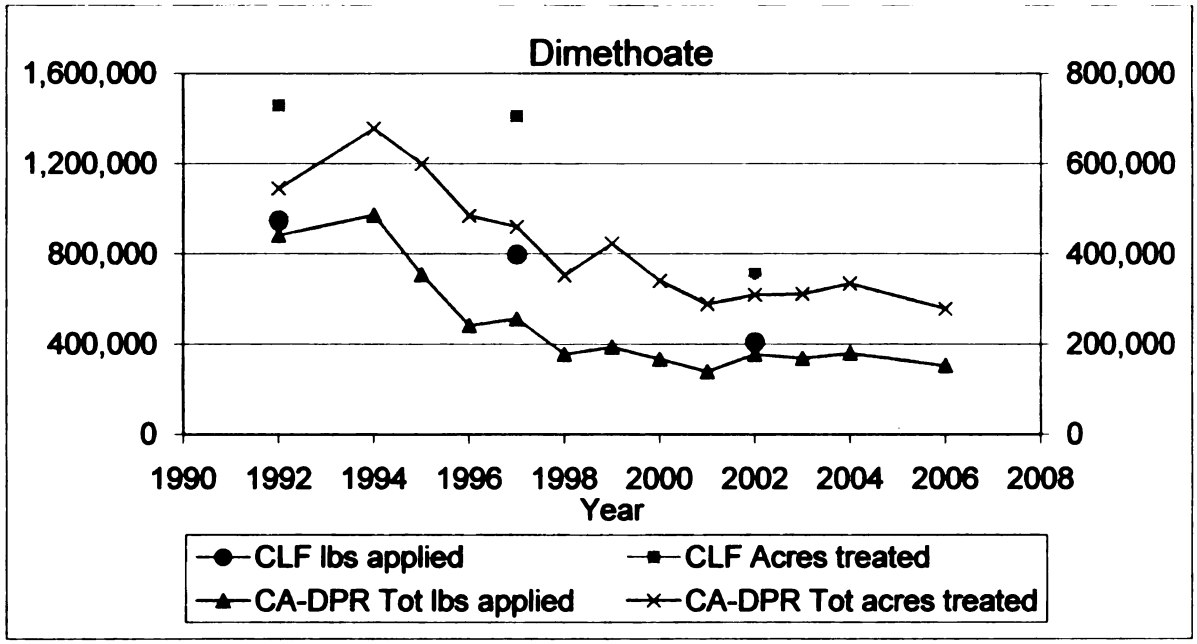

Figure 2.13. Use of dimethoate based on the CA-DPR and the CLF data.

Disulfoton

The initial registration of disulfoton as an insecticide occurred in 1961. It is used on food, feed and non-food crops and in residential applications as well. During the reregistration process several changes to disulfoton registrations were proposed by Bayer Corporation, the technical registrant of disulfoton, that were later accepted by the EPA as interim risk mitigation measures (U.S.EPA 2002e). In 2002, Bayer "elected to voluntarily cancel certain product and/or delete product uses from their product labels rather than develop the data necessary to support reregistration" (U.S.EPA 2002c). Other changes

included application rate reductions and voluntary cancellations and deletions of uses no longer supported by Bayer. The use of disulfoton significantly decreased as shown in Figure 2.14 from 757,000 lbs in 1992 to 111,000 lbs (85%) in 2002, based on the CLF data, and from 114,000 lbs in 1994 to 19,000 lbs in 2006 (83%) based on the CA-DPR data.

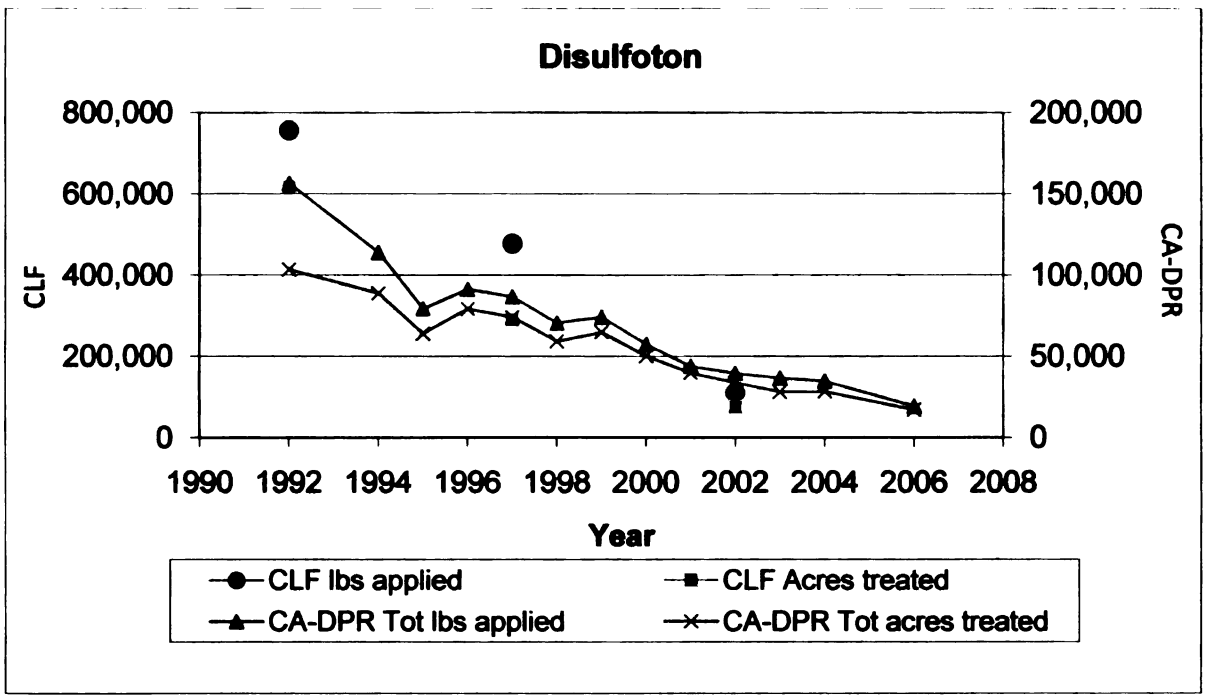

Figure 2.14.Use of disulfoton based on the CA-DPR and CLF data.

Fonofos

Stauffer Chemical Company developed and initially marketed fonofos in 1967. Fonofos was used on fruit and vegetable crops as a soil insecticide. Environmental risk assessment revealed a very high toxicity of fonofos to birds and to freshwater and salt water organisms according to the EPA (U.S.EPA 1999b). In December 1997 Zeneca Ag Products requested voluntarily cancellations of fonofos registrations and all other remaining fonofos products were cancelled by November 2, 1998 (U.S.EPA 1999b). This accounts for the 100% decline in the use of fonofos from 1992 to 2004 as shown in Figure 2.15.

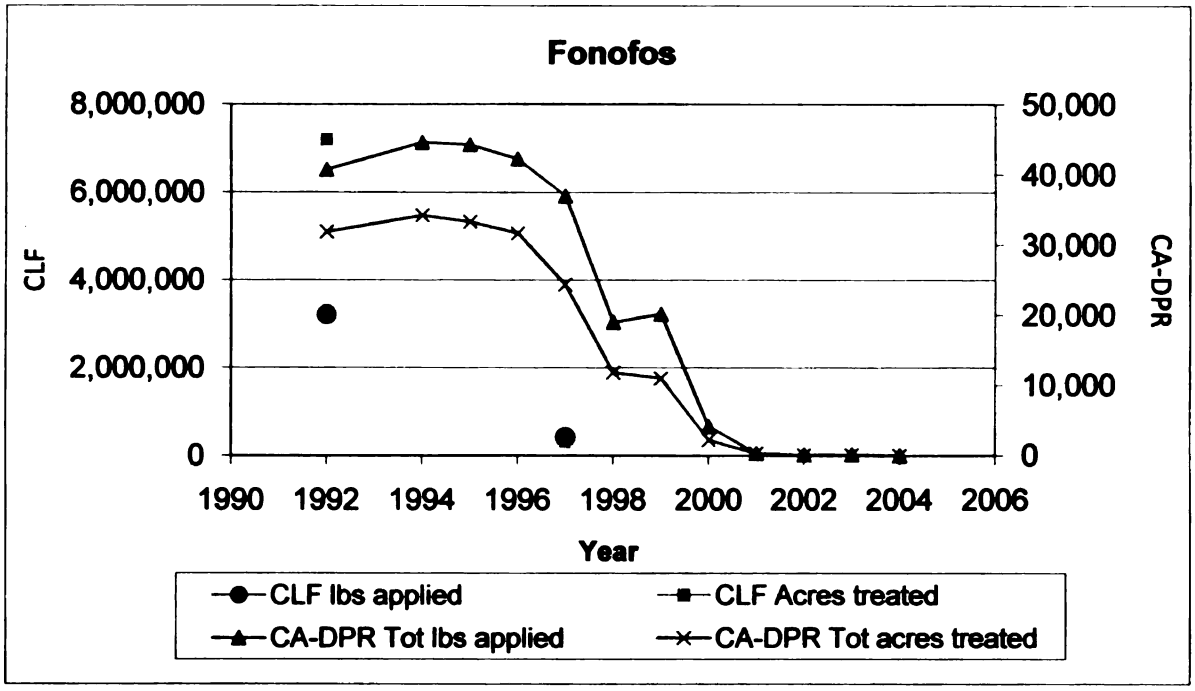

Figure 2.15.Use of fonofos based on the CA-DPR and CLF data.

Methamidophos

Methamidophos was first registered in the U.S. in 1972 to control a broad spectrum of insects on potatoes, cotton and cole crops. The EPA reported risks to agricultural workers resulting from exposure to methamidophos. According to the EPA, the risks to workers of acute exposure exceeded the EPA's level of concern and California human incident data showed acute worker exposure incidents associated with methamidophos use (U.S.EPA 1997c). Bayer Corporation, the technical registrant of methamidophos, voluntarily cancelled all uses in 1997 except for use on cotton, potatoes, tomatoes and alfalfa. In December 1999 the registrant had also voluntarily phased-in closed mixing and loading systems for all remaining uses to address potential worker exposures (U.S.EPA 2002g). Figure 2.16 shows the continuous decline in the use of methamidophos since 1994. The CLF data show that total pounds used has declined from 800,000 lbs in 1992 to only 287,000 lbs in 2002 (64%) while CA-DPR shows a

99% decrease from 154,000 lbs in 1994 to 1,700 lbs in 2006. This continuous decline in use is attributable to the cancellations of most of the uses of methamidophos.

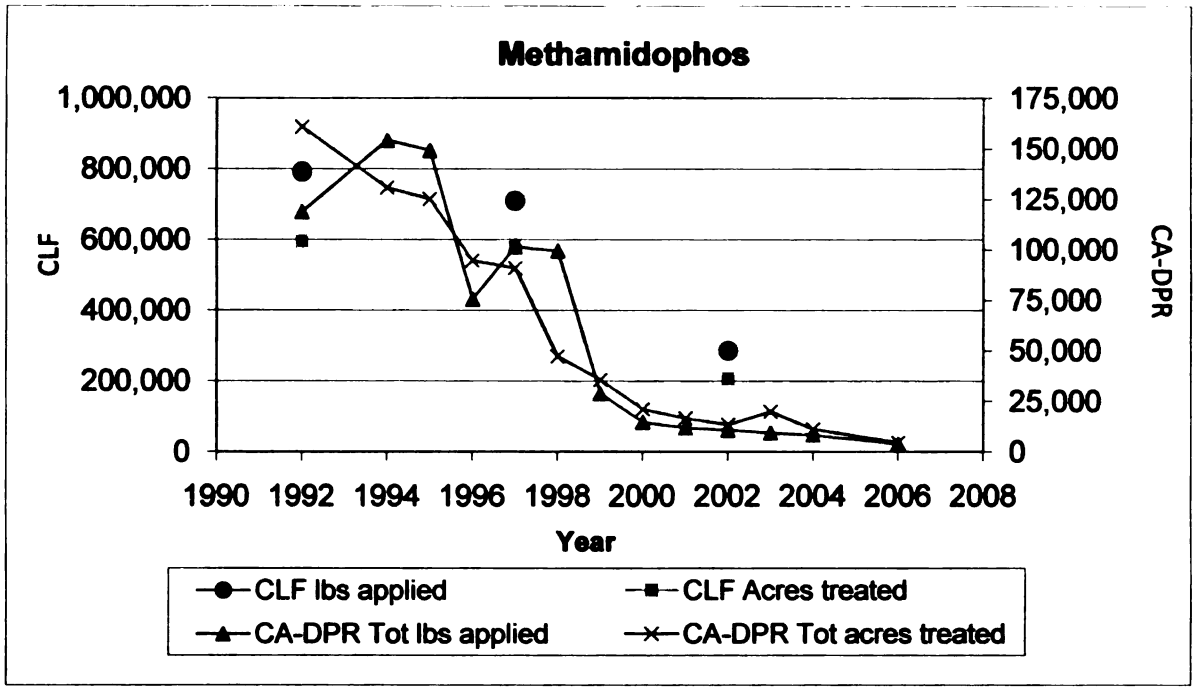

Figure 2.16.Use of methamidophos based on the CA-DPR and CLF data.

Methyl parathion

Methyl parathion was first used in 1954 as an insecticide/acaricide on many terrestrial foods and feed crops. In 1986 label registrations were changed to enhance worker safety. In 1996, the EPA and the registrants of methyl parathion products agreed to change the packaging, formulation and labeling of their products to prevent illegal diversion in indoor use (U.S.EPA 1997g). The EPA and the registrants subsequently agreed to voluntarily cancel a number of crop uses to address dietary concerns and commited to conducting studies to refine potential occupational risk concerns (U.S.EPA 2003a). The cancelations included uses on fruits and vegetables commonly eaten by children. In 2001, tolerances for various fruits and vegetable crops were revoked due to dietary risk concerns and more revocations followed in 2002. Figure 2.17 shows increased use from 1992 to 1997/1998 but it has decreased considerably since then due to

the voluntary cancellations of uses. The pounds applied increased by 61% (CA-DPR) from 1992 to 1999 but decreased by 64% from 1999 to 2002. The use has actually increased since 2002 probably due to its effectiveness and low cost in its remaining uses which minimize food residues.

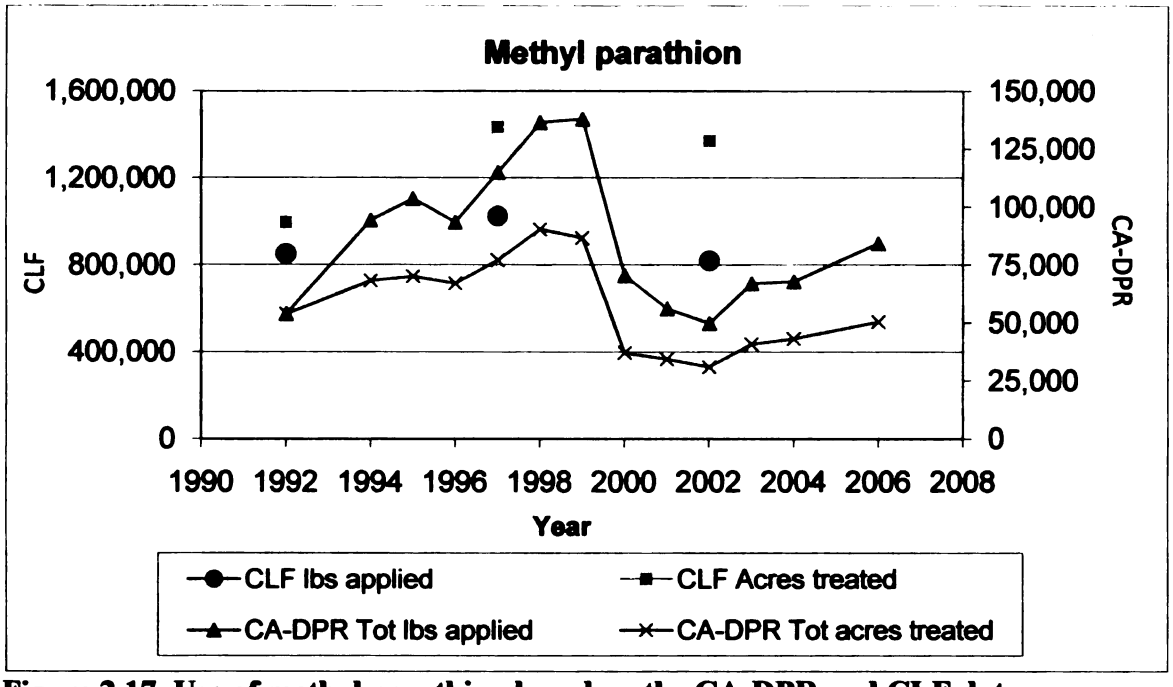

Figure 2.17. Use of methyl parathion based on the CA-DPR and CLF data.

Acephate

Acephate was first registered for ornamental use in the U.S. in 1973 and first used on food in 1974. Uses of acephate include application on food crops, and at residential, public health and other non-food sites. In 1987, a Registration Standard was issued that imposed several interim measures to reduce dietary, occupational, and domestic exposure from the registered uses of acephate (U.S.EPA 2001c). Human health concerns have been reported by the EPA concerning risks to workers who load, mix and/or apply acephate to agricultural sites, golf courses and home lawns, in and around residential, commercial, institutional and industrial buildings and recreational areas (U.S.EPA 2001c). In April 2002 the EPA approved the voluntary cancellations of acephate uses by

various product registrants. Acephate exhibits a downward use trend as shown by the CA-DPR and the CLF data (Appendix C). The use decreased by 25% (CLF) and 59% (CA-DPR) in pounds applied from 1994 to 2006 due mainly to the need to reduce worker exposure risks.

Fenamiphos

Chemagro Corporation first registered fenamiphos in 1972. Food uses of fenamiphos included fruits and vegetables and non-food uses included commercial and industrial sites and ornamental crops. The Registration Standard and data call-in were issued by the EPA in 1987 to better understand the risks associated with using fenamiphos (U.S.EPA 2002f). In 1994, the registrants made voluntary risk mitigation measures including use restrictions and reductions in response to the preliminary health and ecological risk assessments provided by the EPA (U.S.EPA 2002f). In 2002 the EPA approved use deletions on cotton and pineapple. Since 1997, the use of fenamiphos follows a strongly decreasing trend that is attributable to the regulatory actions taken in 1994 (Appendix C).

Methidathion

Methidathion was first used as a broad spectrum insecticide in 1972. Food crop uses of methidathion include fruits and vegetables while non-food uses consist of commercial and industrial applications. In 1983 a Registration Standard was issued for methidathion and was revised and reissued in 1988. Risk assessment was conducted in 1999 to address occupational exposure to pesticide handlers and workers. Results from the risk assessment conducted by the EPA showed five of the 18 agricultural scenarios exceeded the level of concern (U.S.EPA 2002h). The use of methidathion declined

rapidly from 1994 to 2002 and has remained low since then as shown by the CA-DPR data (Appendix C). The EPA reported occupational risks and acute and chronic risk to birds, mammals and aquatic species of concern (U.S.EPA 2002h) which are probable explanations for the downward trend in its use.

2.5.2.4 *Reduced-risk Fungicides*

The registration and use of the reduced-risk fungicides have increased regularly following the passage of the FQPA as previously shown in Figures 2.1 and 2.2. However, apart from the data from CA-DPR, use data on these recent compounds that could be used to assess trends is very limited. In order to simplify the analysis, the acreage use of the reduced-risk fungicides were classified as low, medium or high based on the 2006 CA-DPR data shown in Table 2.3. Among the fungicides, fludioxonil and fenhexamid belonged to the low acreage classification whereas mefenoxam, trifloxystrobin, azoxystrobin and cyprodinil were classified as medium in acreage treated. No reduced-risk fungicides exceeded 500,000 acres in use.

Table 2.3. Level of reduced-risk fungicides acreage based on the CA-DPR 2006 data.

Reduced-risk Fungicides	Acres Treated (CA-DPR /2006)
Fludioxonil	29,241
Fenhexamid	161,025
Mefenoxam	268,961
Trifloxystrobin	386,030
Azoxystrobin	390,552
Cyprodinil	420,155

0 - 199,999 acres	Low
200,000-499,999 acres	Medium
500,000-999,999 acres	High

Azoxystrobin

Azoxystrobin was first registered for use on non-residential turf in 1997. Food use registrations followed in the same year for crops such as grape, peach, tomato and peanut.

More use registrations on crops such as cucurbit, potato and stone fruit were approved in 1999, and on onion, citrus, soybean, leafy, root and tuber vegetables in 2000. Registrations for mostly vegetables and some fruits were also approved in 2001 and 2002. The registrations of azoxystrobin for use on artichoke, asparagus, and the brassica group in 2003 and on herbs, spices, safflower and sunflower in 2006 were obtained by the IR-4 program. Azoxystobin is not classified as a carcinogen and has low acute and chronic toxicity to humans, birds, mammals and bees, but it is highly toxic to some freshwater, marine and estuarine fish and invertebrates" (U.S.EPA 1997a). Figure 2.18 shows the use of azoxystrobin increased rapidly from 1996 to about 2000 and has consistently been used since then based on the CA-DPR and CLF data.

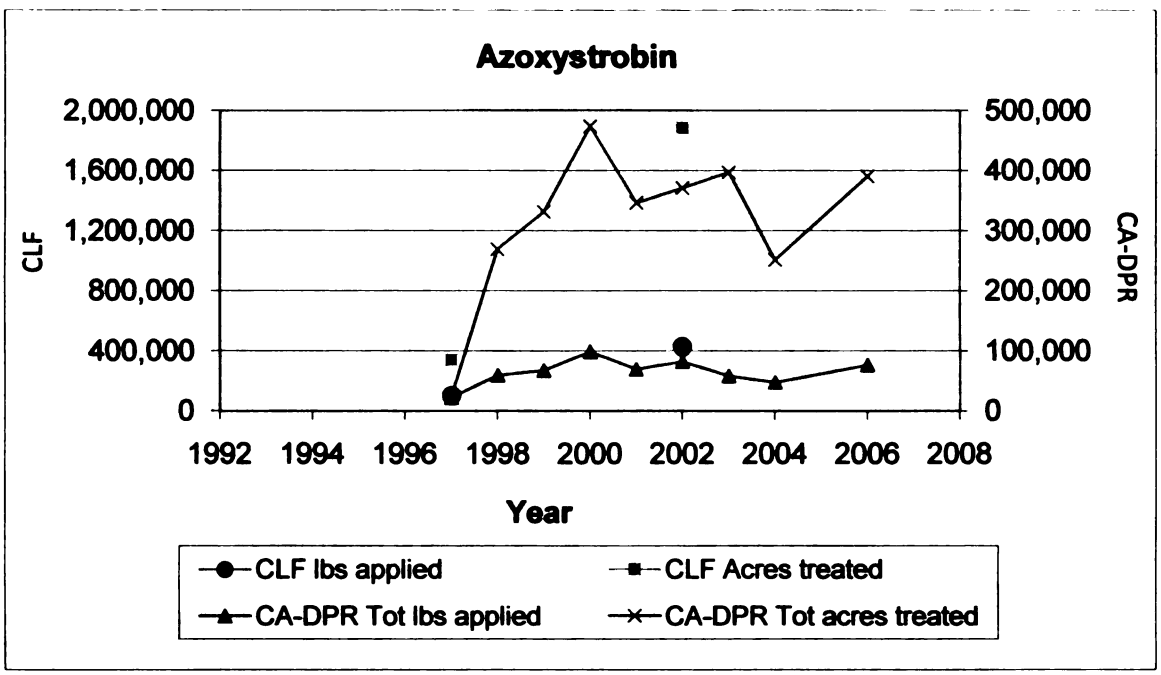

Figure 2.18.Use of azoxystrobin based on the CA-DPR and CLF data.

Cyprodinil

Cyprodinil was first registered for use on stone fruits in 1998 followed by uses on onions and strawberries in 2001. Other uses include foliage applications on almonds, grapes and stone fruits. The EPA (U.S.EPA 1998a) reported no mutagenic,

developmental and reproductive effects and it is classified as a "not likely" (E) carcinogen based on the lack of oncogenic effects on all tested species. In 2003 the IR-4 program registered cyprodinil for use on bushberry, caneberry, pistachio, watercress, brassica leafy vegetables, herbs and lychee fruits. Cyprodinil is of low risk (Appendix B) and appears to pose relatively little human toxicity risk due to low use rate, low risk to groundwater, low dietary risk and low worker exposure (U.S.EPA 1998a) which helps to explain the continuously increasing use with ~183,000 acres treated in 1999 and ~420,000 acres treated in 2006 based on the CA-DPR data (Figure 2.19).

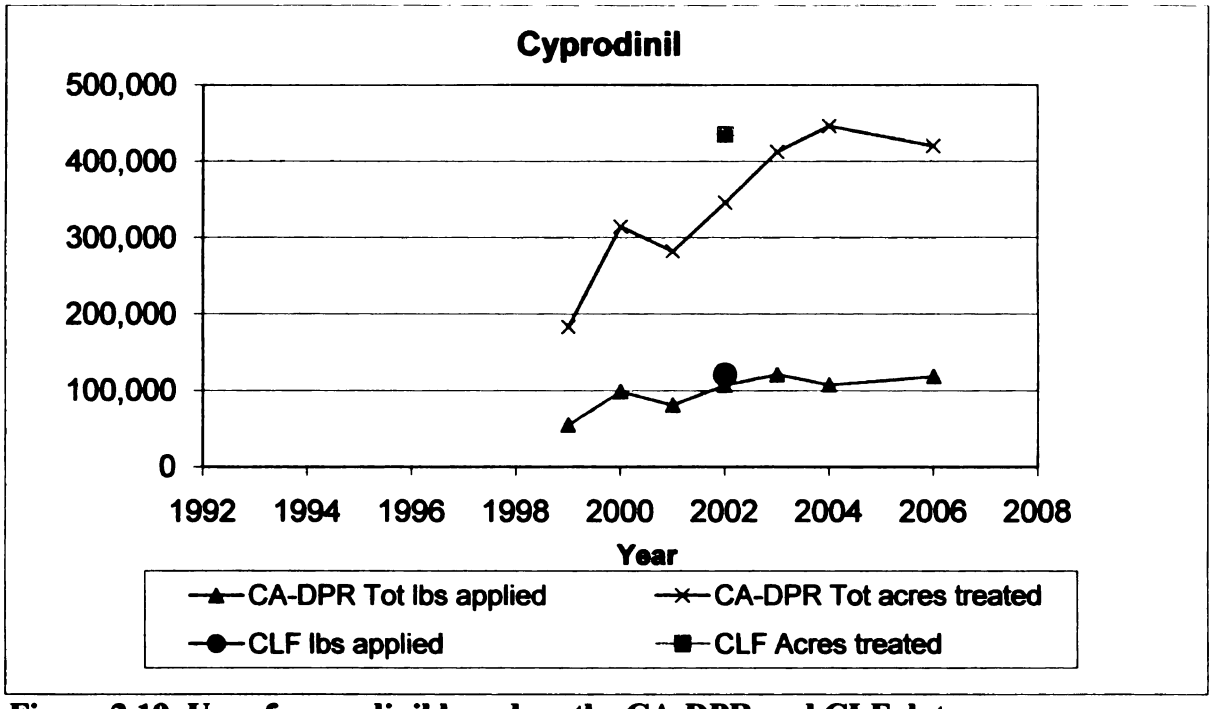

Figure 2.19. Use of cyprodinil based on the CA-DPR and CLF data.

Fenhexamid

Fenhexamid was first registered in 1999 for use on strawberries, grapes and ornamentals followed by uses on almond and stone fruits in 2000. Fenhexamid is classified by the EPA as a "not likely" human carcinogen based on the lack of evidence of carcinogenicity in male and female rats and mice (U.S.EPA 1999a) and no evidence of genotoxicity and mutagenicity has been found. The IR-4 program obtained several

registrations for fenhexamid in 2003 (cucumber, fruiting vegetables, leafy greens and stone fruit), and in 2006 (ginseng, pear, cilantro, pepper and pomegranate). Figure 2.20 shows the continuously increasing use in the pounds applied and acres treated of fenhexamid (12,000 lbs in 1999 and 66,000 lbs in 2006 based on the CA-DPR data).

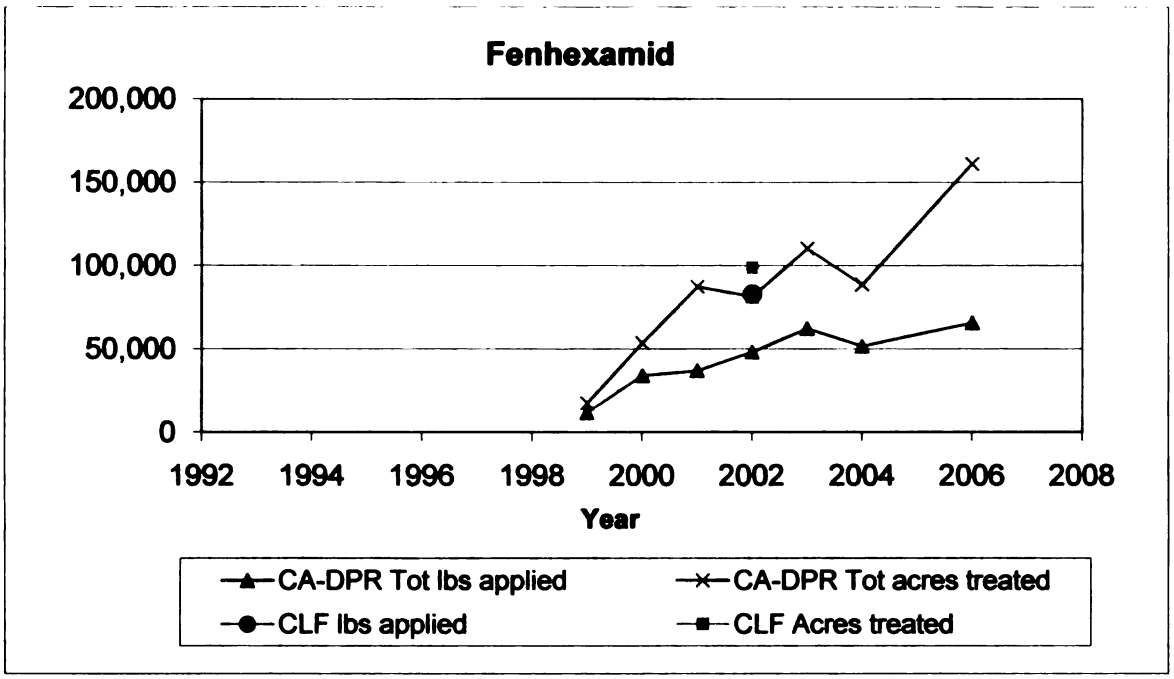

Figure 2.20.Use of fenhexamid based on the CA-DPR and CLF data.

Fludioxonil

The first registration of fludioxonil was in 1995 for use on corn followed by its use on potato and seed treatments for several nuts and vegetables in 1997. In 1998 more tolerances for vegetables such as brassica leafy vegetables, legumes, leaves of root and tuber vegetables, and bulb vegetables were established. The EPA reported no concern for acute dietary risk for fludioxonil and it has been classified as "not classifiable as to human carcinogenicity or Group D, that is, the evidence is inadequate and cannot be interpreted as showing either the presence or absence of a carcinogenic effect" (U.S.EPA 1998b). More uses of fludioxonil were later approved for use on strawberries and bulb vegetables in 2000, for turf in 2001 and caneberry, pistachio, stone fruit and watercress in

2002. Many of these registrations were obtained by the IR-4, i.e. the pome group (e.g. apples and pears), asparagus, beets, the melon subgroup (e.g. cantaloupes and watermelons), carrots, the stone fruit group (cherry, peach, plum and nectarine), citrus, cucumbers, garlic, spinach, squash, tomatoes, sweet potatoes, and yams. The increasing use trend of fludioxonil is shown in Figure 2.21.

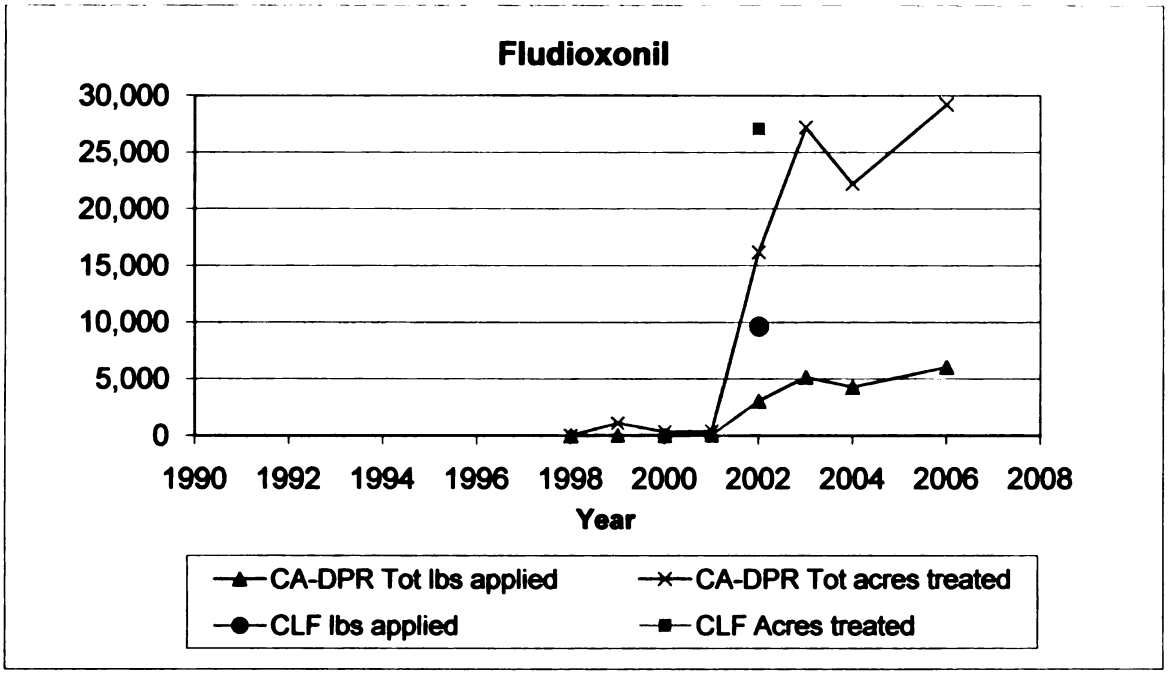

Figure 2.21. Use of fludioxonil based on the CA-DPR and CLF data.

Mefenoxam

Mefenoxam is the active form in the isomer mixture of the fungicide metalaxyl. It was registered in 1996 to replace all previous uses of metalaxyl (U.S.EPA 1996b). Ciba Crop Protection voluntarily cancelled all of the registrations of metalaxyl to allow for the full environmental benefit provided by the registration of end-use products containing mefenoxam" (U.S.EPA 1996b). Mefenoxam has shown a consistent medium level of use in California in replacing metalaxyl since its registration as shown in Figure 2.22 and the CLF data show a clear increase from 1997 to 2002.

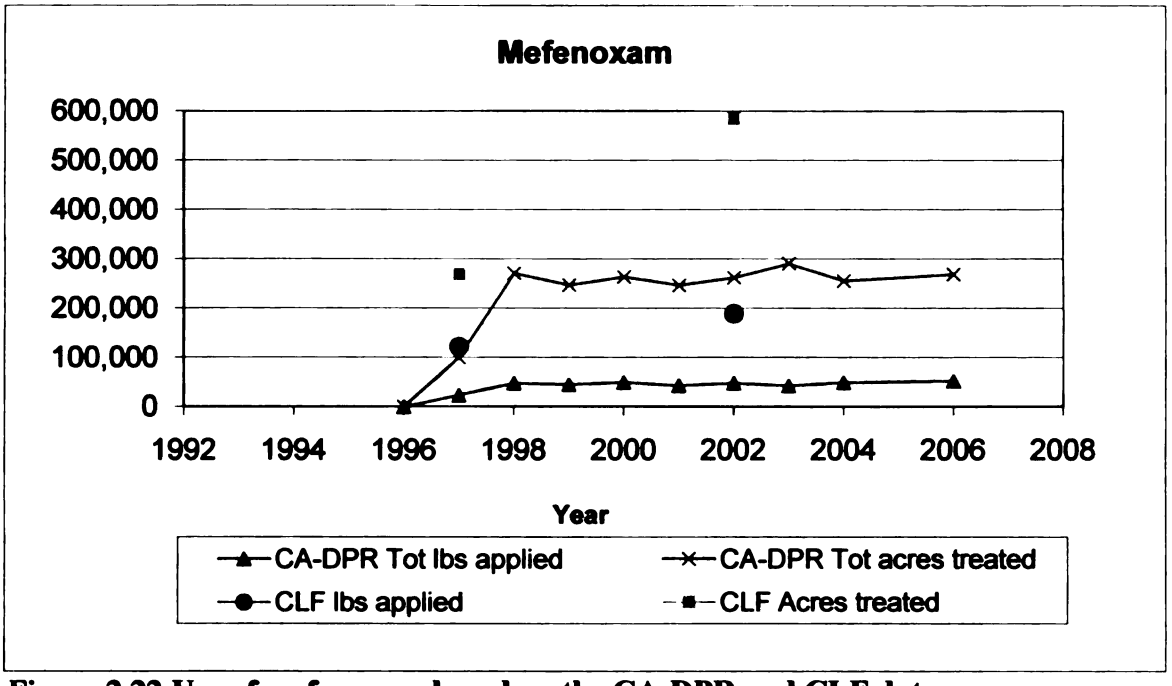

Figure 2.22.Use of mefenoxam based on the CA-DPR and CLF data.

Trifloxystrobin

The first registration of trifloxystrobin, obtained in 1999, was for use on pome fruit, grapes, cucurbits, peanuts, bananas, turf and ornamentals. Further registrations followed in 2000 and 2002 for use on more fruits and vegetables including almonds, citrus, pecans and stone fruit. The IR-4 program obtained registrations in 2003 for the leafy petiole and root vegetable subgroups and barley and oats in 2006. Trifloxystrobin is classified as a "not likely human carcinogen" and exhibited no mutagenic properties (U.S.EPA 1999e). However, kidney and liver toxicity at high doses were noted from subchronic and chronic toxicity studies. Trifloxystrobin has been continuously used at a medium level since its initial registration (Appendix C). In the CA-DPR data there was no clear increase in the pounds applied but the acres treated increased from 2000 to 2006.

2.5.2.5 *Reduced-risk Insecticides*

The levels of acreage treated with the reduced-risk insecticides based on the CA-DPR 2006 data are shown in Table 2.4 and are classified as low, medium or high in the

same way as the reduced-risk fungicides. Among the reduced-risk insecticides, imidacloprid, methoxyfenozide and spinosad were classified as having a high (>500,000) level of acres treated. Tebufenozide had the lowest acres treated (15,517) while its relative, methoxyfenozide, has the second highest acreage treated (840,464). Methoxyfenozide is an analog of tebufenozide which is now preferred since it is active at lower dose and against a broader range of pests than tebufenozide, and shows a high degree of safety to nontarget insects (Borchert et al. 2004). This explains the huge difference in the level of usage between the two analogous insecticides.

Table 2.4. Level of reduced-risk insecticides acreage based on the CA-DPR 2006 data.

Reduced-risk Insecticides*	Acres Treated (CA-DPR/2006)
Tebufenozide	15,517
Thiamethoxam	27,084
Pymetrozine	53,580
Buprofezin	68,682
Bifenazate	153,356
Pyriproxifen	166,208
Acetamiprid	207,705
Indoxacarb	242,607
Imidacloprid	623,030
Methoxyfenozide	840,464
Spinosad	863,977

0 - 199,999 acres	Low
200,000-499,999 acres	Medium
500,000-999,999 acres	High

**Listed as OP alternatives by the EPA (U.S.EPA 2008b).*

Acetamiprid

Registrations for the use of the neonicotinoid insecticide, acetamiprid, on cotton, pome fruit, citrus, grapes, and brassica crops, among others, were completed in 2002 and this was followed by its registration for the use on potatoes in 2005. It has been classified as an "unlikely" human carcinogen and showed generalized non-specific toxicity and did not appear to have specific target organ toxicity (U.S.EPA 2002b). The EPA also reported low mammalian acute and chronic toxicity, and no positive evidence was found

to indicate carcinogenicity, neurotoxicity, mutagenicity or endocrine disruption. Figure 2.23 shows that use of acetamiprid has been increasing from 2002 (~39,000 acres treated) to 2006 (~208,000 acres treated) based on the CA-DPR data.

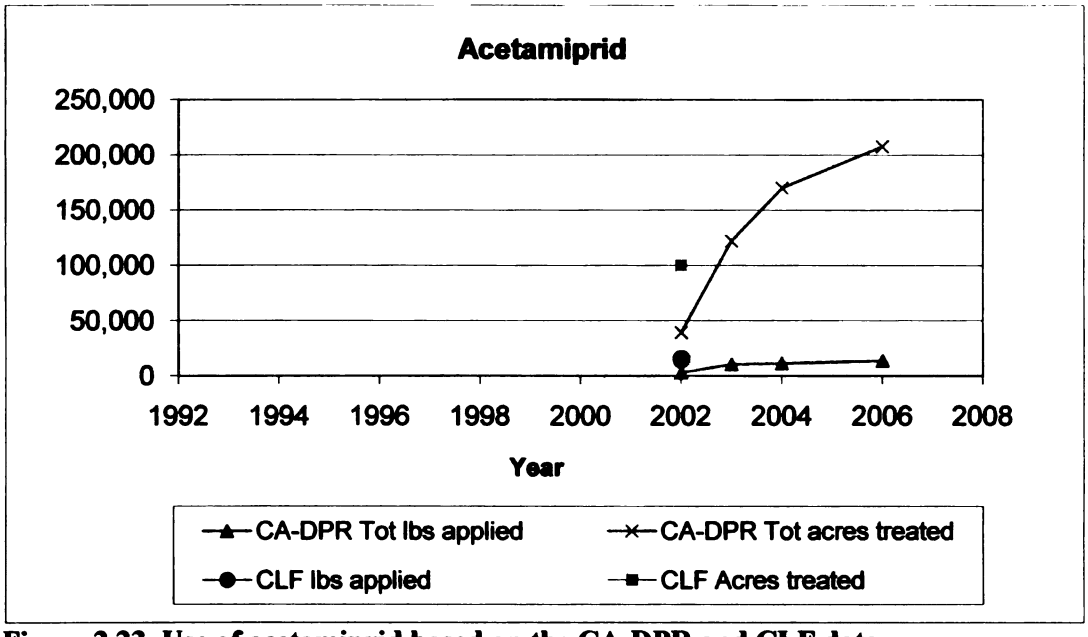

Figure 2.23. Use of acetamiprid based on the CA-DPR and CLF data.

Buprofezin

Buprofezin is an insect growth regulator with very low vertebrate toxicity. In 1997, an emergency exemption for use of buprofezin on cotton was requested but at that time buprofezin was an unregistered material and its proposed use was as a "new chemical" (U.S.EPA 1997d). Requests for pesticide tolerances for emergency exemptions for the use of buprofezin on cucurbits and tomatoes were also made and approved in 1998 and expired in 1999. In 2000 buprofezin was registered for use on cucurbit vegetables and head lettuce, followed by use registration on almonds, citrus, cotton, grapes and tomatoes in 2001. The IR-4 program completed its registration on beans, lychees and pistachios in 2003. In 2005 additional use registrations were completed for avocado, guava, peach, pome fruit, and sugar apple. The EPA identified no concerns for

cancer risks for buprofezin (U.S.EPA 1997b). The use of buprofezin increased from 1997 but declined to zero in 2000 (Figure 2.24) due to the expiration of the emergency registration. It rose rapidly again from 2001 as the registered uses expanded.

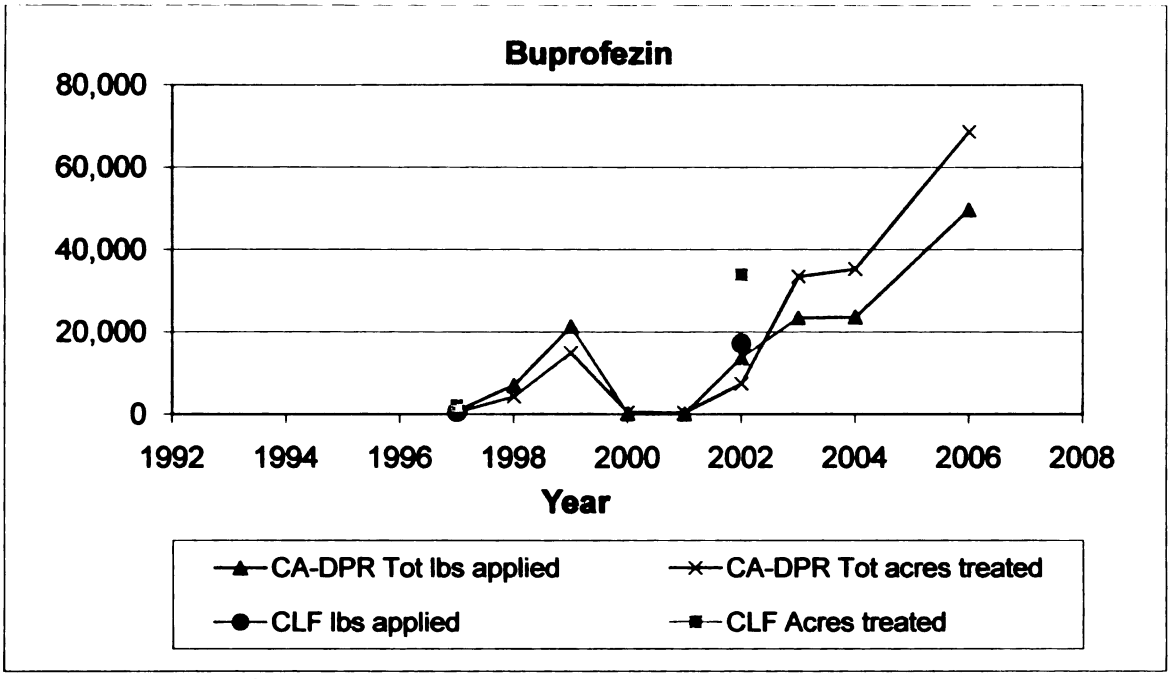

Figure 2.24.Use of buprofezin based on the CA-DPR and the CLF data.

Imidacloprid

Imidacloprid is a systemic insecticide in the neonicotinoid group used to control a wide range of sucking chewing insects that was first registered for use in the U.S. in 1994 and was the first insecticide in its chemical class to be developed for commercial use (Cox 2001). It is now one of the most commonly used insecticides worldwide. Cox (2001) reported its uses on cotton, fruits, vegetables, turfgrass and ornamental plants among others. In 1995, tolerance for imidaloprid residues in or on the raw agricultural commodity dried hops was set as requested by IR-4. Tolerances for sugar beets, sweet corn, safflower and the legume vegetables crop group among others were approved in 1998. In 2001 imidacloprid was registered for use on leaf petiole vegetables and citrus. In 2003 tolerances were established for stone fruits, strawberries, gooseberry and other

berries and for blueberries in 2004. (U.S.EPA 1998c). Imidacloprid was found to cause neurotoxicity in rats following a single high oral dose, and caused alterations in brain weight in rats based on a 2-year carcinogenicity study, but it has been classified under Group E, no evidence of carcinogenicity for humans (U.S.EPA 1998c). Studies have also shown that imidacloprid is non-mutagenic (U.S.EPA 1998c). The use of imidacloprid has increased rapidly and to a high level since its initial registration as shown in Figure 2.25 although most of the increases occurred between 1994 and 1996. It is of low risk, highly effective as an OP replacement and has uses on numerous crops which explain its increasing use trend. Concerns have been expressed about its toxicity to honey bees and possible role in colony collapse disorder. These concerns have yet to be substantiated, although its use has been limited in some countries for this reason (Oldroyd 2007).

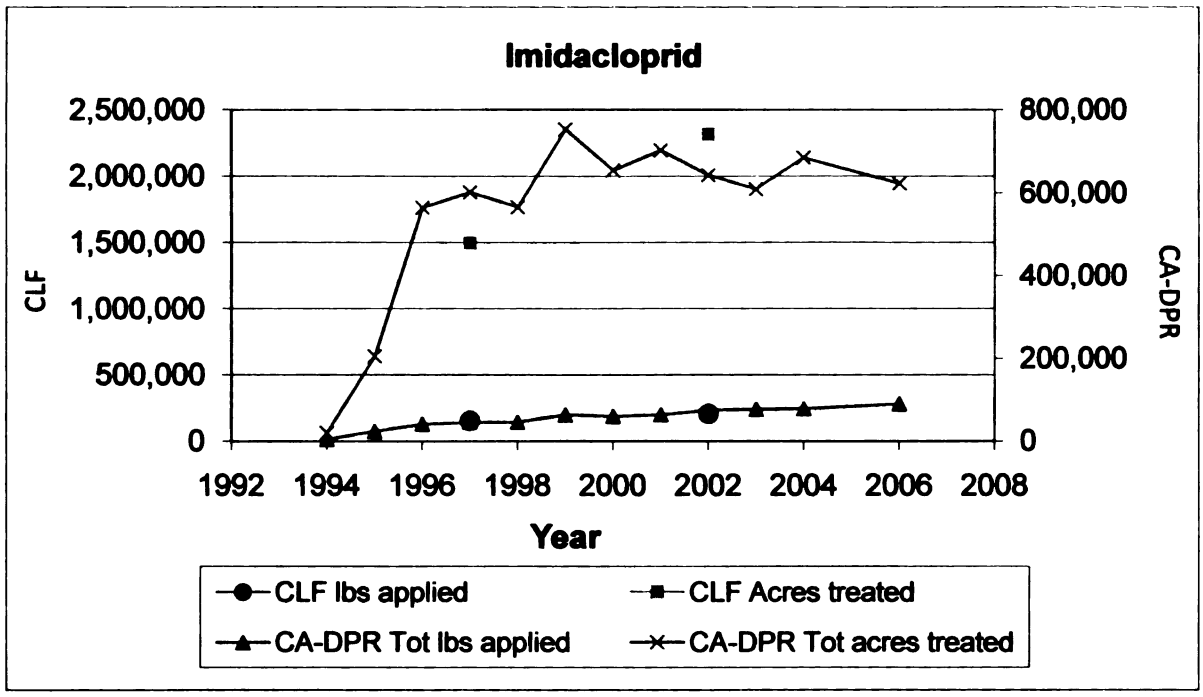

Figure 2.25.Use of imidacloprid based on the CA-DPR and the CLF data.

Pyriproxyfen

Pyriproxyfen, another insect growth regulator, was first registered in 1998 for use on cotton. Walnut, pome fruit, citrus, fruiting vegetables and tree nut uses were approved in 1999. In 2001 use on pistachios was registered; on stone fruits, blueberry, lychee and guava in 2002; and brassicas and cucurbit vegetables, olives, avocados, figs, okra, and sugar apple fruits in 2003. Some of the use registrations in 2002 and 2003 were by IR-4. Pyriproxyfen is a Group E carcinogen which indicates evidence of non-carcinogenicity in humans and it has been found by the EPA to cause no concern for acute dietary exposure to its residues (U.S.EPA 1997e). Figure 2.26 shows a consistent increase in use of pyriproxyfen with an increase in acres treated and pounds applied based from the CA-DPR data from 1997 (50,000 acres treated) to 2006 (166,000 acres treated).

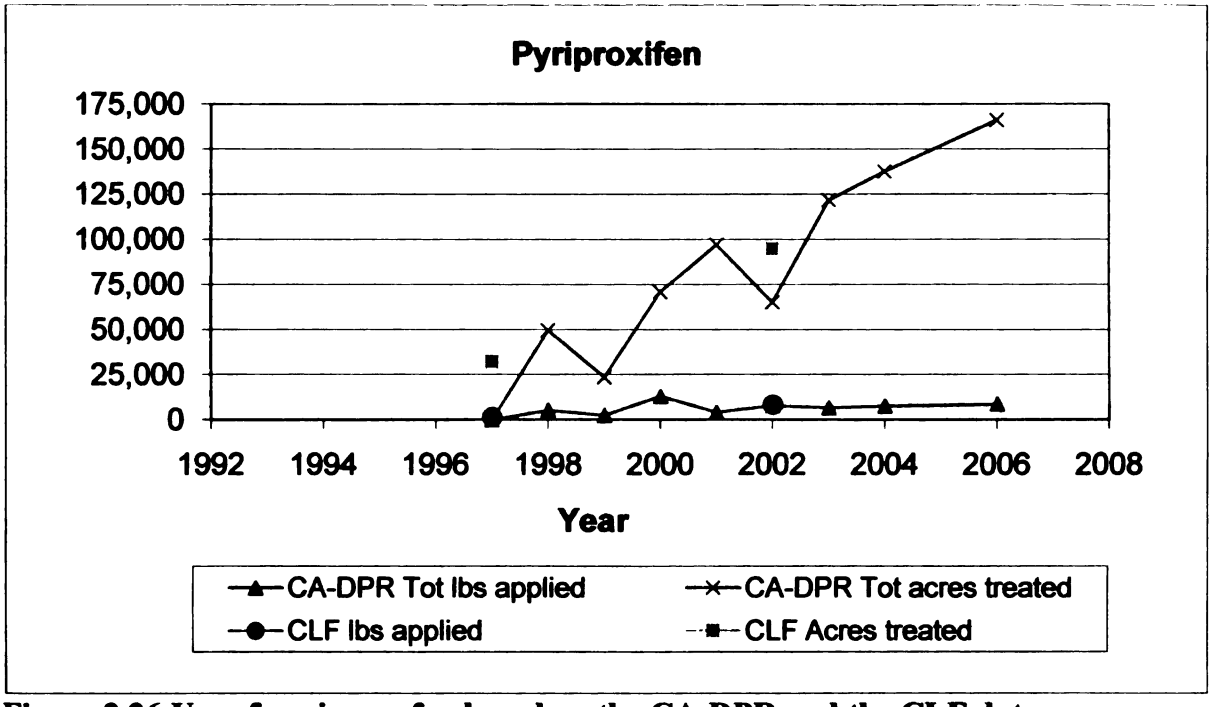

Figure 2.26.Use of pyriproxyfen based on the CA-DPR and the CLF data.

Spinosad

Spinosad is an insect-specific neurotoxic natural product produced by microbial fermentation which is highly effective against chewing insects but shows little, if any,

vertebrate toxicity. The first food uses of spinosad (almonds, apple, citrus, and brassica, fruiting and leafy vegetables) were registered in 1998. More use registrations for fruits and vegetables followed such as: cucurbit vegetables, stone fruit, and legumes in 1999; cilantro, apples, pistachios, tropical fruits, among others in 2000; asparagus, cranberries, pome fruit, strawberries and others in 2001; the berry group, grapes, herbs, peanuts, root and tuber vegetables in 2002; and mint and onions in 2006. The 2002 and 2006 registrations were by the IR-4. No carcinogenic, mutagenic or developmental toxicity effects were observed for spinosad (U.S.EPA Undated-a) and no neurotoxic effects were observed in rats in acute, chronic or subchronic studies. The high efficacy, particularly against chewing insects and very low risk of using spinosad contributes to its high and increasing use (Figure 2.27). Spinosad is also marketed for organic use since it is a natural compound which is an additional explanation for the increasing use.

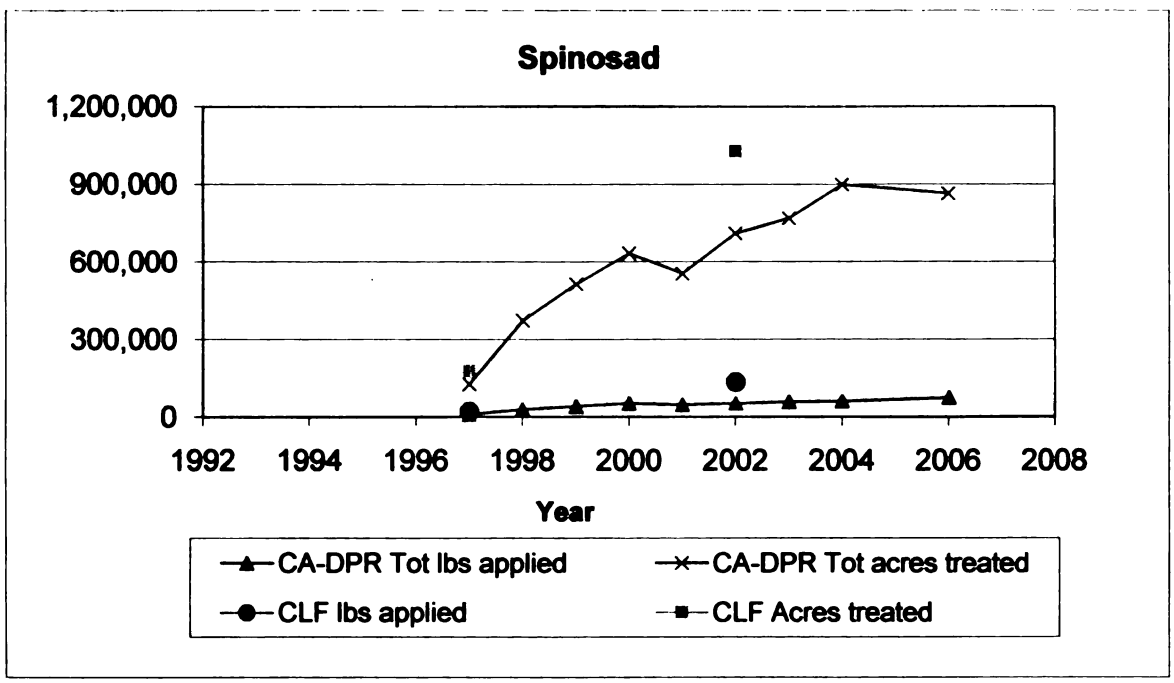

Figure 2.27. Use of spinosad based on the CA-DPR and the CLF data.

Bifenazate

Primarily an acaricide, bifenazate was first used on ornamentals in 1999. In 2002 the EPA classified bifenazate as "not likely" to be a human carcinogen and food use registrations including stone fruits were completed in the same year. The IR-4 registered the uses of bifenazate on cucurbits, fruiting vegetables, mint, pistachio, tomatoes and tree nuts in 2003 and registered it in collaboration with Uniroyal in 2006 for stone fruit, pea, and tuberous and corm vegetables. The continuously increasing use of bifenazate since 1999 is shown in Appendix C.

Indoxacarb

The initial registrations of indoxacarb in 2000 were on cotton, fruiting vegetable, leafy vegetables, lettuce, sweet corn and pome fruit; and on peanut, potato and soybean in 2002. According to the EPA, indoxacarb has moderate to low acute and chronic toxicity and does not cause mutagenic, carcinogenic, developmental and reproductive effects (U.S.EPA 2000c). Although neurotoxicity was observed in some studies, it was only at fatal doses (U.S.EPA 2000c). In 2007, the EPA approved more tolerances of indoxacarb on various groups of fruits and vegetables as requested by E.I. du Pont de Nemours and IR-4 (U.S.EPA 2007d). Indoxacarb use increased sharply after its introduction in 2000 and has remained about constant since then (Appendix C) which is presumably due to its effectiveness as an OP replacement against chewing insects and its relatively low toxicity.

Methoxyfenozide

Methoxyfenozide is an insect growth regulator and was registered in 2000 for use on pears, apples and other pome fruits (U.S.EPA Undated-b). In 2002, tolerances were

established for methoxyfenozide and its metabolites for residues on various agricultural food commodities as requested by IR-4 and Rohm and Haas Company. More tolerances requested by IR-4 and Dow AgroSciences for residues on various fruits and vegetables were established in 2004 (U.S.EPA 2004d). Requested tolerances on soybeans and their byproducts were set in 2006. Methoxyfenozide exhibit effectiveness at lower dose against a broader range of pests and little effect on non-target organisms (Borchert et al. 2004; Carlson et al. 2001) than an earlier analog, tebufenozide. This explains the increasing use of methoxyfenozide both in pounds applied and acres treated from 2005 to 2006 (Appendix C).

Pymetrozine

Pymetrozine is primarily a systemic insecticide acting against sucking insects. It was first registered in 1999 for use on tuberous and corm vegetables, ornamentals, and tobacco. More registrations followed on cucurbits and fruiting vegetables in 2000, and on leafy and brassica vegetables and pecans in 2001. In 2005 the IR-4 was responsible for its registration for use on asparagus. It is non-mutagenic and is of low acute toxicity to humans, birds, aquatic organisms, mammals and bees. However, it has been classified by the EPA as a "likely" human carcinogen because of tumor occurrence in some of the species tested, and mechanistic arguments have been advanced to explain the carcinogenicity (U.S.EPA 2000e). However, the EPA concluded that due to "limited sites, low use rates, and low exposure, the carcinogenic risk to humans is below the level of concern (U.S.EPA 2000e). Pymetrozine has been used continuously since 2000 as shown in Appendix C but in relatively small amounts.

Tebufenozide

The first completed registration of the insect growth regulator tebufenozide was in 1995 for use on walnuts. In 1998 use registration was approved for pecans; in 1999 for leafy, brassica and fruiting vegetables, cranberries, the berry group and mint, pome fruit, sugarcane, turnips, and canola; for tree nuts in 2000; and for citrus, grapes, and tuberous and corm vegetables in 2004. Several of the use registrations completed in 1999 and 2004 were by IR-4. Several tolerances for emergency exemptions for the use of tebufenozide have been approved by the EPA for various crops such as cranberries, peppers, peanuts and non-brassica leafy vegetables since its first use was registered. Tebufenozide has been classified as a Group E carcinogen, with no evidence of carcinogenicity based on a 2-year carcinogenicity study in rats and an 18-month study in mouse (U.S.EPA 1997f). Its use increased until 2003 but decreased rapidly since then as shown in Appendix C due to its substantial replacement by methoxyfenozide.

Thiamethoxam

Thiamethoxam, another member of the neonicotinoid group, was registered in 2000 for use on barley, canola, cotton, sorghum and wheat for seed treatments. Approved registrations for fruits and vegetables including cucurbits, fruiting vegetables, tuberous and corm vegetables, and pome fruit followed in 2001; for beans, stone fruit and sunflowers in 2003; and for mint in 2004. Thiamethoxam is considered as slightly acutely toxic via the oral route and of low toxicity via the dermal and inhalation routes of exposure and did not show evidence of reproductive, developmental or mutagenic toxicities (Antunes-Kenyon 2001). Thiamethoxam has been used continuously since its initial registration as shown in Appendix C.

2.5.3 *IR-4's Role in Registering Reduced-risk Pesticides*

Numerous reduced-risk fungicides and insecticides have been registered by the IR-4 for use on fruit, vegetable and nut crops. Among the fungicides are azoxystrobin, cyprodinil, fenhexamid, fludioxinil, and trifloxystrobin, and the insecticides include bifenazate, buprofezin, indoxacarb, methoxyfenozide, pymetrozine, pyriproxyfen, spinosad, tebufenozide and thiamethoxam. All of these insecticides are listed by the EPA as OP alternatives (U.S.EPA 2006e, 2008b). The overall use of these IR-4 registered reduced-risk pesticides has increased noticeably since the inception of the FQPA (as previously discussed and shown in Figures 2.1 and 2.2). Gianessi and Silvers (2000) reported that the use of older pesticides decreased by 3.0 M pounds due to "newly registered, more cost-effective fungicides" such as azoxystrobin. Azoxystrobin is among the several newly-introduced broad-spectrum reduced-risk fungicides adopted on a broad range of crops between 1997 and 2002 and it has significantly reduced the use of older active ingredients such as chlorothalonil (Gianessi and Reigner 2006a). Azoxystrobin is also very effective against fungal diseases not controlled by chlorothalonil and many growers alternate azoxystrobin with chlorothalonil for a more effective control against fungal diseases (NSF-CIPM 1999). It was ranked 41st among the top 100 pesticides used in California in 2006 judged by acres treated (CA-DPR 2007a). The IR-4 obtained registrations on 34 (47%) of the 72 crops with reported uses of azoxystrobin.

Spinosad and imidacloprid are among the reduced-risk insecticides that have been widely and increasingly used since their initial registration. Spinosad was rank 23rd out of the top 100 pesticides by cumulative acres treated (901,535 acres) in California (CA-DPR 2007b). Spinosad was used on 110 fruits and vegetables based on the 2006 Summary

Report by the CA-DPR and 36 of these uses were registered by IR-4 (33%). Imidacloprid was ranked 31st by the CA-DPR among the top 100 pesticides by acres treated in 2006 (765,752 acres) (CA-DPR 2007b). Imidacloprid uses were on 79 fruits and vegetables and 47 (60%) of these were registered by IR-4. Imidacloprid is sold under the trade names Admire and Provado, the main chemical used on Colorado potato beetle, and is very effective at low dosages. Admire has largely replaced oxamyl as the insecticide in soil-applied drenches whereas Provado has replaced many of the standard foliar insecticides (NSF-CIPM 1999). Also according to NSF-CIPM (1999), there have been essentially no chemicals that can serve as effective alternatives to imidacloprid. From these examples it would be reasonable to conclude that IR-4 has been responsible for roughly 50% of the registrations of reduced-risk pesticide currently in major use on fruit vegetables and nut crops in California.

A further example of the impact of the IR-4 registration of reduced-risk products is found in the post-harvest treatment of stone fruits such as peaches, nectarines and plums. The common use of iprodione, a B2 carcinogen, for this purpose was canceled by EPA in 1998 because of the high residues left at consumption. As described further in Chapter 4 iprodione has been entirely replaced in this use by the reduced-risk fungicide, fludioxonil with concurrent improvements in consumer safety. The fludioxonil registration for the entire stone fruit group was obtained by IR-4.

2.5.4 *Decrease in Application Rates with Reduced-risk Compounds*

The reduced-risk pesticides are generally used at significantly lower application rates than the conventional compounds they are replacing which have the effect of decreasing the amount of chemical applied to the environment (environmental load). The

data in Figure 2.28 show the environmental loads (calculated as the ratio of the total lbs of pesticide applied and the total acres treated based on the CA-DPR data) of the anticholinesterase and the reduced-risk insecticides, and Figure 2.29 shows the same data for the B2 carcinogenic and the reduced-risk fungicide groups. The OPs show a constant environmental load (~1.2 lbs/acre) over the years from 1992-2006, while the NMCs were used at 1.32 lbs/acre in 1992 and this decreased to 0.84 lb/acre in 2006. The environmental load for the reduced-risk insecticides is 5 to 12-fold lower than for the anticholinesterase group with an environmental load of 0.08 to 0.25 lb/acre from 1992 to 2006. The environmental loads of the reduced-risk fungicides show a slight increase from 0.12 lb/acre in 1997 to 0.21 lb/acre in 2006 but these are still considerably lower than the environmental load of the B2 fungicides which stayed constant in the range of 1.0 to 1.5 lbs/acre.

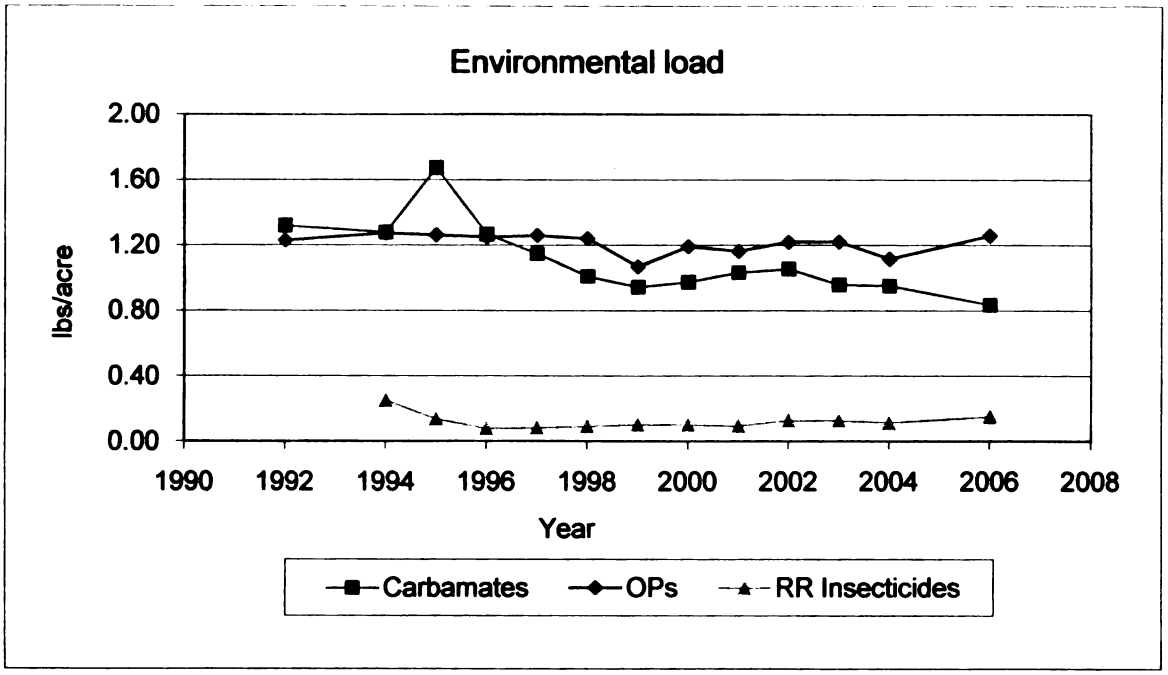

Figure 2.28. Environmental load of the anticholinesterase and the reduced-risk insecticide groups.

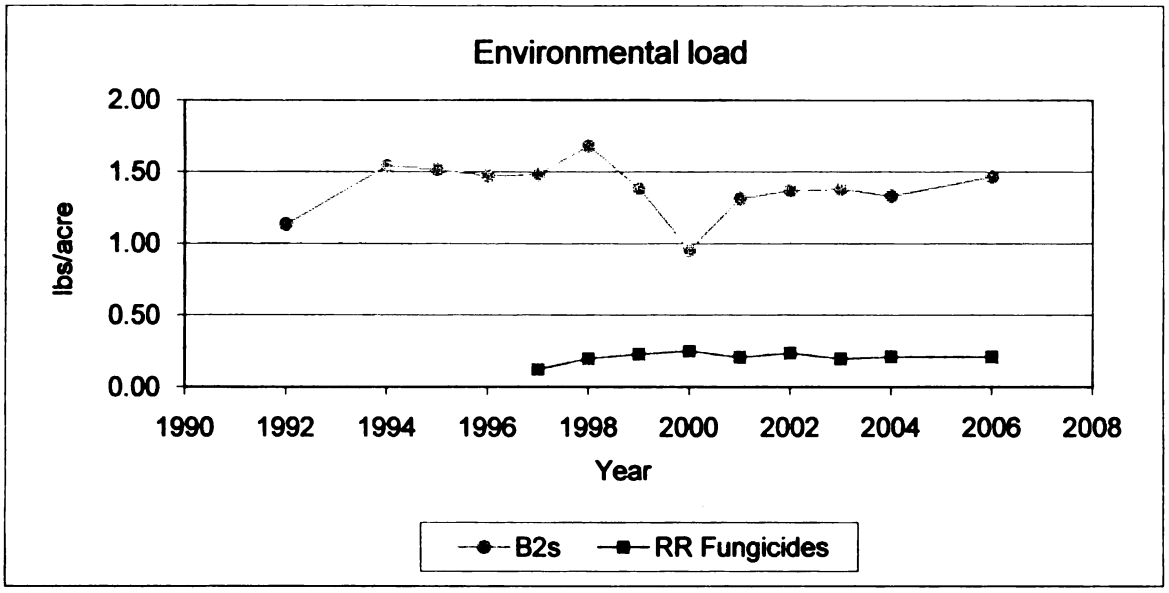

Figure 2.29. Environmental load of the B2 carcinogenic and the reduced-risk fungicide groups.

Figure 2.30 shows the combined environmental loads of the new and the old pesticides grouped into insecticides and fungicides. This demonstrates the impact of the increasing use of the reduced-risk compounds on the overall environmental loads of the insecticide and fungicide groups. The reduced-risk pesticides have substantially decreased the overall loads in these groups from 1994 to 2006 by 45% for the insecticides and by 54% for the fungicides. These results lead to the conclusion that the use of the reduced-risk pesticides is likely to lead to a lower impact on the environment compared to the conventional pesticides because of both their lower use rates and their decreased level of toxicity in many cases.

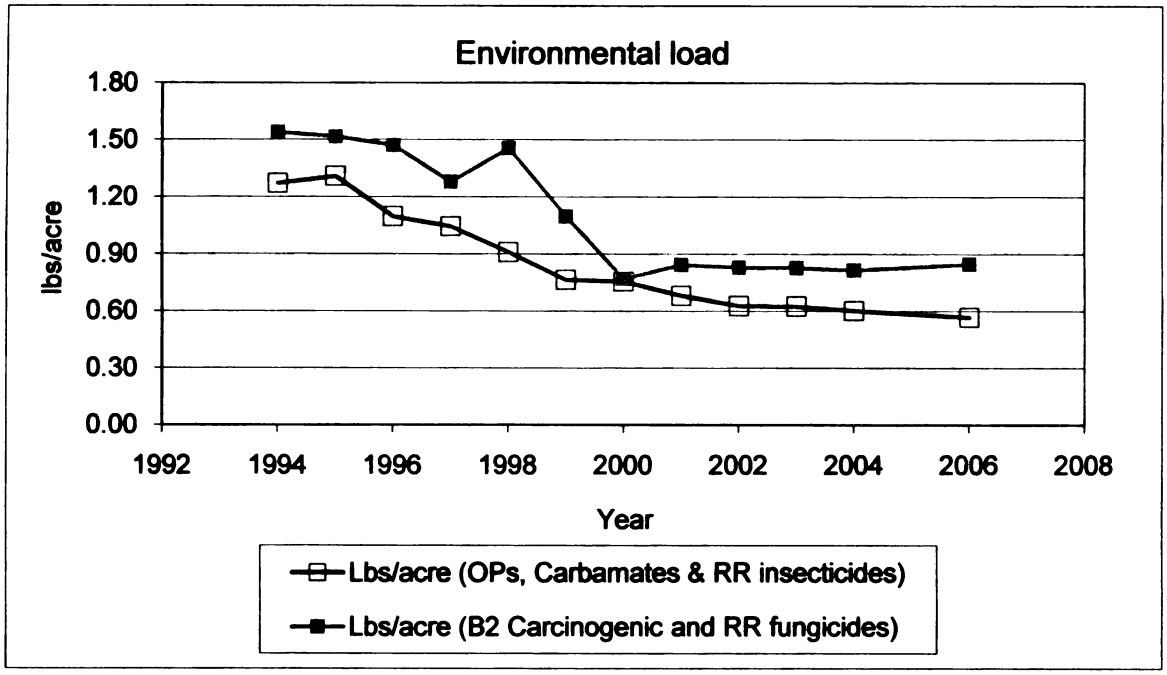

Figure 2.30. Overall environmental load of the insecticide and the fungicide groups.

Trends in the amount (lbs) of pesticide used in an application (application rate) for the insecticide and fungicide groups are shown in Figure 2.31. These application amounts also follow a declining trend for both groups from 1994 to 2006 with an approximately 50% decline in the amount of fungicides and a 60% decrease in the quantity of insecticides used in each application. This is another indicator of the positive effect that reduced-risk compounds (at lower application rates) have replaced the conventional chemicals.

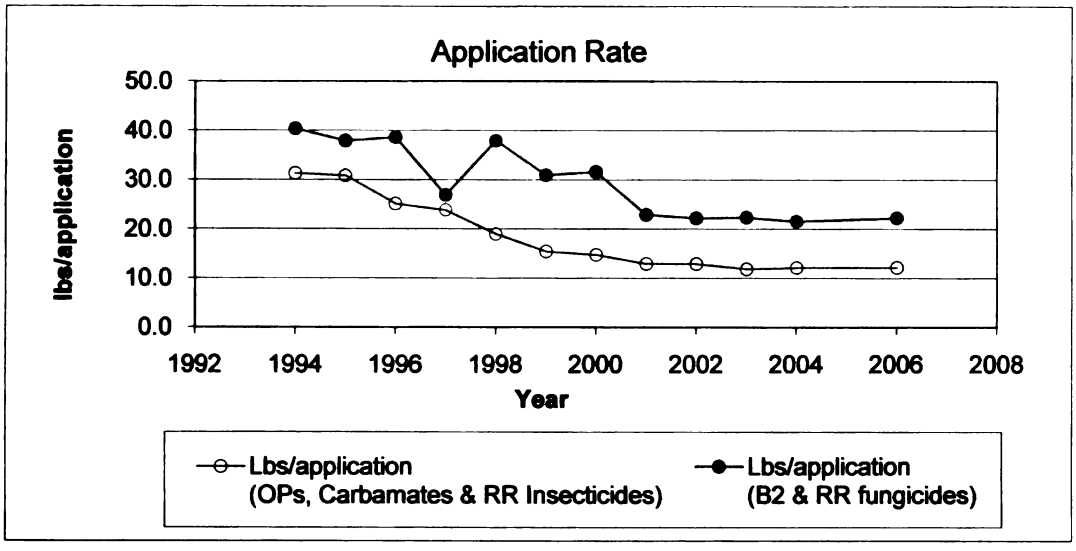

Figure 2.31. Application rates of the insecticides and the fungicides groups.

2.6 Conclusion

Based on the data available from CA-DPR and CLF, the use of the OP and NMC anticholinesterase insecticides has decreased substantially over the years from 1992 to 2006, especially since the enactment of the FQPA in 1996. As a class, the OPs have declined by approximately 50% in pounds applied and the NMCs even more by 70-75%. The use of many of the most important members of these classes has declined by over 80%, e.g. the decline in pounds applied based on the 1992 and 2002 CLF data were carbofuran (81%), disulfoton (85%), fonofos (100%) and methidathion (81%). Based on the 1994 and 2006 CA-DPR data the OPs and the NMCs that had the most significant decrease in pounds applied were carbofuran (93%), aldicarb (91%), carbaryl (84%), azinphos-methyl (91%), fonofos (100%), and methamidophos (99%). These two groups were the initial focus of regulatory attention after FQPA and much of the corresponding decrease in use is due to the cancellation and restriction of uses and lowering of tolerances. However, the decreased use is not uniform for all OPs and NMCs, e.g. the use of chlorpyrifos remains high based on the CA-DPR data and the decline in use of acephate has been relatively modest. Similarly oxamyl use has declined less than that for the rest of the NMCs.

In parallel with the decreased use of the anticholinesterase insecticides, the reduced-risk insecticides, many of them specifically classified as OP replacements, have increased regularly in use so that now they play a central role in the management of arthropod pests. This transition is likely to continue as additional regulatory actions remove anticholinesterase uses and pest management strategies further increase their emphasis on safer chemistries with lower environmental impacts.

In contrast to the anticholinesterases, the B2 fungicides have undergone only a limited decline in use of 10-20% since the FQPA was passed. Individual members of the group such as iprodione have been the target of specific actions because of elevated risk and thus have undergone larger decrease in use, but generally it appears that, despite their classification as probable human carcinogens, these compounds have not been found in the diet at levels that cause regulatory concern for the EPA. These B2 compounds have strong advantages for pathogen control including low cost, low resistance potential and broad spectrum activity. However, there has also been a regular increase in use of the reduced-risk fungicides since FQPA. This can be attributed to the need to replace specific B2 uses lost to the limited regulatory activity such as the elimination of iprodione for postharvest use, but also because many newer compounds have distinct advantages including very high efficacy, broad spectrum, and systemic activity that allows more limited curative treatments for pathogens rather than being restricted to preventative uses as with the older B2 compounds.

Finally, most of the reduced-risk pesticides are used at significantly (5 to10-fold) lower application rates than the older compounds evaluated in this study. The decreasing use of the OPs and the NMCs and the increasing use of the reduced-risk insecticides and fungicides have therefore led to an appreciable overall decrease in the amounts of chemical pesticides being applied in the production of fruit, vegetable and nut crops. Taken in conjunction with the greatly improved toxicological properties of many of the reduced-risk compounds, this decrease in application rates is likely to lead to a lower environmental impact in addition to the significant improvements in worker safety and lowered dietary risks that have resulted from the passage of the FQPA.

Overall, the available pesticide use databases are not well set up for trend analyses. There is a lack of continuous and comprehensive collection of national pesticide use data. They are not well integrated and do not allow for cross-database analysis. Each of the databases follows a different protocol in the monitoring procedures. The sampling procedure, as well as the commodities sampled and the pesticides analyzed each year, varies for each database which make the data discontinuous and inconsistent. Pesticide use databases that are possibly more complete and comprehensive such as the Doane AgroTrak and the Buckley Report are available but at a very high acquisition cost. Due to their proprietary nature, their accuracy and sampling methods cannot be compared to publicly-accessible and widely-used databases. The deficiencies of the databases maintained by government agencies have been recognized and an Advisory Committee was recently appointed by the U.S.DA-NASS to assess whether there was support to expand and improve them including the development of an integrated national system for pesticide use data collection and distribution. It was concluded that the current data collection approach was currently regarded as "adequate" and that there was a lack of sufficient interest in developing more comprehensive and continuous databases to justify an increased budget request. In particular, the proprietary Doane Report system currently satisfies the needs of both EPA and the agrochemical industry (Gianessi and Mitenbuler 2006). However, the fact remains that no comprehensive data collection system exists that allows ready public access, and that there are significant gaps and discontinuities in those databases to which the public does have access.

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CHAPTER 3
PESTICIDE RESIDUE TRENDS

As EPA administered the FQPA, the use of some older pesticides, particularly the organophosphates (OPs) and the *N*-methylcarbamates (NMCs), and to a lesser extent some B2 carcinogenic fungicides, has declined, as demonstrated in Chapter 2. This should have decreased the frequency of occurrence and levels of their residue in the food supply and thus have led to an increase in food safety to meet the ultimate objective of these regulatory actions. In this section, changes in these key pesticide residues since the passage of the FQPA are examined to determine to what extent such reductions can be documented and the degree to which residues of the newer, lower risk replacements can now be found in the diet.

3.1 Pesticide Residue Databases

Federal or state agencies that maintain substantial pesticide residue databases include the U.S. Department of Agriculture Pesticide Data Program (USDA-PDP), the Food and Drug Administration (FDA), and the California Department of Pesticide Regulation (CA-DPR). The residue databases are developed for different purposes often based on specific regulatory priorities, vary in important ways, and have advantages and disadvantages for other specific purposes such as trend analysis. The FDA mainly samples surveillance type commodities which are those of which it has "no prior knowledge or evidence that a specific food shipment contains illegal pesticide residues" (U.S.FDA 2000b) but also for many years FDA has run an annual market basket survey of chemical residues in samples of foodstuffs collected in several cities across the U.S. and converted into cooked meals. The PDP residue database is comprehensive in national

coverage but has limited continuity of data over the years. The CA-DPR also maintains a comprehensive and relatively continuous state level residue database. The downside of both the PDP and the CA-DPR databases for trend analysis is the variability in the crop samples analyzed and sampling procedures and frequency, and changes in the limits of detection in the sample analyses with time.

3.1.1 *U.S. Department of Agriculture Pesticide Data Program (USDA-PDP)*

The Pesticide Data Program (PDP) was initiated in 1991 by the U.S. Department of Agriculture to collect pesticide residue data in fresh and processed foods. It is "administered within the Agricultural Marketing Service (AMS) which employs specialists that provide standardization, grading and market news services for many major commodities vital to U.S. agriculture (cotton, dairy, fruit and vegetable, livestock and poultry)" (Punzi et al. 2005). The PDP data are used by the FDA, the U.S.DA Economic Research Service and Foreign Agricultural Service, and by the U.S. Environmental Protection Agency (EPA) as a primary source for dietary risk assessment. It also provides data on minor crops and on foods consumed mostly by infants and children to meet specific regulatory requirements. It is intended to provide a statistically valid sampling of human dietary intakes across the U.S.

Several states (California, Colorado, Florida, Maryland, Michigan, Minnesota, Montana, New York, Ohio, Texas, Washington and Wisconsin) participate in the sampling and testing programs of the PDP. The collection of commodities depends on the production volume and population from where the samples are taken. Foods analyzed since the program started represent foods which are consumed in relatively high amounts, often by children and with the exception of meats and frozen commodities, can be eaten

raw (Punzi et al. 2005). Samples are collected from terminal markets and chain store distribution centers. Sampling at these locations allows for residue measurements that include pesticides applied during crop production and those applied after harvest (such as fungicides and growth regulators) and takes into account residue degradation while food commodities are in storage (U.S.DA-PDP 2006a). Both imported and domestic commodities are represented in the commodities sampled by PDP, but almost all of the samples are of domestic origin. However, several commodities are grown domestically for some part of the year and imported for the remaining part. The choice of crops, and to some extent the pesticides, is governed by priorities set by the EPA based on their data needs and on information about the types and amounts of food consumed by infants and children (U.S.DA-PDP 2006b). As a dietary risk assessment support program, PDP focuses its pesticide testing on registered uses for the commodities in the program rather than screening for all potential illegal uses (U.S.DA-PDP 2006a). More extensive residue data are required for pesticides with current registered uses and for compounds that show a need for more extensive residue data based on toxicity data and preliminary estimates of dietary exposure. Other pesticides monitored by the PDP are those for which EPA has instituted modified use directions as part of risk mitigation requirements. Thus, the data collected vary from year to year so that continuous records of the residues in specific crops are generally not available, and, not unreasonably, the results are focused on commodities that play a major role in the U.S. diet and PDP rarely if ever assesses residues in more minor dietary components such as apricots, blueberries or cauliflowers.

Multiresidue methods (MRMs) are used to analyze for pesticide residues in the participating laboratories and allow for detection of numerous compounds in a single

analysis. However, some pesticides, such as the dithiocarbamate fungicides, are not amenable to this MRM methodology. After residue analysis, the data are stored in the electronic database and include sample collection and product information, residue findings, and process control recoveries for each sample analyzed as well as the fortified recoveries for each set of samples. Summary reports are published annually and the data are available on the USDA website.

3.1.2 *California Department of Pesticide Regulation (CA-DPR)*

The California Department of Pesticide Regulation (CA-DPR) analyzes pesticide residues to enforce the tolerances set by the U.S. EPA. Samples are collected from channels of trade such as points of entry (seaports and state border stations), packing sites, and the wholesale and retail markets. The commodities are collected from individual lots of domestic and imported foods. The CA-DPR only samples fresh produce and analyzes them as the unwashed, whole (unpeeled), raw commodity. Around 8,000 samples are collected annually covering about 150 different commodities. Eighty percent of the samples are of approximately 75 commodities important in the diets of infants and children, or in the population overall. Multiresidue screens are then used in the analysis of the samples. Selected samples receive specific analysis for non-screenable pesticides of enforcement concern (CA-DPR 2001).

The CA-DPR classifies domestic and imported food samples as either "surveillance" or "compliance". Surveillance samples are those with no prior knowledge or evidence that a specific food shipment contains illegal pesticide residues; and compliance samples are those that follow up to the finding of an illegal residue or when

other evidence suggests that a pesticide residue problem may exist as defined by CA-DPR. Most of the samples collected are the surveillance type.

According to the CA-DPR the "data collected under regulatory monitoring are extensive but are not statistically representative of the overall residue situation for a particular pesticide, commodity, or place of origin" (CA-DPR 2001). This may be due to biases incurred by focusing on factors such as commodities or places of origin with a history of violation, or with large volume of production or significant levels of importation. The number of commodities sampled and analyzed for a particular pesticide each year may not be sufficient to represent the overall residues for a commodity in commerce (CA-DPR 2001).

The CA-DPR coordinates with other agencies in the conduct of pesticide residue analysis. The U.S. FDA is one of the agencies the CA-DPR works closely with to plan sampling strategies so as to avoid duplication of samples collected and analyzed. Results are shared between the two agencies and they also cooperate on necessary investigations of potential violations. California is also part of USDA's Pesticide Data Program (PDP) wherein data are provided for dietary exposure assessments.

3.1.3 *Food and Drug Administration (FDA)*

The Food and Drug Administration (FDA) pesticide monitoring program has two components: regulatory and incidence level monitoring, and the Total Diet Study (TDS). Regulatory monitoring includes sampling of domestic and international fresh and processed produce. Factors considered by the FDA in planning the types and numbers of samples to collect include review of recently generated state and FDA residue data, regional intelligence on pesticide use, the dietary importance of the food, information on

the amount of domestic food and imported food that enters interstate commerce, the chemical characteristics and toxicity of the pesticide, and the production volume and pesticide usage patterns. Domestic produce, mostly raw agricultural produce, are sampled as close as possible to the distribution system; import samples are collected at the point of entry into U.S. commerce and analyzed as the unwashed, whole (unpeeled), raw commodity (U.S.FDA 2000b). Sampled commodities are mostly "surveillance" types which according to U.S. FDA (2000b) mean "there is no prior knowledge or evidence that a specific food shipment contains illegal pesticide residues". In instances when an illegal residue is found or if there are other pesticide residue problems, follow-up or compliance samples are collected. Multiresidue methods (MRMs) are used to analyze for pesticide residues.

Incidence/level monitoring is used by the FDA, complementary to regulatory monitoring, "to increase FDA's knowledge about particular pesticide/commodity combinations by analyzing certain foods to determine the presence and levels of selected pesticides" (U.S.FDA 2000b). The FDA uses statistically based monitoring surveys to assess whether the data from regulatory monitoring are representative of the overall residue situation for a particular pesticide, commodity or place of origin.

The market basket survey is carried out by the FDA for the Total Diet Study (TDS), a major constituent of its pesticide and chemical contaminant monitoring program. In conducting the TDS, foods from the supermarkets or grocery stores are sampled four times a year, once from each of the four geographic regions of the country. The four market baskets (each market basket a composite of like foods purchased in three cities in a given region) is comprised of 285 foods that are representative of over 3,500

different foods reported in the USDA food consumption surveys. Food is prepared to be table-ready and then analyzed for pesticide residues by multi-residue methods. The levels of pesticides found are used in conjunction with the USDA food consumption data to estimate the dietary intakes of the pesticide residues (U.S.FDA 2000b, 2003). The program is not established to develop a statistically valid cross-section of food consumption in the U.S. and many of the newer reduced-risk pesticides are not yet included in the analytical methodology.

3.2 Objectives

The objective of this section of the study is to assess the changes in the incidence of residue detections of selected higher risk pesticides (anticholinesterase insecticides and B2 carcinogenic fungicides) and their safer replacements in fruit, vegetable and nut crops since the enactment of the FQPA in 1996.

3.3 Methods

3.3.1 *Survey and Evaluation of Pesticide Residue Databases*

The available pesticide residue databases were surveyed for comprehensiveness and continuity of data over time. The PDP and the CA-DPR databases have the most complete and comprehensive residue data over the time period of interest and were selected for the analysis of the residue trends. The FDA ongoing market basket surveys also provided additional useful confirmatory data.

Although assessing actual residue levels would be the most direct measure of changing exposure and risk, there are difficulties in developing a single summary measure for the varying residues detected in multiple samples. The residue levels do not show a normal distribution, the median value is typically zero, and the mean is often

driven by one or more high values which are outliers and do not accurately represent the dataset. For this reason, the frequency of detections, expressed as the percentage of the samples analyzed that contained the pesticide at or above the level of detection (LOD), was calculated as the major indicator for trends in the occurrence of residues.

3.3.2 *Pesticide Residue Trends*

3.3.2.1 *Individual Pesticide Residue Trends*

The annual CA-DPR residue databases from 1994 to 2006 were downloaded from the CA-DPR website (CA-DPR 2009). The PDP residue data were from the PDP Search Utility containing searchable data for pesticides and commodities for each year from 1993-2006 and was obtained from Roger Fry (USDA Agricultural Marketing Service, Manassas, VA). The number of times a given pesticide was detected (reached the LOD) was determined for each of the fresh fruits, vegetables and nuts in the survey. Grains, meats, and processed foods were not included. The value for percent detects was calculated based on the total number of detects and the total number of samples analyzed. The annual PDP and CA-DPR percent detects were plotted for each pesticide for each year from 1994 to 2006 and the trends analyzed and correlated to pesticide use and regulatory history. The commodities sampled and analyzed each year vary for both the databases, which mean that a commodity analyzed in one year may not be analyzed in the following year.

3.3.2.2 *Individual Pesticide Residue Trends with High Percent Detects*

The pesticides (both conventional and reduced-risk) with %detects $\geq$ 10% and with % detects $\geq$ 5% but < 10% at any point from 1994 to 2006 were identified and were the focus for trend analysis. The percentage detects classifications were based on

the percentile ranking of all the compounds showing detects based on the PDP data. Approximately 10% of the pesticides in the PDP database have exceeded the 10% detects level at some time during the study period, and 20% have been within the 5% to 10% detects range.

3.3.2.3 *Residue Trends for Pesticide Groups*

The sum of all the percent detects for each group of the older pesticides (OPs, NMCs, and the B2s) was calculated for each year from 1994 to 2006 both for the PDP and the CA-DPR data. The overall percent detects were plotted and the trends analyzed.

3.3.2.4 *Pesticide Residue Detection Frequency in the FDA Total Diet Study (TDS)*

The U.S. FDA publishes annual reports on the Total Diet Study (TDS) that contain summary data for the frequency of occurrence of detectable pesticide residues which are found in at least 2% of the food samples in the study. These data are collected both for the diets of infants and toddlers, and for the rest of the U.S. population (termed here "adults"). The results from 1995 to 2006 were evaluated for pesticides that have at least five years of residue occurrence at the 2% or greater level. The trend in percent occurrence for these pesticides were plotted, and analyzed for trends in comparison to results from the other databases.

3.4 Results and Discussion

3.4.1 *Overall Residue Trends of Pesticide Groups*

The occurrence of detectable residues for all pesticide groups (OPs, NMCs, B2s and reduced-risk compounds) vary considerably in the data taken from PDP (Figure 3.1). This makes any trend analysis somewhat speculative. Considering the most recent results from 1999 to 2006, all three groups of older compounds do show a downward trend in detections, but this conclusion depends heavily on the low level of detects observed in 2006. Additional data for more years would be needed to confirm these trends. A strong downward trend would be expected for the anticholinesterases in view of the 50% decrease in use of OPs and 70% decrease in use of NMCs found in Chapter 2. On the other hand, only a modest decrease in residue detections would be predicted for the B2 fungicides based on changes in use.

Surprisingly, the CA-DPR data do not confirm any decrease in residue detections for these groups (Figure 3.2). No clear trend is evident in the data for either OPs or NMCs from 1994 to 2006, and there is a slight increase in residue detection for the B2s. Also, the incidence of residue detections from the CA-DPR data is less than that from PDP by about 50%. The reduced-risk compounds have percent detection records from only a few recent years and distinct residue trends cannot be determined although the results again tend to be very variable and the percent detects for some individual compounds are high, such as acetamiprid and imidacloprid where the detection rates are as high as 20% to 25%.

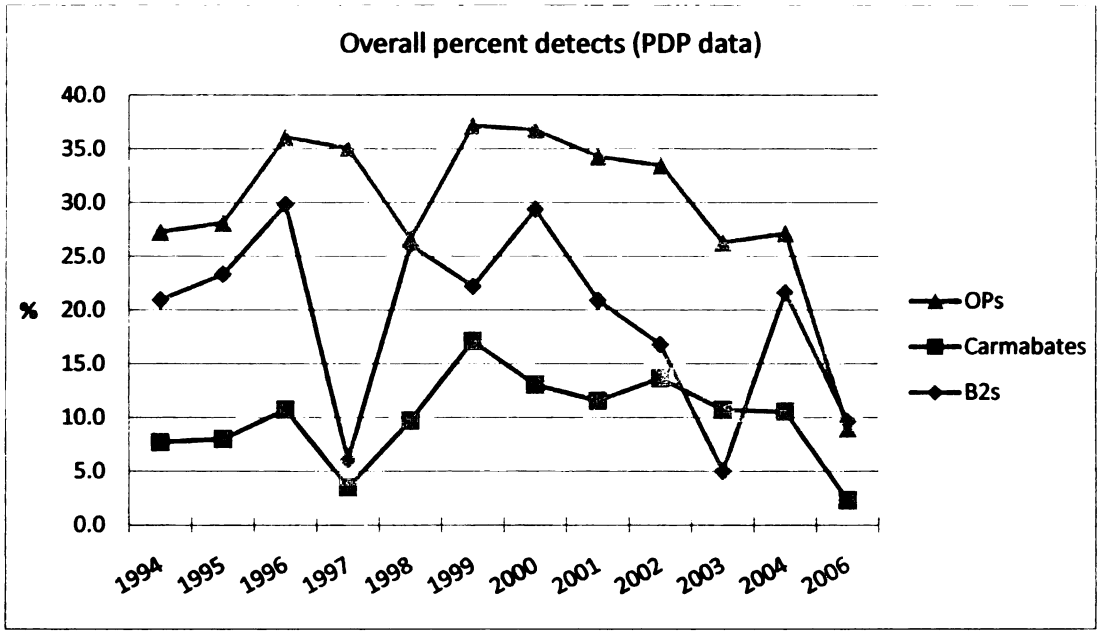

Figure 3.1. Residue detections for the OP, NMC and B2 pesticide groups based on the PDP residue data.

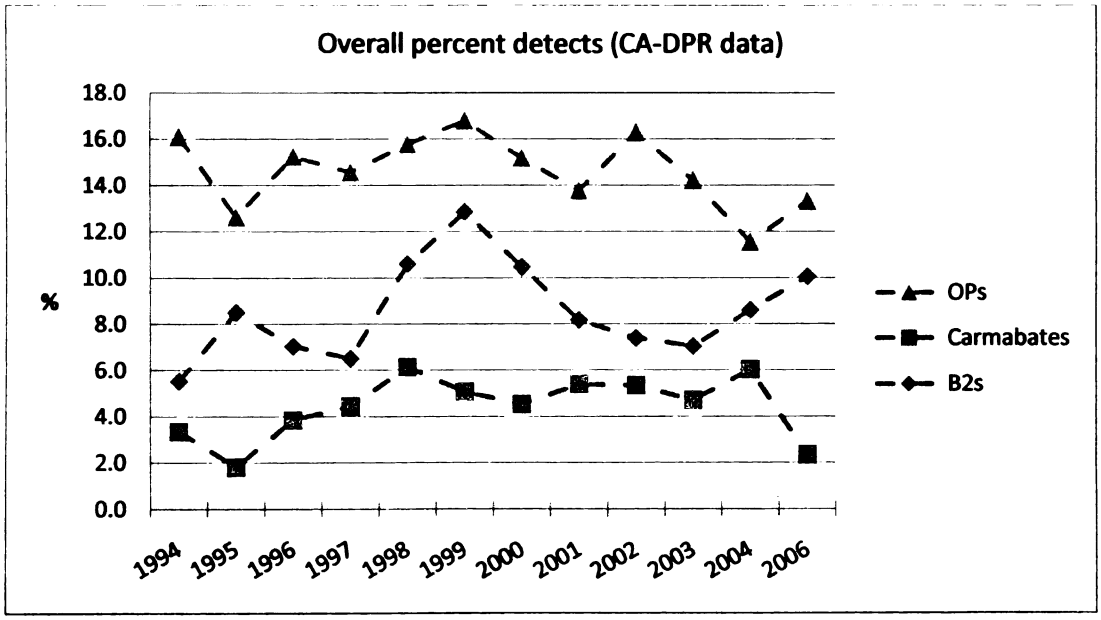

Figure 3.2. Residue detections for the OP, NMC and B2 pesticide groups based on the CA-DPR residue data.

A third source of information on trends in residue detection frequencies come from the FDA's annual Total Diet Studies (TDS) from 1995 to 2006 as provided in

annual FDA reports (U.S.FDA 1995, 1996, 1997, 1998, 1999, 2000a, 2001, 2002, 2003, 2004, 2005, 2006). The trends in incidence of detects for selected pesticides is shown in Figure 3.3 for the "adult" diets, and in Figure 3.4 for infant and toddler diets. The results are for individual compounds that appear at least five times in the FDA data over this time period. Clear post-FQPA trends for the adult diets are not clear except that iprodione falls below the FDA's 2% detects reporting limit after 2001 in keeping with the regulatory history described for this compound in Chapter 2. The data are clearer for the infant and toddler diets where most compounds have downward trend over the post-FQPA period with the exception of the NMC, carbaryl. Iprodione, methyl parathion and dimethoate residue detects all decrease considerably, in keeping with their much reduced use.

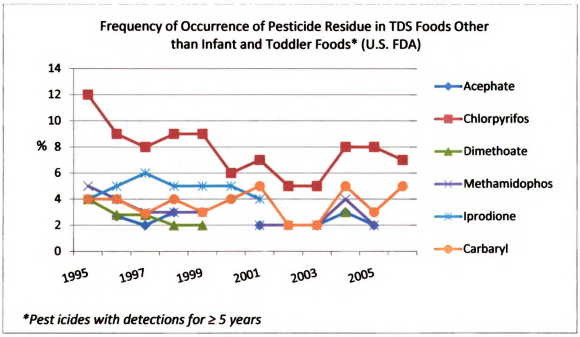

Figure 3.3. Frequency of pesticide occurrence in adult foods.

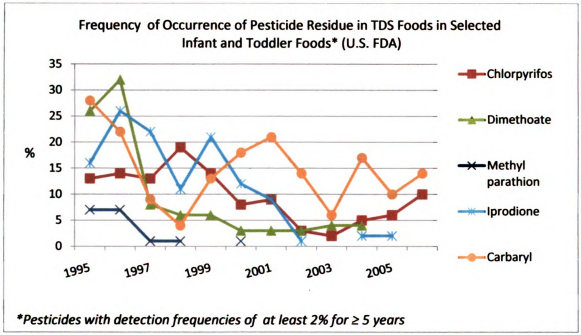

Figure 3.4. Frequency of pesticide occurrence in selected infant and toddler foods.

Carbaryl and chlorpyrifos residues are still regularly found even in 2006. The use of these two compounds, although reduced, has not been eliminated and large amounts are still applied in the U.S. based on the CLF data (Figures 2.7 and 2.11), so the regular occurrence of measurable residues is not unexpected. The clear decline in residue occurrences in the infant and toddler diet fits with one of the primary goals of FQPA to specifically reduce exposure and risk in this group. However, it is interesting to note that the frequency of pesticide occurrences in the infant and toddler foods is still approximately twice that in the adult foods.

3.4.2 *Individual Pesticides with High Percent Detects and/or Distinct Trends in Residue Detection*

The percent detects for the individual pesticides (both conventional and reduced-risk) have a wide range of values (0.01 to 26%) based on the PDP and the CA-DPR data. The pesticides with percent detects ≥ 10%, and percent detects ≥ 5% but < 10% at any

point from 1994 to 2006 were identified as the greatest contributors to food residues and were the main focus for trend analysis (Figures 3.5 through 3.6).

Individual pesticides from all the groups, except NMCs, are found in the highest percent detects category (%detects $\geq$ 10% at any point). The OPs in this highest occurrence class include azinphos-methyl (Figure 3.5), chlorpyrifos (Figure 3.6) and methamidophos (Figure 3.8), and the B2s include captan and iprodione (Appendix D). Rather surprisingly in view of their low use rates, several reduced-risk compounds also showed high residue detects. This includes imidacloprid (Figure 3.11), acetamiprid (Figure 3.12); and cyprodinil, fenhexamid, and tebufenozide (Appendix D). The pesticides that had percent detection between 5% and 10% include the OPs-acephate (Appendix D), dimethoate (Figure 3.7) and methamidophos (Figure 3.8); B2-chlorothalonil (Appendix D); NMCs-carbaryl (Figure 3.10), methomyl and oxamyl (Appendix D); and the reduced-risk pesticides-azoxystrobin, methoxyfenozide and spinosad shown in Appendix D. The 5% detections for these pesticides were all from periods after the FQPA was enacted except for dimethoate that had approximately 5% detects only in 1994 and has not exceeded this level since then.

The high percent detects (>10%) for the conventional pesticides are often variable and occurred in different years between 1994 and 2006. The detections for azinphos-methyl, chlorpyrifos in the years pre-FQPA were consistent with the high usage of these pesticides at that time. Methamidophos on the other hand, showed >5% detects despite the steep decline in use due to cancellation of most if its uses in 1997. The higher levels of residue detects for the B2s were from years both before and after FQPA and are consistent with the relatively constant use of many of the B2s.

Individual OPs showed the most distinct decline in residue detects compared to other pesticides. Among these OPs are azinphos-methyl, methyl parathion, dimethoate, methamidophos and methidathion. These pesticides were also among those with >5% and >10% detects (at any point) except for methidathion.

3.4.2.1 *Azinphos-methyl*

The percent detects for azinphos-methyl (AZM) showed an increasing trend from 1994 to 1997 but this decreased from 16% in 1997 to 1% in 2003 based on the PDP data. The CA-DPR residue data shows much lower percent detects values than that of the PDP and no obvious trend with time (Figure 3.5). However, it is interesting to note that azinphos-methyl is not among the FDA report on the frequency of occurrence of pesticide residues although it is analyzed in the FDA total diet study. This means that the residue occurrence is below the 2% limit set by the FDA and this low level of azinphos-methyl residue is due to the different sample preparation used in the total diet study in which food is prepared table-ready and then analyzed for residues. The decline in the PDP residue detections corresponds well with the overall decreasing use trend based on both national (CLF) and California (CA-DPR) data as previously shown in Figures 2.10. The decline in the detection is attributed to changes in the use patterns and safety issues of AZM. Worker safety and ecological effects were concerns in some parts of the U.S. in the early 1990s and in 1999 the EPA took mitigation measures to address these concerns. Cancellations and terminations of uses of AZM started in 1999 and final decision to phase out all remaining uses of AZM by September 2012 are consistent with the continuous decline in the detection of AZM residues.

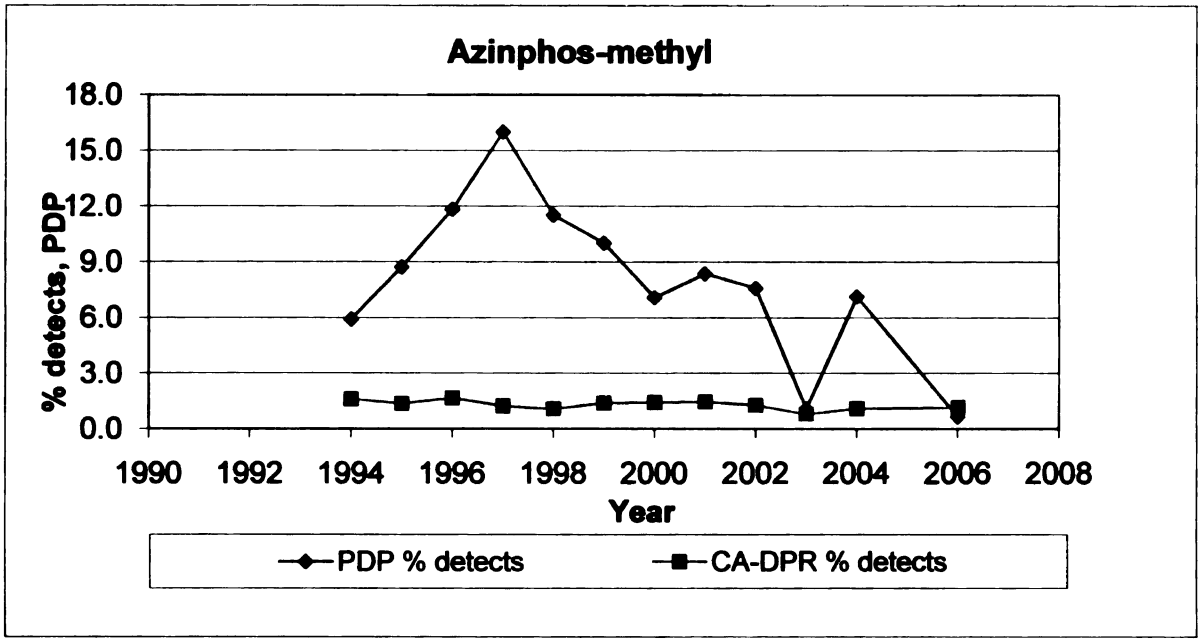

Figure 3.5. Percent detects for azinphos-methyl.

3.4.2.2 *Chlorpyrifos*

In the PDP national residue data, chlorpyrifos shows a slow decline in residues since FQPA (Figure 3.6) from a transient peak at ~12% in 1996 to ~3% in 2006. This corresponds reasonably closely to FDA Total Diet Study (TDS) results in Figures 3.3 and 3.4. These residue detection results also parallel the decreasing use trend for chlorpyifos nationally as shown in the CLF use data (Figure 2.11). However, the CA-DPR residue results are differnet. They show a slight but steady increase in detects with time. This too fits with the use data which did not show the same decline in California that was seen nationally (Figure 2.11). The national decline figures are attributable to the revision of tolerances for several raw agricultural commodities in 1996 and the revocation of tolerances for a number of uses in 2002 (U.S.EPA 2002a). There were also excessive acute dietary risks for infants and children and nursing females from EPA studies, and registrants agreed to eliminate use on tomatoes and restrict use on apples to address the risk (U.S.EPA 2002b). Punzi (2005) presented data in a poster which has not been

published that tracked the changes in percent detects in the PDP program from 1994 to 2004 for chlorpyrifos on several individual crops. On apples, the percentage detects fell, they were fairly constant on peppers and lettuce, and rose on peaches. This illustrates the complexity of trend analysis over a variety of crops and agricultural production systems. The decline in apple detects was steep from 25% in 1999 to <1% in 2002 and was attributed to the restriction of chlorpyrifos applications to the prebloom period by EPA in 2000.

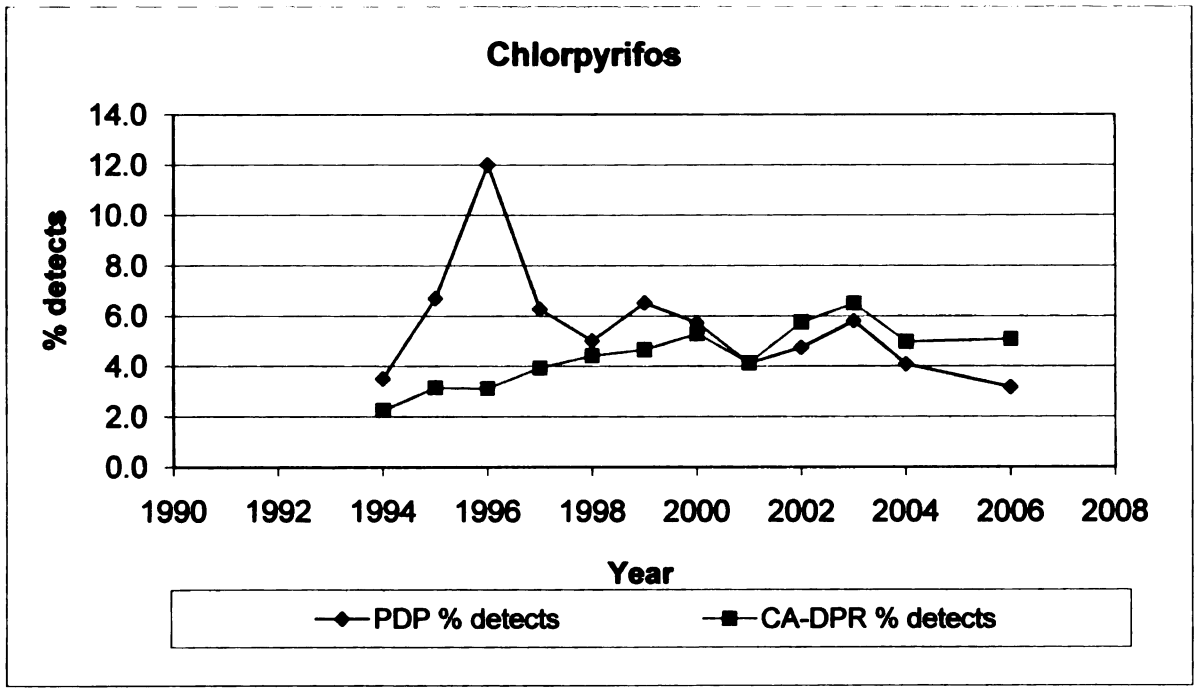

Figure 3.6. Percent detects for chlorpyrifos.

3.4.2.3 *Dimethoate*

Dimethoate shows a decrease in residue detection from 4.7% in 1994 to 1.4% in 2006 based on the PDP data as shown in Figure 3.7. This is parallel to the decline in use based on both the CLF and the CA-DPR data (Figure 2.13). As the result of a developmental neurotoxicity study that led to revised risk assesments, seven crops (apples, broccoli raab, cabbage, collards, grapes, head lettuce, and spinach) were

identified as significant dietary risk contributors and these uses were cancelled in 2005 (U.S.EPA 2006), so a further decrease in dimethoate residues is to be expected in future data.

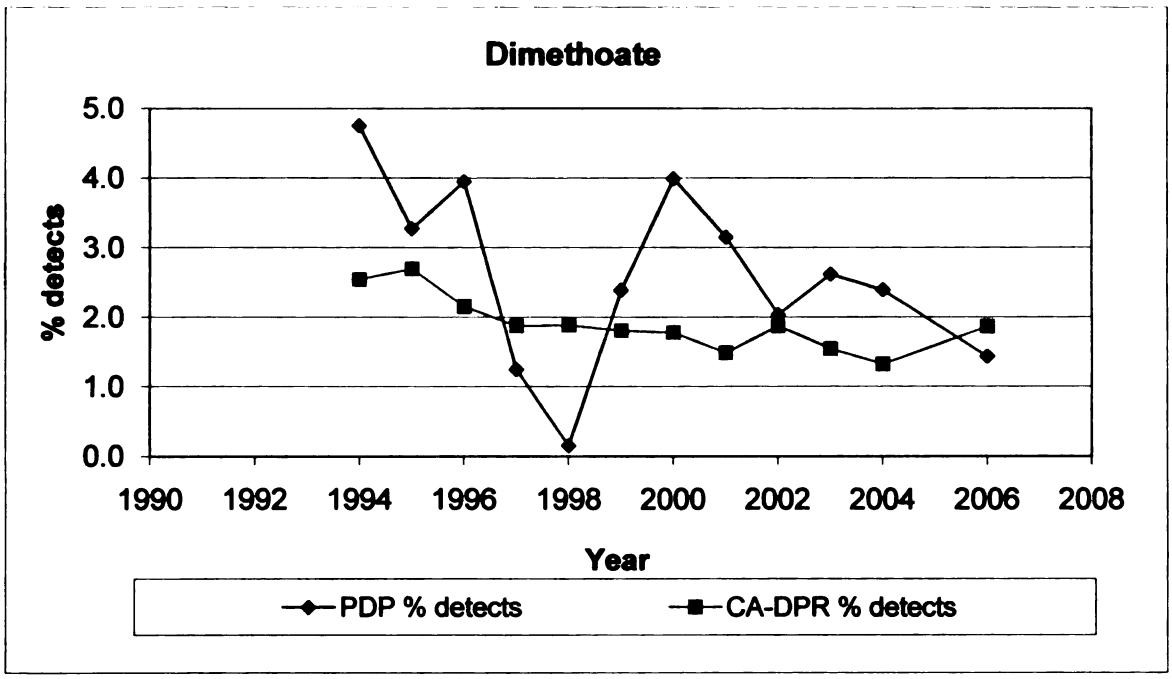

Figure 3.7. Percent detects for dimethoate.

3.4.2.4 *Methamidophos*

The decline in residue detection of methamidophos (Figure 3.8) since 1999 is attributed to the cancellation of almost all its uses on food crops, especially in 1997 when Bayer Corporation, its technical registrant, voluntarily canceled all its uses except for cotton, tomatoes (special local need only) and potatoes. This is also consistent with the strong decrease in use as shown and discussed in Chapter 2. However, it is notable that the slight decline in residue detects in the California data does not correlate well with the extremely steep drop in its use over the same time period and very limited use on food crops since 1999 (Figure 2.16). The reasons for this are unclear. These residues presumably were from the few remaining uses of methamidophos (eg. potatoes and tomatoes).

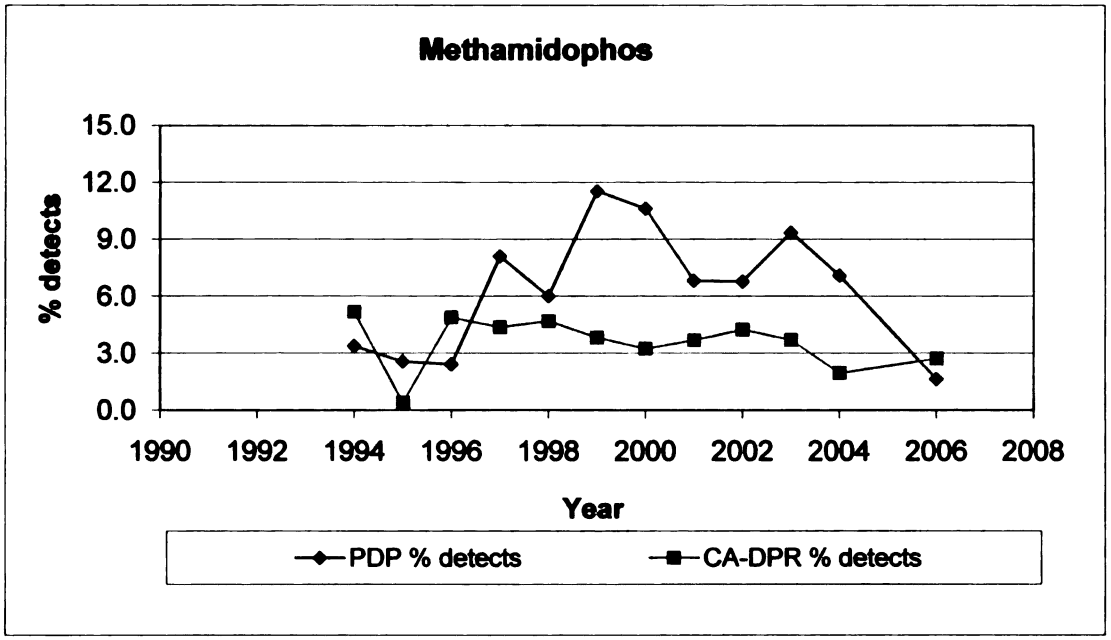

Figure 3.8. Percent detects for methamidophos.

3.4.2.5 *Methyl parathion*

The decline in the percent detections of methyl parathion is the most significant and continuous among the other pesticides (Figure 3.9). Although the residue detects were never very high, the PDP percent detects in 1996 were ~3% and fell to zero by 2004. Dietary concerns and occupational risks were the main driving forces in the voluntary cancellations of many of its uses that started in 1997 as described previously in Chapter 2. The use trends for methyl parathion do not follow the same track to zero as the residue detects (Figure 2.17) because the cancellations focused on those uses that left the highest residues in fruits and vegetables and those uses with low levels of dietary residue levels were left intact. Thus there is continued use but much lower dietary residues.

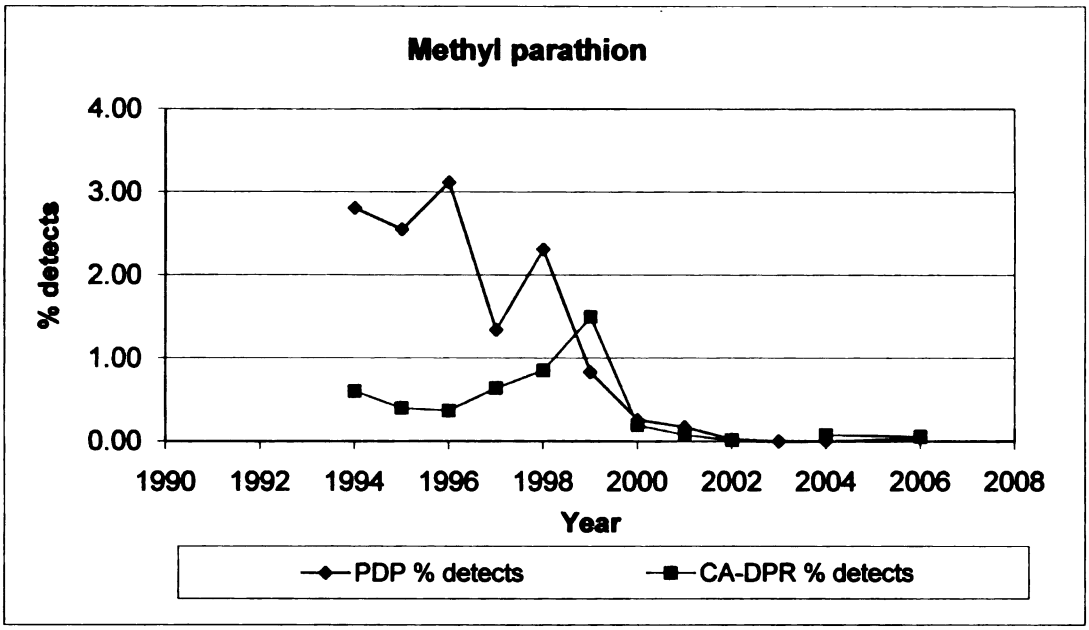

Figure 3.9. Percent detects for methyl parathion.

3.4.3 *Unexpected Residue Trends*

The FQPA and other regulatory actions mostly address the conventional pesticides that are of the greatest human health and ecological concern. These pesticides are expected to decline both in the use and the detected residues. This in fact is true for most of the pesticides considered in this study but unexpected trends were also observed in some of the OPs, the NMCs and the reduced-risk compounds. Among the OPs, the CA-DPR percent detects for chlorpyrifos show a slight increase over the years contrary to the declining trend based on the PDP data. The NMCs in general do not show distinct downward residue trends, e.g. carbaryl as shown in Figure 3.10, despite showing the highest declines in use. The reasons for this are unclear and merit further study. The OPs were the first focus of the EPA following the enactment of the FQPA and attention only turned to the carbamates later, so many of the regulatory actions for the carbamates have been quite recent. Although the EPA identified a common mechanism of toxicity for the

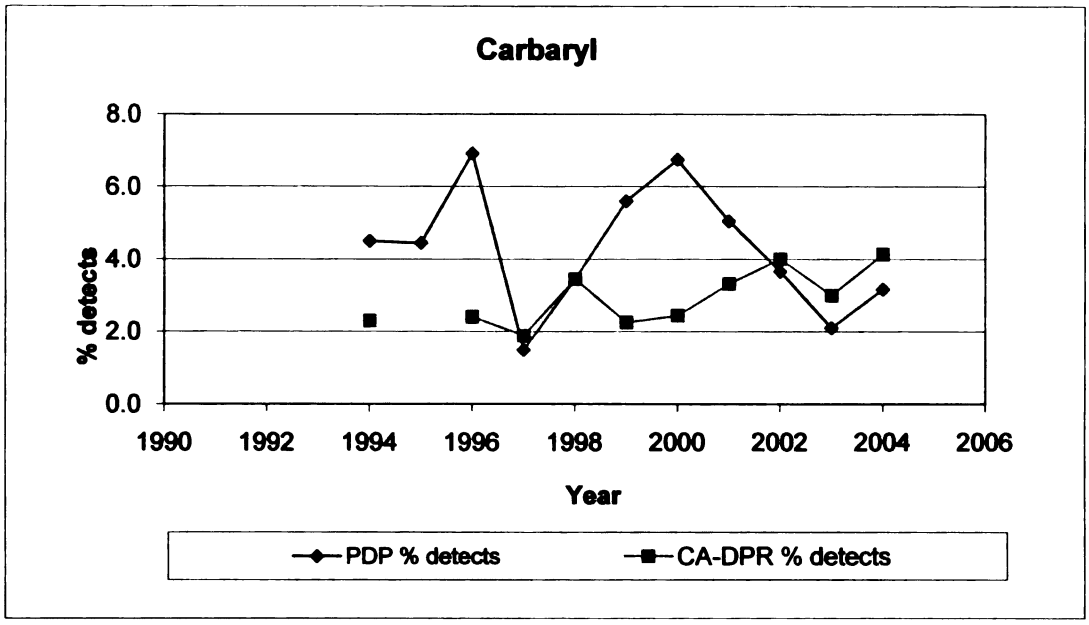

Figure 3.10. Percent detects for carbaryl.

carbamates in 2001, the preliminary cumulative risk assessment was published in 2005 and the revised cumulative risk assessment for the carbamates, taking into account recent regulatory changes, was issued for comment late in 2007. Many uses of carbaryl, carbofuran and methomyl were only canceled or modified in the period from 2005 to 2007. Further reductions in use and residues may show up in the future, but the cumulative risk assessments indicate that as a group the carbamates are now not of dietary concern if these cancelations and use changes are included. The dietary risks for the individual carbamates generally were below the EPA's level of concern and this conclusion was in part based on the rapid reversibility of inhibition of cholinesterase by carbamates compared to the OPs. Also, fewer carbamates than OPs are included in the cumulative risk assessment, and there are fewer individual chemicals to fill the carbamate cumulative risk cup. However, despite the later focus on the carbamates the data from

Chapter 2 (e.g. Figure 2.1 and data for individual compounds), show that the use of NMCs has been declining steadily since the mid-1990s, before the passage of FQPA.

Several of the reduced-risk pesticides have high level of percent detects (>10%) and in some case >20% as shown in Figure 3.11 for imidacloprid and in Figure 3.12 for acetamiprid, which is unexpected since the use rates of these chemicals is generally much lower than that of the OPs, NMCs and B2 fungicides (Figures 2.28 and 2.29). In keeping with this observation, Punzi (2005) noted that imidacloprid was detectable in almost 80% of the samples of peppers analyzed in the PDP program in 2003 and 2004. These high rates of reduced-risk compound detection may be attributable to several factors. Many of the reduced-risk compounds are now widely used on fruits and vegetables because of their low dietary risks. For the same reason, legal applications can be made close to, or even after, harvest potentially leading to higher residues. Some of these pesticides are also systemic (e.g. the neonicotinoid inseticides such as imidacloprid and the strobilurin fungicides) and spread through the plant tissues unlike other pesticides that stay on or near the surface and would be removed if samples are washed and peeled prior to analysis as in the PDP methodology (Punzi et al. 2005). The systemic reduced-risk compounds therefore tend to leave higher residues at harvest which are not removed before analysis. One factor that is probably not involved is the possibility that the LODs are lower for these newer compounds than the older conventional ones. An examination of the LODs in the PDP analytical program did not reveal any obvious trends in this direction.

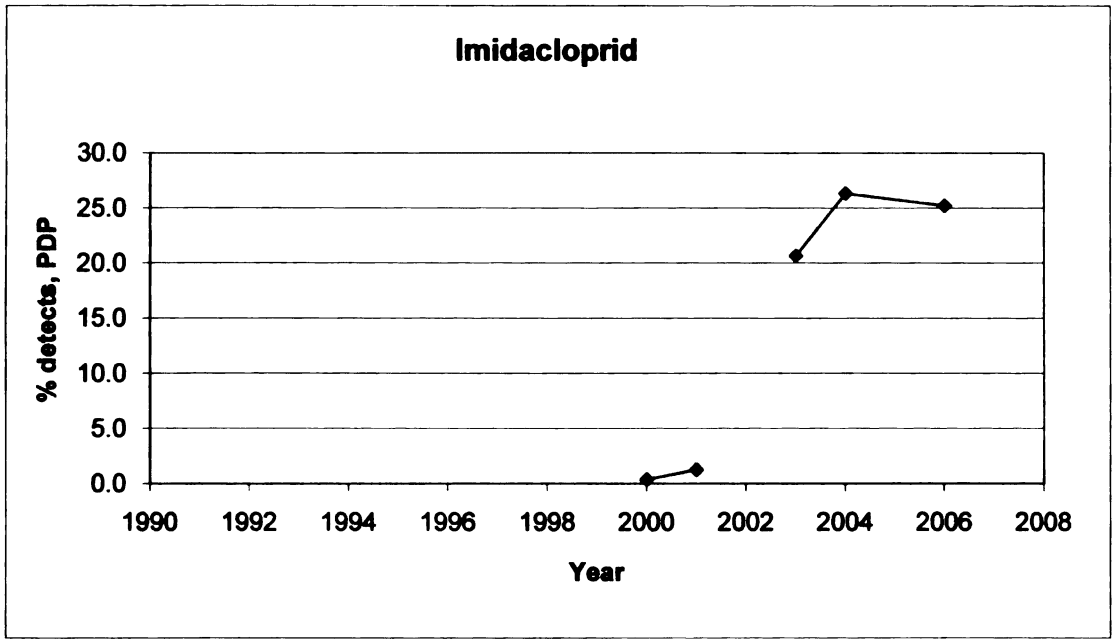

Figure 3.11. Percent detects for imidacloprid.

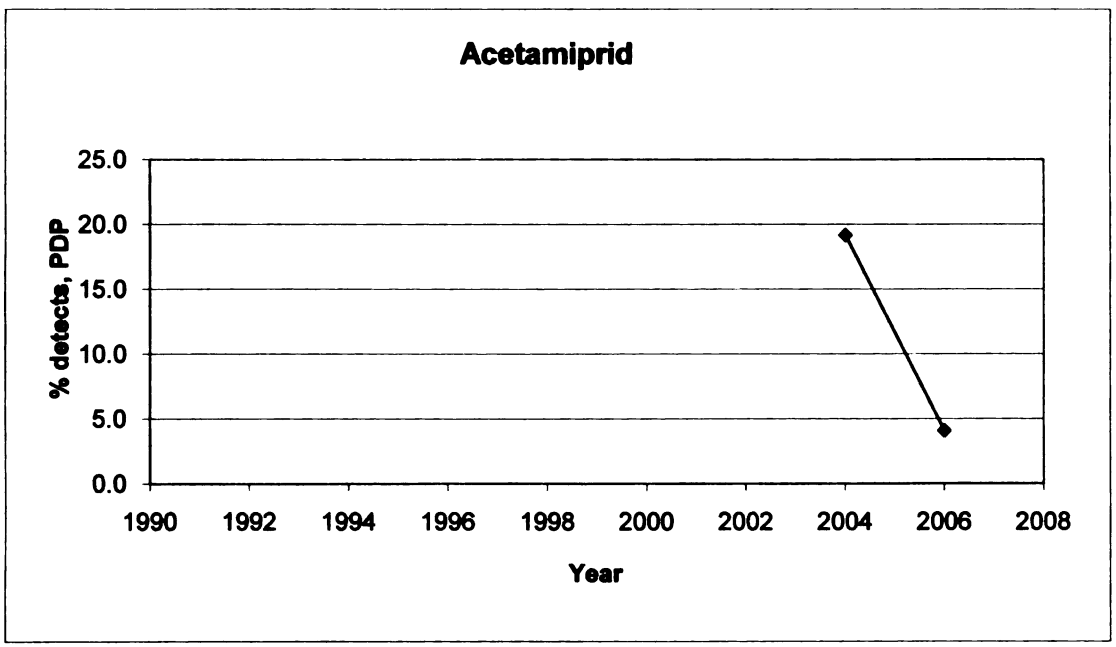

Figure 3.12. Percent detects for acetamiprid.

3.4.4 *Pesticide Residue Databases and Trend Analysis*

Despite the trends with selected OPs described above, overall the PDP percent detects do not show distinct residue detection trends for most of the pesticides and are

quite variable from year to year in many cases. This could be due to differences in sampling methods, changes in the use patterns for the pesticides, and changing LODs in residue analysis. The variability in the residue detects trend is consistent with Punzi's study on the percent detects of chlorpyrifos on apples and dimethoate on spinach using the PDP residue data that showed variation in the residues with different LODs (Punzi 2005). In another study by Punzi et al (Punzi et al. 2005), where the overall percent of samples with detects (65% of which were fruits and vegetables) decreased from 1993 to 2003 based on the PDP residue data, noted that varying groups of commodities are analyzed every year and different pesticides measured on each commodity. On the other hand, the trend in the residue detects based on the CA-DPR data are more consistent, which implies more uniform monitoring and perhaps sampling methods but with relatively very low detects. Both the PDP and the CA-DPR databases residue data are useful for the purposes for which they were established and have been of tremendous use especially in dietary risk assessments. However, these databases are not set up for trend analysis, hence the variabilities and inconsistencies of residue data over the years.

The sampling procedures vary for each residue database. The PDP randomly samples commodities using a statistical design to obtain a statistical representation of the U.S. food supply. The CA-DPR also employs random sampling of surveillance commodities. The FDA samples individual lots of domestic and imported foods; imported samples are collected at the point of entry while the domestic samples are collected as close to the point of production in the distribution system (U.S.FDA 2003). Although statistical random sampling is done, the commodity or crops sampled at different times still vary depending on factors such as production volume, dietary

importance, and pesticide toxicity among others as well as the information/data priorities set by EPA as in the case of the PDP. These lead to inconsistencies in the commodities sampled each year and thus they do not show continuity over time.

The differences in the limits of detection (LODs) from the use of different and increasingly sensitive analytical instruments are another factor that contributes to the variability in residue detections. The PDP, the CA-DPR and the FDA use various methods to analyze for pesticide residues in food, e.g. multi-residue and single residue methods. These methods vary in their sample preparation and the analytical instruments used in the residue analyses and have different LODs. The EPA defines LOD as "the lowest concentration that can be determined to be statistically different from a blank (negative control sample)" and assigns "non-detects" (NDs) to samples that "do not bear at or above the LOD" (U.S.EPA 1998). Continuous testing of new technologies and development of new techniques are being done by program scientists to improve the level of detection according to PDP (U.S.DA-PDP 2006b). More advanced instruments have lower LODs and are capable of detecting very small residue concentrations, thus resulting in more residues detected. Although this is certainly likely to be a factor over time, its actual impact on the percent detects is less clear. A study by Punzi (2005) indicated that variations in the LODs as high as 10-fold for the same compound between different laboratories conducting residue studies for PDP often did not greatly change the percent detects that were obtained, with an estimated maximum 2-fold increase.

3.5 Conclusion

The OPs showed an overall decrease in residue detection frequency in accord with their declining use as intended by regulations instituted under FQPA although the data were often quite variable. The downward trend in residues was particularly clear with some individual compounds such as azinphos-methyl and methyl parathion that have been subjected to the most rigorous regulation. The residue detection frequency was also variable for the B2 fungicides and they did not generally show a strong decline in either the use or residue trends. The NMCs showed considerable variability in the residue detections but no clear downward trend. This does not correspond to their rapid decline in use. It is unclear why this should be. The record for residue detections with the reduced-risk pesticides is brief, and for several the detection rates were low and variable. This made establishing a trend difficult. Some of these pesticides, however, showed unexpectedly high percent detects, e.g. imidacloprid, acetamiprid, tebufenozide, cyprodinil and fenhexamid. These detections could be due, at least in part, to the systemic properties of some of these pesticides particularly those with considerable use on fruits and vegetables, and to applications that are made close to harvest.

Limited data from the FDA's Total Diet Study suggest that residue reductions in the diets of infants and toddlers for pesticides with the most frequent detection patterns were greater than those in the diets of older children and adults, and this would be in agreement with one of the primary goals of FQPA.

The residue databases are set up according to the requirements and needs of the regulatory agencies and these apparently do not include a primary focus on trend analysis. Establishing pesticide residue trends is therefore difficult because of the

variability in sampling procedures and the types of commodities sampled each year. Innovations in instrumentation have led to considerably higher sensitivity in residue determinations and the consequent lowering of LODs over time potentially increases the number of detections which would tend to confound trend analysis based on the percentage of samples containing a residue above the LOD. With fairly modest modifications, these databases, particularly that of the PDP, could be utilized for purposes other than those for which they are established at present. To allow residue trends, and therefore dietary risk trends, to be assessed over time, more consistent and continuous sampling of selected important dietary commodities would be required. This expansion would require an increased budget but it would greatly enhance the current usability and significance of these databases. With more consistent sample analysis and a more comprehensive and consistent residue databases, dietary risk trend analysis could be accurately determined. Most important, this would allow the direct assessment of the impact of major regulatory actions such as those initiated under the FQPA and would allow adjustments to be made, if necessary, to assure that their goals of risk management are being achieved. In a recent review by the EPA's Office of the Inspector General of the EPA Office of Pesticide Program's implementation of FQPA, criticisms were made of the lack of measurement of direct impacts and outcomes. In response EPA-OPP stated that "OPP is in agreement that a scientifically-sound, risk-based measure would provide a more accurate and effective indicator" but that "despite considerable effort, OPP has been unable to develop a scientifically sound measure that uses available data and can be implemented efficiently" (U.S. EPA, 2006f). This clearly underlines the current difficulty

in establishing reliable data and approaches to conduct comprehensive risk assessments on pesticide residues in the U.S. diet.

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CHAPTER 4
IMPLICATIONS OF THE FQPA FOR DIETARY RISK: A CASE STUDY

4.1 Pesticide Risk Assessment

The U.S. Environmental Protection Agency (EPA) conducts pesticide risk assessment as required by the FQPA. The process involves four major steps: hazard identification, dose-response assessment, exposure assessment and hazard characterization (Figure 4.1). Hazard identification involves review of toxicological information to determine the harmful effects a chemical might cause. In the dose-response assessment step, the dose level at which the effects occurred, and the population group in which the effects are most likely to be exhibited are identified. The exposure assessment step evaluates the amount of pesticide to which an individual is exposed from oral, dermal, and inhalation routes of exposure. The final step in the process is the characterization of risk. This is the process of combining hazard, dose-response, and exposure information to describe the overall magnitude of the public health impact, reviewing the assessment for quality and consistency and finally, setting acceptable levels of risk (U.S.EPA 1999).

The dietary exposure assessment of pesticides is an integral part of and is equally important as the other components of the risk assessment process wherein both acute (contact with a substance over a short period of time) and chronic (contact over a long period of time) exposures are assessed. Major inputs in conducting the dietary exposure assessment are pesticide residue levels and food consumption data, corrections for the percent of the crop treated with the given compound, residue modifications during

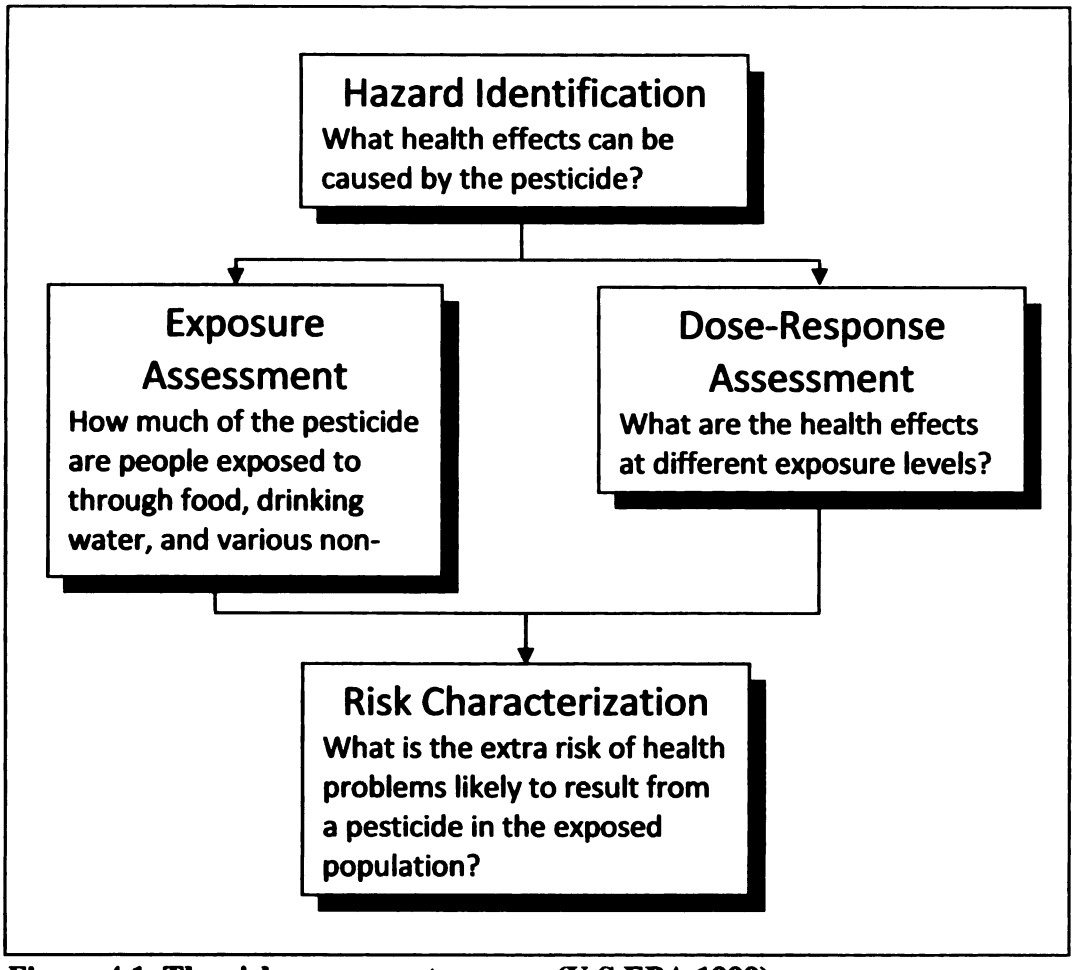


Figure 4.1. The risk assessment process (U.S.EPA 1999).

food processing (processing factors), and other data that might influence residue levels. The EPA uses a tiered approach consisting of four tier levels to obtain increasingly more realistic exposure assessment values (Table 4.1). The initial screening of pesticides is done at the first tier level. This is the worst case scenario and uses the pesticide tolerance as the assumed residue level and a conservative assumption of 100% crop treated. A considerable overestimation of actual pesticide residue is expected from these very conservative assumptions because, according to Suhre (2000), they reflect the maximum

Table 4.1. The EPA's tiered approach for exposure analysis[1]

Tier	Acute Exposure	Chronic Exposure	Result
Tier 1	▪ Tolerance-level residues ▪ Assume 100% crop treated	▪ Tolerance-level residues ▪ Assume 100% crop treated	▪ Tolerance value used in risk assessment
Tier 2	▪ Tolerance-level residues (or highest residue found in a field trial) for items consumed as single-servings ▪ Average field trial residues for blended commodities (e.g., wheat) ▪ Assume 100% crop treated	▪ Tolerance-level residues ▪ Incorporate % crop treated information	▪ For acute assessment, tolerance or field trial value used in risk assessment ▪ For chronic assessment, multiply residue level by % crop treated (e.g., 10 ppm x 20%CT=2ppm)
Tier 3	▪ Use probabilistic techniques ▪ Use distribution of crop field trial residues for items consumed as single servings ▪ Use average of crop field trial residues or 95th percentile from monitoring data for blended commodities ▪ Use % crop treated information (as part of probabilistic techniques) ▪ Use processing factors	▪ Use average of crop field trial residues or monitoring data for blended commodities ▪ Use crop treated information ▪ Use processing factors ▪ Use refined livestock dietary burdens for meat, milk, poultry, and eggs residue values	▪ For acute assessments, use a distribution of residues, incorporating % crop treated data (e.g., if 20% of the crop is treated, there will be an 80% chance of choosing zero residue) ▪ For chronic assessments, multiply the field trial or monitoring residue value by the % crop treated (e.g., 8 ppm x 20%CT=1.6 ppm)
Tier 4	▪ Market basket survey (single-serving-sized samples) ▪ Use processing factors or other studies	▪ Special studies (market basket surveys, consumer processing studies, residue degradation studies, etc.)	▪ Allows additional refinement; produces more realistic exposure estimates

[1] *EPA's Risk Assessment Process for Tolerance Reassessment. U.S. Environmental Protection Agency. Staff Paper #44. October 8, 1999*

application rate and shortest pre-harvest interval. If the risks calculated from the initial screening are acceptable, no further analysis is required, but if the tier 1 results are unacceptably high, more refined data would be used and higher tiers of analysis would be

employed. The level of resources and data needed to refine exposure estimates increase with each tier (U.S.EPA 2000a). In tier 2 acute analysis, field trial residues are used with the tolerance level retained for chronic exposure but a correction for percent crop treated is included. Tier 3 involves the use of probabilistic techniques (Monte Carlo analysis) and residue distributions for acute exposure. Even more refined data such as market basket survey data and special residue studies are used in the tier 4 analysis.

4.2 Dietary Risk Assessment Computer Models

Requirements by the FQPA to conduct cumulative risk assessment (in which risks from all compounds having a common mode of action are summed) and aggregate risk assessment (where exposure from all sources (dietary, water and residential) are summed) presented many technical challenges to the EPA and resulted in the development of three software programs for conducting such complex assessments, i.e. Dietary Exposure Evaluation Model (DEEM), LifeLine, and Cumulative Aggregate Risk Evaluation System (CARES). These competing programs all address these challenges but in somewhat different ways and all are used by regulators. These programs use probabilistic methods of analysis which give distributions for population exposure and for food consumption and thus provide more realistic results. The deterministic (single value) approach is the traditional method of conducting risk assessment. It is based on average diets and 'worst case' single estimates of potential exposure and provides no quantification of the proportion of the population at risk (Petersen 2000). Deterministic methods are now being supplemented with probabilistic models to better inform quantitative risk management decisions (Harris et al. 2001). A probabilistic method of analysis is defined as an analysis in which frequency (or probability) distributions are

assigned to represent variability in quantities having a distribution as the form of output, making it possible to estimate the proportion of the population at risk (Cullen and Frey 1999; Kempton 2001). It employs the Monte Carlo simulation approach which is used for generating representative distribution of values for each of the inputs (residue levels and dietary intakes) in a generic exposure (or dose) equation to derive an output distribution of exposure (or doses) in the population (Cullen and Frey 1999; U.S.EPA 1997).

4.2.1 *Dietary Exposure Evaluation Model (DEEM)*

The Dietary Exposure Evaluation Model (DEEM) was developed by Novigen Sciences, Inc. (now Exponent, Inc.) as a model for conducting Monte Carlo dietary risk assessments. It contains food consumption data from the USDA 1989-1992 and 1994-1996 Continuing Surveys of Food Intake by Individuals (CSFII) translated into food ingredients using the model's translation database. The consumption surveys were conducted by personal interviews of statistically selected individuals who were asked to recall everything they ate and drank in the previous 24 hours. DEEM is composed of four modules: the main DEEM module, the Acute and the Chronic analysis modules and the RDFgen module. The dietary exposure assessment models based on the CSFII are provided by the Acute and the Chronic modules. The RDFgen module automates single analyte and cumulative residue distribution adjustments and the creation of summary statistics and Residue Distribution Files based on the USDA Pesticide Data Program (PDP) monitoring data or user-provided residue data. The main DEEM module is used to create and edit residue files for specific chemical or cumulative applications and to launch the Acute, Chronic and RDFgen modules (Kidwell et al. 2000). DEEM uses the distribution of the daily consumption data to calculate acute dietary exposures. A simple

distribution approach is used for non-Monte Carlo application, and the probabilistic method is provided by Monte Carlo applications. Chronic exposures "are typically derived as point estimates using average consumption and residue estimates" (Barraj et al. 2000). The mean food consumption files are fixed data sets included in DEEM and are unalterable (Kidwell et al. 2000). They are pre-calculated on a per capita basis for each raw agricultural commodity (RAC) and food/form reported in the CSFII surveys (Barraj et al. 2000). DEEM's chronic exposure is expressed either as percent reference dose (%RfD), margin of exposure (MOE), or as a cancer risk estimate, depending on the toxicological information provided by the user. The reference dose (RfD) is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" and is determined by using the equation (Barnes and Dourson 1988; U.S.EPA 1993):

$$RfD = NOAEL / (UF \times MF);$$

NOAEL=No Observed Adverse Effect Level
UF= Uncertainty Factor
MF=Modifying Factor

The MOE is the ratio of the highest dose that is free of toxicity to animals (e.g. NOAEL) and the human dietary exposure level (U.S.EPA 2000a) and is expressed as:

$$MOE = NOAEL / dietary\ exposure$$

The MOE in effect is the margin between human exposure and the safe dose for animals and represents a "safety" factor. The user has the option of specifying which of the measures to use. The chronic module uses a "data base of pre-calculated per-capita means of food consumption data (g/kg-bw-day) for each raw agricultural commodity (RAC) and food form reported in the CSFII surveys" (Barraj et al. 2000) to calculate the chronic

exposures. The per capita daily mean exposures are calculated for each of the standard populations and the per capita exposure for all the standard population groups are reported directly, along with the risk estimates based on the user-specified endpoint. DEEM is the default program used by the EPA to assess pesticide dietary risks since approximately 1998.

4.2.2 *LifeLine*

The LifeLine model was developed by the Hampshire Research Group (now managed by The LifeLine Group) under a cooperative agreement with the EPA and the USDA "to develop publicly accessible risk assessment software for a wide range of anticipated users" (U.S.EPA 2004). LifeLine uses a probabilistic model for the characterization of pesticide risk from dietary, residential and drinking water related sources as well as population-based aggregate and cumulative exposure. It provides a powerful tool to understand the relative contributions of these sources and how they vary across the individuals' lives, and it estimates the history of each individual's exposures to a pesticide from all sources; the patterns of exposure for a population over time; the distribution of exposure across a population at any age and season; and the corresponding risks for non-cancer toxic effects associated with those exposures, as well as the lifetime cancer risk (LifeLine 2002a, 2007). The software models exposure for each day of an individual's life from a simulated population (1-40,000) across their lifetime (0 to 85 years). LifeLine generates exposure files for each simulated individual, from which exposure estimates are extracted for the age and gender based subpopulations. Exposure assessment from pesticides includes the use of residue data, processing factors and probability of use that are integrated to generate a complete set of potential residues. This

set of residues is then used to generate residues for the food as consumed. The dietary exposure calculation uses a recipe file or a translation file that "provides on a proportional basis, the ingredients (specific food forms of commodities) in a food that was reported to be eaten in the dietary consumption survey" (LifeLine 2002b). It identifies the mass contribution of the food's ingredients, and the distribution of residues from the food as consumed is calculated using the residue distributions from the ingredients. LifeLine is also used by EPA in conducting dietary risk assessment of pesticides.

4.2.3 *Cumulative Aggregate Risk Evaluation System (CARES)*

The Cumulative Aggregate Risk Evaluation System (CARES) is a program that accommodates both aggregate and cumulative risk assessment analyses and can model exposure from various sources such as dietary, residential and drinking water. It uses the deterministic approach to calculate risks for tier 1 analysis and employs the probabilistic method using Monte Carlo simulation for higher tiered analysis. CARES randomly generates a reference population (100,000 individuals) based on the 5 million individuals from the 1990 U.S. Census Public Use Micro Data Sample (PUMS) dataset and a 365-day exposure profile is created for each individual. The reference population is then "matched" with other databases (e.g. CSFII) to obtain other variables needed in the exposure assessment. The unique feature of CARES is the ability to identify and statistically describe specific exposure contributions across the matrices of source, route, and population sub-group and this includes conducting a comprehensive suite of contribution, sensitivity and other data analysis (ILSI 2003). CARES is now maintained by the International Life Sciences Institute (ILSI) but was originally funded and

developed by member agrochemical companies of CropLife America to conduct complex exposure assessments and to address FQPA mandates for short-term, intermediate duration, and lifetime food, drinking water and residential and aggregate and cumulative exposure and risk calculations (U.S.EPA 2004). There is no final version of CARES yet but there have been several evaluation versions released. Computer bugs and glitches have been discovered in previous versions of CARES; hence it is continuously undergoing development. The development of CARES temporarily ceased after its transfer to ILSI due to lack of funding. The EPA lists CARES among the models "in common use in EPA's Office of Pesticide Program" (U.S.EPA 2007b) in addition to DEEM and LifeLine.

4.2.4 *Comparison of the DEEM, LifeLine and CARES Programs*

The EPA Scientific Advisory Panel (SAP) (U.S.EPA 2004) compared the three risk assessment models using a common data set for a hypothetical pesticide and identified various factors through which the models differ from one another. Differences between the results from the three programs were relatively minor. Design assumptions, data sources and databases were identified as the variations associated with the dietary modules which may lead to differences in estimated exposures (U.S.EPA 2004). These factors are shown in Table 4.2 followed by individual discussion of the factors based on the SAP report.

Table 4.2. Differences between DEEM, LifeLine and CARES (U.S.EPA 2004).

Factor	DEEM	LifeLine	CARES
Reference Population	CSFII Survey	Natality (NCHS)	Census (PUMS)
Binning Methodology	Random (2 Day Diaries)	Random (Age, Season)	Gower Dissimilarity Index
Reference Population Bodyweight	CSFII Normalized	LifeLine (NHANES)	CSFII Normalized
Model Weight	CSFII Survey	Equal Weights (Random)	CARES (Stratified)
Modeled Population	US Population	US Population (Natality, Mortality)	US Population

4.2.4.1 *Reference Population*

LifeLine models the "starting population" when individuals are "born" based on natality data from the National Center for Health Statistics (NCHS). The modeled individuals then grow, move to new areas, age and die. According to the EPA, "LifeLine tracks each day in each individual's life and develops an internally consistent exposure history based on cross-linked databases such as the U.S. Census Bureau's American Housing History, National Home and Garden Pesticide Use Survey, etc." (U.S.EPA 2004). DEEM uses all individuals in the CSFII in its exposure calculations. CARES on the other hand uses a reference population (100,000 individuals) from a 5% Public Use Microdata Sample (PUMS) file from the U.S. Census.

4.2.4.2 *Binning Methodology*

LifeLine groups individuals into "bins" by age and season. According the SAP report (2004), "to generate a series of diets for an individual over that individual's lifetime, LifeLine matches (and draws from) only those individuals which have similar ages and only from those consumption diaries that arose from the specific season of interest". CARES uses similar binning method with some additional criteria and the

GOWER dissimilarity index is used to create the matches. DEEM uses the CSFII food diaries for individuals with reported two days of consumption.

4.2.4.3 *Reference Population Bodyweights*

In LifeLine, bodyweight is determined through correlation of the individual's height and age. This allows for the body weight and the surface areas of an individual to be "kept internally consistent across an individual's entire life" (LifeLine 2002b). LifeLine obtains the amount of food consumed from the CSFII. DEEM and CARES calculate exposure from the product of consumption (based on the CSFII) and the pesticide residue concentration in that food.

3.2.4.4 *Model Weights*

DEEM uses the CSFII weights directly to reflect the U.S. population. In CARES the reference population is weighted to produce a population similar to that of the U.S. population (U.S.EPA 2004). The LifeLine model is "self-weighting in the sense that individuals are "born" on the basis of (and in direct proportion to) natality data from the National Center for Health Statistics (NCHS) National Health and Nutrition Examination Surveys (NHANES) and DEEM uses CSFII sampling weights directly which, in turn, reflect the U.S. population" (U.S.EPA 2004).

Other than this EPA model study, there appears to be nothing published regarding the results provided by the different exposure and risk assessment programs that were developed in response to FQPA.

4.3 Dietary Risk Assessment Using Tiered Analysis

Although the results of the EPA dietary risk assessments have often been the subject of public discussion, little has been published that examines the effects of the tier analysis system or of different risk assessment models on risk estimates. In one of the few published studies on the tiered system of dietary exposure analysis, Wright et al. (2002) showed that estimated exposures to the OP insecticide, chlorpyrifos, from the highest tier level were much lower than from the tier 1 (tolerance level) exposure assessment. Oliver et al. (2000) reported a significant decrease in the estimated acute and aggregate dietary risks of chlorpyrifos using typical refinements at higher tiers of analysis (Oliver et al. 2000).

4.4 Objectives

The risk assessment process has increased in complexity and improved in realism tremendously in the past decade and has evolved from the use of the deterministic approach to probabilistic methods of analysis. The probabilistic approach is widely used in the U.S. and Europe and has been employed in various studies to determine exposures to pesticides. However, little has been published that shows the impact of the FQPA on pesticide exposure and dietary risk, or the variability in risk estimates that arise from the different assumptions involved in the EPA's tiered approach to risk assessment, or from the use of different risk analysis programs. This study therefore aims to:

1. Assess the change in dietary exposures and risks through replacing an older, higher risk pesticide with a safer replacement compound registered by IR-4 on selected crops as a typical example of such changes made in response to FQPA.

2. Evaluate and compare the dietary exposure estimates at the different tier levels using standard risk assessment models.
3. Evaluate and compare the dietary exposures using different dietary risk assessment models.

4.5 Methods

4.5.1 *Selection of a Pesticide-Crop Combination for the Case Study*

The selection of the pesticides and the crop for the dietary exposure assessment was based on the following criteria:

1. Crop was frequently treated with anticholinesterases or B2s in its production.
2. The pesticide(s) have a reasonably continuous record of use and residues in databases from before the passage of FQPA to present;
3. Alternative apparently safer pesticide(s) were registered by IR-4 and were used to directly replace the older compound(s);
4. Crop makes a measurable contribution to the diet and the risk can be assessed using newer risk assessment programs, with a focus on infant-child diets and other sensitive populations.

After extensive analysis, which revealed very few situations that met all these criteria, the use of the fungicides iprodione (B2 carcinogen) and fludioxonil on peaches and other stone fruit satisfied the criteria and was selected as the case study for the dietary exposure assessment. One of the major uses of iprodione was as a postharvest dip or spray on peaches, nectarines and other stone fruits to prevent rotting during storage and transport with an application rate of 50,000 to 65,000 pounds per year (U.S.EPA 1998b). Peaches

are among the EPA's list of 10 commodities significant in the diets of children (U.S.FDA 2002). In 1998 the use of iprodione for postharvest treatments was canceled by EPA and fludioxonil was used very widely as a replacement (Thompson 2008). Various uses of fludioxonil have been registered by IR-4, including its use on stone fruits, and it has "replaced iprodione completely (100%)" since 1999 for post-harvest uses on peaches, plums and nectarines (Adaskaveg 2008). It was identified as having a spectrum of activity and efficacy comparable to the canceled iprodione based on a study on reduced-risk fungicide effectiveness on stone fruits (Adaskaveg et al. 2005). Fludioxonil also has had 70-80% usage as an iprodione replacement on peaches in Georgia since 1997 when most uses of iprodione was removed from commerce (Brannen 2008). Several studies have also identified the potential of fludioxonil as a replacement for iprodione. The study conducted by Northover and Zhou (2002) showed the activity of fludioxonil against rhizopus rot on peaches. Fludioxonil at 25 μg/mL concentration caused a 95% reduction in infection comparable to iprodione at a higher concentration (250 μg/mL) with a 77-95% reduction. In another study on the control of brown rot and gray mold on peaches and nectarines, fludioxonil applications resulted "in very high levels of decay control, similar to that of the former industry standard, iprodione" (Förster et al. 2007). The pre-harvest use of iprodione was also restricted around the same time as the post-harvest uses were cancelled to further decrease iprodione residues, i.e. through an increased pre-harvest interval to more than seven days and reduced application rates (U.S.EPA 1998b). The reduction in iprodione residues after 1997 thus could originate from these changes in both pre- and post-harvest uses on stone fruits.

4.5.2 *Dietary Risk Exposure Assessment Scenario*

Tiered dietary exposure assessments (tiers 1, 2 and 3) were conducted for iprodione and fludioxonil on peaches alone and on the entire stone fruits group (EPA crop group 12 including apricots, peaches, nectarines, plums and cherries), using DEEM and LifeLine for different population age groups. Several preliminary trial runs were done using CARES but computer bugs and crashes were encountered (and reported to the software developers). Since CARES is still being developed and evaluated, it was not used further in the dietary assessment. Acute and chronic exposure levels at the different tier levels were determined using the corresponding parameters for each tier shown in Table 4.3. Residue values reported as zeroes or non-detects (NDs) from the PDP residue database were assigned one-half of the limit of detection (LOD) according to the EPA default policy (U.S.EPA 1998a). The percent crop treated data for iprodione were derived from the ratio of the total area treated and the total area planted for each crop based on the National Center for Food and Agricultural Policy/CropLife Foundation (NCFAP/ CLF) 1992, 1997 and 2002 data. The percent crop treated used for the fludioxonil dietary risk assessments were those used by the EPA for the tolerance establishments of fludioxonil on stone fruits (U.S.EPA 2002). The processing factors used were the default factors published in the DEEM manual (Kidwell et al. 2000).

The toxicity values used in the analyses were compiled from published documents (Table 4.4) and are those used by the EPA in the dietary risk assessments of iprodione and fludioxonil. Other studies considered by the EPA were also looked at and based on the review of these studies, the toxicity values selected are reasonable. The %RfD was used as an estimate of risk and calculated based on the NOAEL and the uncertainty

factors. The RfD approach is based on assumptions that a threshold exists and lies between the NOAEL and the LOAEL but there is no way of knowing the "true" threshold from these data. Another assumption is that the errors from the NOAEL and LOAEL studies are minimal. However, this approach involves uncertainties and limitations. Uncertainties come from various sources: a) uncertainty (errors) from the "distance" of the NOAEL to the true threshold; b) uncertainty from the doses used in determining the NOAEL; and c) uncertainty factors used in calculating the RfD. A limitation of the RfD approach is that it can only be used to compare across compounds having the same mechanism of toxicity. The "net result is that exposures resulting in the same RfD do not imply the same level of risk for all chemicals, and that exposures above the RfD do not represent the same increase in risk for all chemicals" (Beck et al. 2001). The comparison of iprodione and fludioxonil is difficult because of the differences in the mechanisms of toxicity. However, assessment of the changes in risk for individual compound using the RfD approach is possible and although it has limitations, it is a reasonable and accepted method. It also incorporates the different uncertainty factors set by the EPA for different compounds.

The acute and chronic exposures from tiers 1, 2 and 3 were compared for the stone fruit group as a whole and for peaches alone. The changes in the dietary risks before and after the FQPA were assessed using the tier 3 acute exposure analysis. At this tier level, the 1995, 2000 and 2006 PDP residue data and corresponding 1992, 1997 and 2002 NCFAP/CLF calculated percent crop treated were used to estimate the exposure levels and represent the risks before and after the enactment of the FQPA. The exposure

values from using DEEM and LifeLine models were also evaluated to determine how the two compare.

The license for DEEM was purchased from Exponent (1150 Connecticut, Ave. NW, Suite 1100 Washington, DC 20036). The copy of LifeLine was obtained from The LifeLine Group, Inc. (4610 Quarter Charge Drive, Annandale, VA 22003) and the CARES model was downloaded from the ILSI website (http://cares.ilsi.org/). Both LifeLine and CARES are available with no license fees.

Table 4.3. Dietary exposure assessment input parameters for iprodione and fludioxonil.

Tier	Acute Exposure	Chronic Exposure			
1	Tolerance level residue: Iprodione = 20 ppm Fludioxonil = 5 ppm Percent crop treated=100%	Tolerance level residue: Iprodione = 20 ppm Fludioxonil = 5 ppm Percent crop treated=100%			
2	Highest field trial residue[1] Percent crop treated=100%	Tolerance level residue Percent crop treated (PCT)			
		Iprodione[2]			Fludioxonil[3]
		Crop	PCT 1992	PCT 1997	PCT 2002	
		Apricots	78	54	37	Cherries=16%
		Cherries	41	14	10	Nectarines=49%
		Nectarines	77	34	29	Peaches=22%
		Peaches	60	25	30	Plums=25%
		Plums/Prunes	28	18	8	Other stone fruits=20%
3	PDP residue data[4]; Non-detects=1/2 LOD Processing factors[5] Percent crop treated: Iprodione[2] Fludioxonil[3]	Average crop field trial residue[1] Processing factors[5] Percent crop treated: Iprodione[2] Fludioxonil[3]			

[1] *IR-4 field trial data*
[2] *(CLF/NCFAP)*
[3] *(U.S.EPA 2003)*
[4] *(U.S.DA-PDP 2007)*
[5] *(Kidwell et al. 2000)*

Table 4.4. Toxicity parameters used in the dietary exposure assessment for iprodione and fludioxonil

Toxicity Parameters	Iprodione[1]	Fludioxonil [2,3]
Acute	NOEL=20 mg/kg/day LOEL=120 mg/kg/day Based on decreased anogenital distance (AGD) in male pups from a prenatal developmental toxicity study in rats. FQPA Factor=3X (females 13+ years old) UF=100 aRfD=0.2 mg/kg/day	NOAEL=100 mg/kg/day LOAEL=1000 mg/kg/day Based on increase in the fetal incidence and litter incidence of dilated renal pelvis and dilated ureter from a prenatal developmental toxicity study in rats. FQPA Factor=1X UF=100 aRfD=1.0 mg/kg/day
Chronic	NOEL=6.1 mg/kg/day LOEL=12.4 mg/kg/day Based on histopathological lesions in the male reproductive system and effects in adrenal glands from a combined chronic toxicity/carcinogenicity study in rats. FQPA Factor=3X UF=100 cRfD=0.02033 mg/kg/day	NOAEL=3.3 mg/kg/day LOAEL = 35.5 mg/kg/day (F) Based upon decreased weight gain (F) and decreased body weight, reduction in hematological parameters (platelets), increase in cholesterol and alkaline phosphatase, and increased relative liver weight (M) from chronic toxicity study in dogs. FQPA Factor=1X UF=100 cRfD=0.033 mg/kg/day
Q*	4.39×10^{-2}	NA

[1] *(U.S.EPA 1998b)*
[2] *(U.S.EPA 2002)*
[3] *(U.S.EPA 2000c)*

4.6 Results and Discussion

The exposure levels (mg/kg/day) and the percent of the acute or chronic reference doses (%RfD) calculated by both the DEEM and LifeLine models were used in assessing the exposure of various population groups to iprodione and fludioxonil residues on peaches and on the stone fruits group. The EPA reference doses (RfDs) are exposures that are likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups). The chronic reference dose (cRfD) is an estimate of a daily oral exposure for a chronic duration (up to a lifetime), and the acute reference dose (aRfD) is an estimate of a daily oral exposure for an acute duration (24 hours or less) (U.S.EPA-IRIS 2008). Exposure estimates that are less than 100 percent of the RfDs are generally regarded as "not likely to be associated with adverse health effects, and are therefore less likely to be of regulatory concern" (U.S.EPA 1993). However, "it should not be categorically concluded that all doses below the RfD are 'acceptable' (or will be risk-free), and that all in excess of the RfD are 'unacceptable' (or will result in adverse effects)" according to the EPA (1993). The EPA employs the 95^{th} percentile of exposure for the less refined exposure assessments (tiers 1 and 2) and the 99.9^{th} percentile when probabilistic assessment techniques are used (tiers 3 and 4) (U.S.EPA 2000b). According to the EPA Office of Pesticide Programs (OPP), "with probabilistic assessments, the use of the 99.9^{th} percentile generally produces reasonable high-end exposure such that if that exposure does not exceed the safe level, OPP can conclude there is a reasonable certainty of no harm to the general population and all significant population groups" (U.S.EPA 2000b). In this study the tier 1 and tier 2

exposures were assessed at the 95th percentile of the population and the tier 3 exposures at the 99.9th percentile.

The carcinogenicity of a chemical is expressed in terms of the cancer potency factor (Q*). A higher Q* value indicates a higher potency of a chemical as a carcinogen judged from animal studies (U.S.EPA 2000a). The measure of cancer risk is expressed as a probability, e.g. $1x10^{-6}$, which means that "for every one million exposed persons, one would expect, at the most (upper boundary), one more cancer than would otherwise occur, and the increased incidence may be less" (U.S.EPA 2000a). This has generally been regarded as an "acceptable" carcinogenic risk by the EPA.

While the use of a tiered approach in risk assessment and regulation is logical to focus activity on those situations where additional attention is needed to assess whether risk is acceptable, it should be kept in mind that tier 1 acute and chronic exposures and cancer risks are upper estimates and do not represent estimates of real risk. It is important to note this to avoid common misunderstandings of the level of risk when these are communicated to the public. The cancer risk value of $1x10^{-6}$ is an upper bound estimate which is unlikely to be exceeded and often will considerably overestimate cancer risk. Again, if communicated to the public as actuarial predictions of cancer cases, the use of these "worst case" cancer risk estimates can lead to misunderstandings and undue public concern. A disadvantage of quantitative cancer risk assessment is that it is subject to considerable uncertainties and it is difficult to communicate the results concisely and accurately to the public.

4.6.1 *Variation in the Dietary Exposure at Different Tier Levels*

The iprodione and fludioxonil acute and chronic exposure estimates and the cancer risks from iprodione for peaches are shown in Figures 4.2 to 4.6 (%RfDs are shown on separate y-axes). The raw data for peaches and the stone fruits group are given in Appendix E for iprodione and in Appendix F for fludioxonil. The results for these two commodities were generally very similar. The estimated iprodione and fludioxonil acute and chronic exposures were highest at tier 1 and, as expected, decreased substantially at higher tier analysis in most cases.

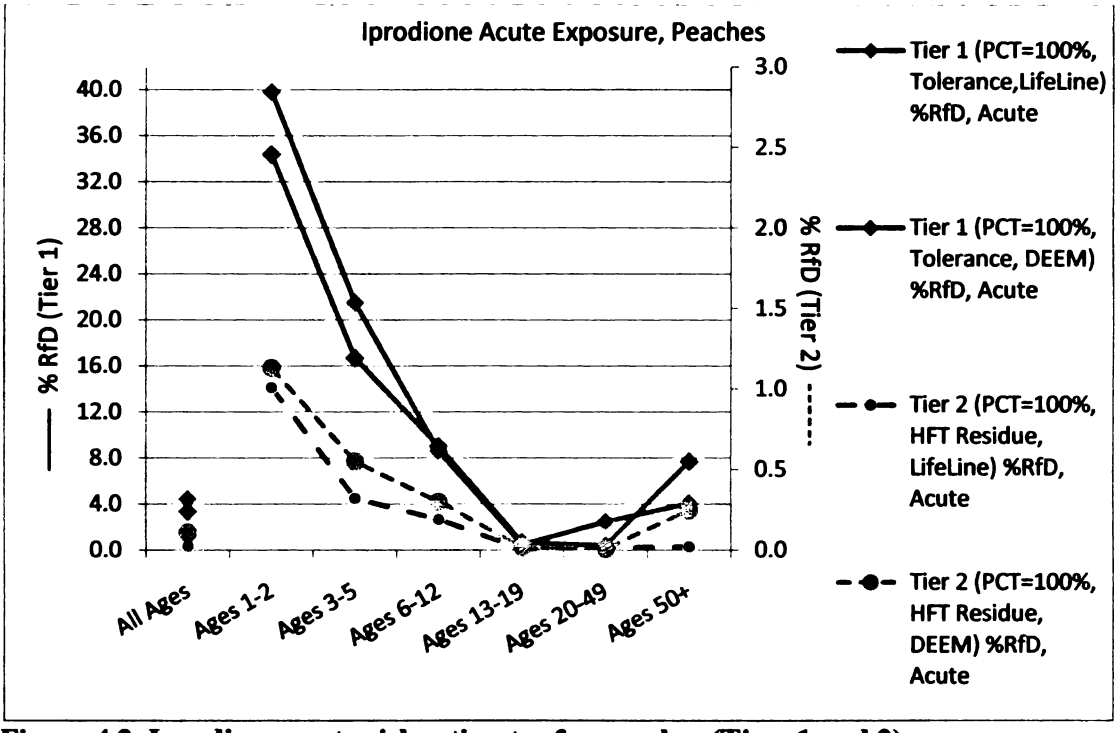


Figure 4.2. Iprodione acute risk estimates for peaches (Tiers 1 and 2).

Figure 4

Figure

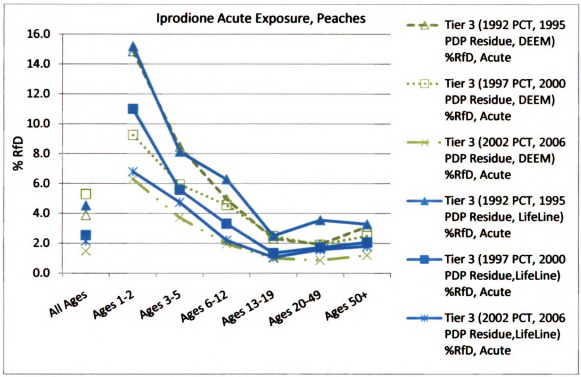


Figure 4.3. Iprodione acute risk estimates for peaches (Tier 3).

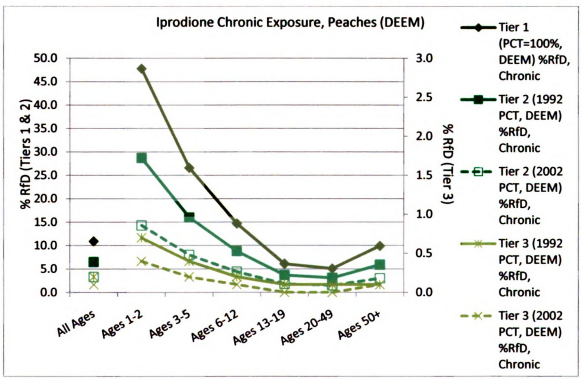


Figure 4.4a. Iprodione chronic risk estimates for peaches (DEEM).

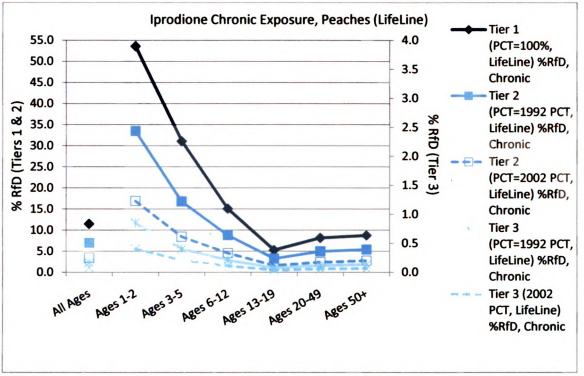


Figure 4.4b. Iprodione chronic risk estimates for peaches (LifeLine).

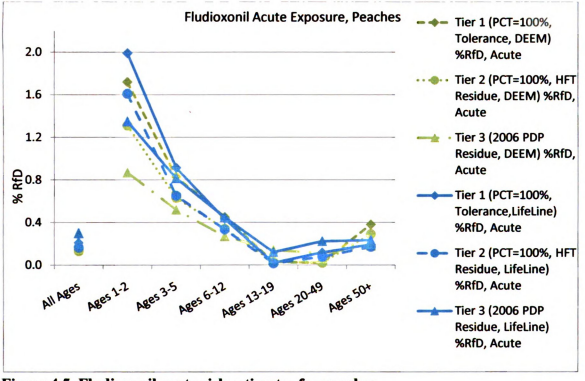


Figure 4.5. Fludioxonil acute risk estimates for peaches.

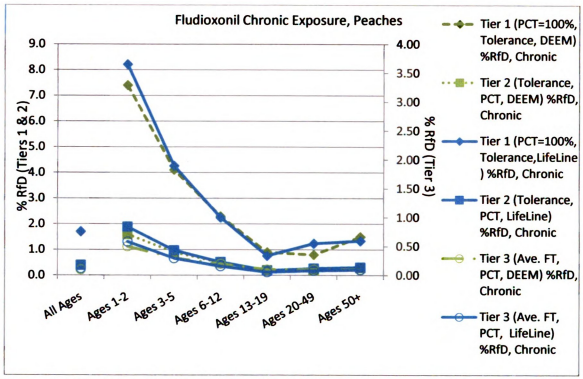


Figure 4.6. Fludioxonil chronic risk estimates for peaches.

In the one exception to the tier 1> tier 2 > tier 3 trend found in all the other examples, the estimated acute risk from tier 1 to tier 2 with iprodione (Figure 4.2) shows an unusually large drop due to the great difference between the exposure calculated using the tolerance level (tier 1) and from using actual field trial residue data (tier 2). The estimated risk then rises again at tier 3. The iprodione residue level used at tier 1 was very high (tolerance = 20 ppm) and this remained as the tolerance level although it had been proposed to be lowered by the EPA in 2004; in 2007 the EPA did not take any action on the iprodione tolerances and it remains at 20 ppm (U.S.EPA 2007a). Usually there is a much closer relationship between the highest field trial residues and the tolerance level that is derived from them. The calculated risk rises again in tier 3 since at this level the exposure is calculated for the 99.9th percentile of the population and not the 95th percentile (for tiers 1 and 2). The iprodione estimated risks (%RfD) for ages 1-2 for

tier 1 and tier 2 are 34% and 1.1%, respectively; for tier 3 the risks are 15.0%, 9.2% and 6.3% for 1992, 1997 and 2002, respectively based on assessments using DEEM. In most other studies conducted as part of this work, risk typically falls in the order tier1 > tier 2 > tier 3, as expected. However there is considerable variation in the degree of decrease in risk calculated under these scenarios, e.g. for acute exposure at ages1-2 to fludioxonil, the ratio of the tier 1 estimate to that for tier 3 is only 2.0, whereas for fludioxonil chronic exposure the ratio is 15 based on DEEM results; for iprodione chronic exposure it is approximately 120 (using 2002 PCT at tier 3) and 68 (using 1992 PCT at tier 3), and for iprodione's cancer risk it is approximately 135 (using 2002 PCT at tier 3) and 68 (using 1992 PCT at tier 3). The iprodione acute risk tier 1 and tier 3 ratio for 1-2 y.o. is 2.3 (1992 PCT at tier 3) and 5.5 (2002 PCT at tier 3).

The chronic exposure estimates for iprodione on peaches shown in Figures 4.4a and 4.4b declined significantly from tier 1 to tier 3 in these analyses. From tier 1 to tier 2 the %RfD decreased from ~48-54%RfD to ~29-33%RfD (using higher percent crop treated from 1992) and ~14-17%RfD (using the lower percent crop treated) and declined further to <1% at tier 3 for ages 1-2. Within the tier 2 and tier 3 levels, the exposure levels varied due to the percent crop treated values used in the analyses. Higher exposure estimates were derived using the 1992 PCT (with higher percent crop treated) compared to using the 2002 PCT (with lower percent crop treated).

The carcinogenic property of iprodione is the major concern for dietary risk, although risk from its endocrine effects has yet to be fully evaluated. Figure 4.7 shows the cancer risks for iprodione on peaches and these follow the same declining trend with tier level as the acute and chronic exposures. At tier 1, the cancer risk for peaches is

$1x10^{-4}$ which is considerably greater than the $1x10^{-6}$ guideline and would cause cancer risk concerns at this level of analysis. The cancer risks decrease, as expected as the tier level inputs become more refined. At tier 3 the cancer risk is significantly lower and ranged from $1.4x10^{-6}$ to $7.5x10^{-7}$ and is less than the $1x10^{-6}$ guideline for level of concern. This indicates that the several regulatory actions taken to reduce exposure to acceptable levels were successful. But it should be noted that additional exposure and risk can come from dietary residues of iprodione from additional food uses, e.g. grapes and almonds and a number of other fruits and vegetables.

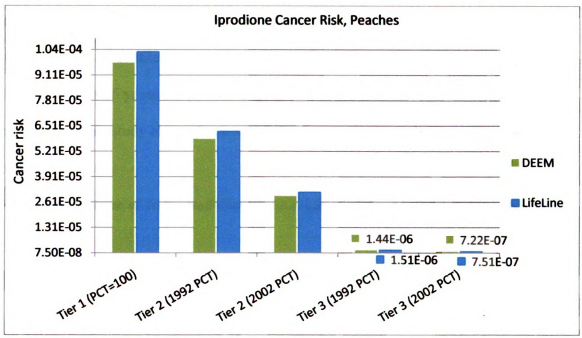


Figure 4.7. Iprodione cancer risk for peaches.

The effect of the exposure refinements underlying the increasing tier levels seen here were generally consistent with the results from the study on the comparison of exposures to chlorpyrifos at different levels of refinements of exposure that included tolerance levels, highest field trials residues, residue monitoring data and percent crop

treated conducted by Wright et al. (2002) and Oliver et al. (2000). Results from the study by Wright et al. (2002) showed an approximately 55% reduction in exposure estimates by using tolerance value compared to using the highest field trial value, and inclusion of the percent crop treated "further decreased the exposure estimates" (Wright et al. 2002). The inclusion of food residue measurements from a specially designed market basket study, government-sponsored residue monitoring data, probabilistic methodologies, market share information and food processing data were identified by Wright et al. (2002) as contributing factors to the significant reduction in the estimated exposures at higher tier levels. A study of the effect of higher tiered analysis on the acute dietary risk of chlorpyrifos using DEEM showed a 26-fold decrease in estimated risk from tier 2 to tier 4 at the 99.5th percentile and a 7-fold decrease from tier 3 to tier 4 at the 99.9th percentile for children 1 to 6 years old (Oliver et al. 2000). These trends are also consistent with the results from this study although, as noted, the degree of change between tiers varies from study to study.

4.6.2 *Comparison of Estimated Exposures from the DEEM and LifeLine Assessment Models*

The DEEM and Lifeline programs use quite different approaches in modeling dietary exposure and would not be expected to give exactly the same results. Despite these differences, this study shows that the exposure estimates from DEEM and from LifeLine are closely comparable with a difference of only ~5% in most cases. This is consistent with the findings of the EPA Scientific Advisory Panel (SAP) on the comparison of the dietary risk assessment models which, using a hypothetical data set, showed "close agreement between DEEM and LifeLine estimated exposures" and "little

substantive difference" between exposures predicted by the two computer softwares (U.S.EPA 2004). In a few cases, differences > 5% were seen e.g. DEEM tends to give higher exposure estimates for the 50+ years old age group than LifeLine (e.g. Figures 4.2 and 4.5) but this was not the case in all comparisons. Differences in %RfD of >5% between the two models were only found for iprodione on stone fruits (ages 1-2) at tier 1, with differences in %RfD of 11% and 14% for acute and chronic exposures (Appendix E), respectively; 9% at tier 2 (1992 PCT) chronic exposures on stone fruits and 6% at the tier 1 chronic analysis on peaches for the same age group. However, the cancer risk estimates for iprodione on peaches using DEEM and LifeLine were almost exactly the same as shown in Figure 4.7. The fact that the results from the two programs are remarkably similar despite their different methodologies tends to give confidence that the risk estimates are realistic.

4.6.3 *Dietary Risk Before and After the FQPA*

The dietary risk comparison and trend analysis from before and after the FQPA were based on the tier 3 acute analysis (Figure 4.3). The acute risk levels from using the 1995 PDP residue level (representing pre-FQPA) were highest (15%RfD for ages 1-2) and follow an overall decline after the FQPA, i.e. 9 to 11%RfD (2000 PDP residue level) and 6 to 7%RfD (2006 PDP residue level) for the same age group, even though these exposures were not at the level of concern even before the FQPA. A similar drop in risk is seen with the chronic exposure to iprodione in 2002 compared to 1992 (Figures 4.4a and 4.4b). This is due to lower percent crop treated values in 2002 (30%) compared to that in 1992 (60%). Both the acute and chronic data reveal that the estimated risks are highest for children from ages 1 to 2 and this is followed by the risk from ages 3 to 5.

Risks to other age groups and the population in general tend to be much lower. This arises from the high consumption of peaches and other stone fruit by infants and young children and underlines the importance of giving special consideration to these age groups in assessing and reducing risk. This distinction would be lost in simpler risk assessments that utilize average consumption data for the population as a whole. Overall, the younger age groups tend to have higher exposure estimates than the other subpopulations.

One source of uncertainty in these estimates lies in the substitution of ½LOD for the non-detects in samples from treated crops, as typically practiced by EPA. In 1995, 2000 and 2006, the ½LODs for iprodione on peaches were 30%, 37% and 57%, respectively of the total non-zero values used in the assessment. The assumption of ½LOD could have driven most of the exposure estimates especially in 2006 when more than half of the residue values used in the assessment were ½LODs, and this might tend to overestimate actual residue levels and risk. Also, Monte Carlo techniques were used at this level of analysis and different results are likely for each run since different sets of variables (e.g. consumption) are sampled each time the analysis is done. Such variability in results was observed in this study from repeated analyses using the same input parameters, especially for LifeLine, but the variability between runs was 5% or less.

A similar decrease in trend in the dietary exposure and risk estimates of iprodione before and after the FQPA for stone fruits is shown in Appendix E. However, the acute exposure at tier 3 (using the 1995 PDP residue for iprodione) is underestimated since the only available stone fruit residue data for that year was for peaches, thus the exposure estimates (~15%RfD) are the same for peaches and for the stone fruits group. This again

illustrates the problems in obtaining residue data that are recorded on a consistent basis from year to year.

The decline in the risk estimates from before and after the FQPA in this study is consistent with results of the OIG study using the dietary risk index (DRI) approach to measure the impact of the FQPA (U.S.EPA-OIG 2006a), e.g. the DRI for chlorpyrifos on apples show a large decrease in exposure, and thus in risk. The DRI decreased by 98% in 1996 to 4% in 2002 due to strong regulatory actions specifically intended to reduce chlorpyrifos residues on apples. Although the DRI approach is questionable in assessing overall risk from multiple compounds or residues in multiple crops because the additivity of the risks cannot be assumed, it is a more reasonable approach to assessing changing risk from single pesticides on a single crop.

4.6.4 *Dietary Risks of Iprodione Compared to Fludioxonil*

The fludioxonil acute and chronic exposure estimates for peaches are shown in Figures 4.5 and 4.6 and in Figures 4.2 to 4.4 for iprodione. None of these three tier estimates for either compound would give cause for regulatory concern. However, the mechanisms of toxicity for iprodione and fludioxonil are different and the uncertainty factors used were also different (i.e. chronic FQPA factor=3X for iprodione) and do not allow for a direct comparison of the acute and chronic risk estimates of the two pesticides. But the most significant risk reduction is that the cancer and endocrine disruptor effects are eliminated where fludioxonil has replaced iprodione. Although regulatory actions were taken after FQPA to reduce the cancer risk estimates to less than 1×10^{-6} for iprodione, as illustrated in Figure 4.7, this involved the cancellation of its

uses on stone fruit for all postharvest uses, and the modification of its uses for preharvest applications.

4.6.5 *Generalizability of the Iprodione-Fludioxonil Case Study*

The significant impact of the replacement of several iprodione uses with fludioxonil is the lack of iprodione's potentially serious carcinogenic (and possibly its endocrine-disrupting) properties. To what degree is this conclusion generalizable in assessing the impact of the FQPA? Each case is different in detail, and the extent to which the use of older compounds have been reduced and replaced in specific uses by the reduced-risk chemicals is often partial, complex, and difficult to analyze. However there is reason to believe that on a broader level the case study developed here is a reasonably typical representation of the contribution of the FQPA to food safety.

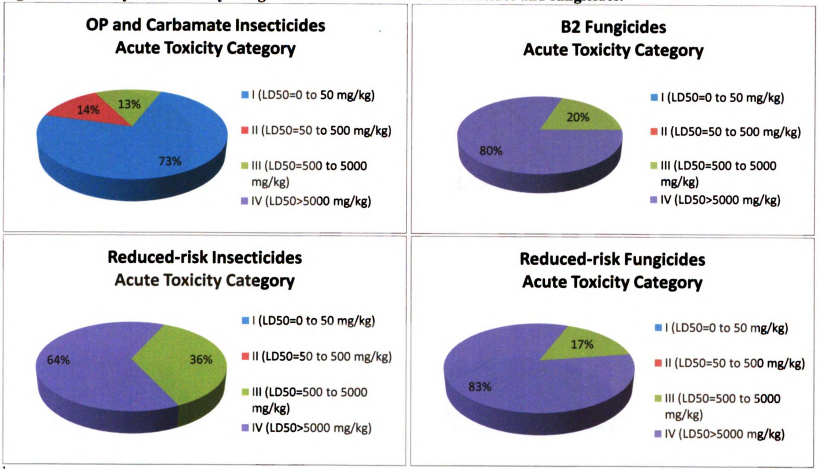
To enable a broad comparison, the toxicological properties of typical FQPA target compounds and their reduced-risk replacements were collected in Appendix B and are shown graphically in Figures 4.8 and 4.9. Figure 4.8 shows the dietary acute categories and Figure 4.9 shows the cancer classifications of the compounds. The cancer classification guidelines have undergone several revisions and changes since they were first introduced in 1986. There have been three sets of guidelines used by the EPA for classifying carcinogenic potential (the 1986, 1996 and 2005 guidelines). As a result of the revisions, chemicals have been given cancer classifications depending on the year they were evaluated and which classification guidelines were being used at that time. The different pesticides considered in this study have classifications based on all the three guidelines, which makes direct comparisons difficult. According to the EPA, the different designations "cannot be directly compared" and "the designation for any

substance must be considered in the context of the system under which it was reviewed" (U.S.EPA 2006). For the purpose of this study (that is to show and compare the overall carcinogenic properties of the old compounds and the newer pesticides) the cancer classifications for the pesticides were simplified to lessen the number of categories. The carcinogenic classifications that are as reasonably close as possible in their descriptions were combined and grouped into five "clusters". However, these "clusters" do not imply that the classifications across the three carcinogenic guidelines are equivalent.

Table 4.5. Carcinogenic "clusters" based on the 1986, 1996 and 2005 cancer classification guidelines.

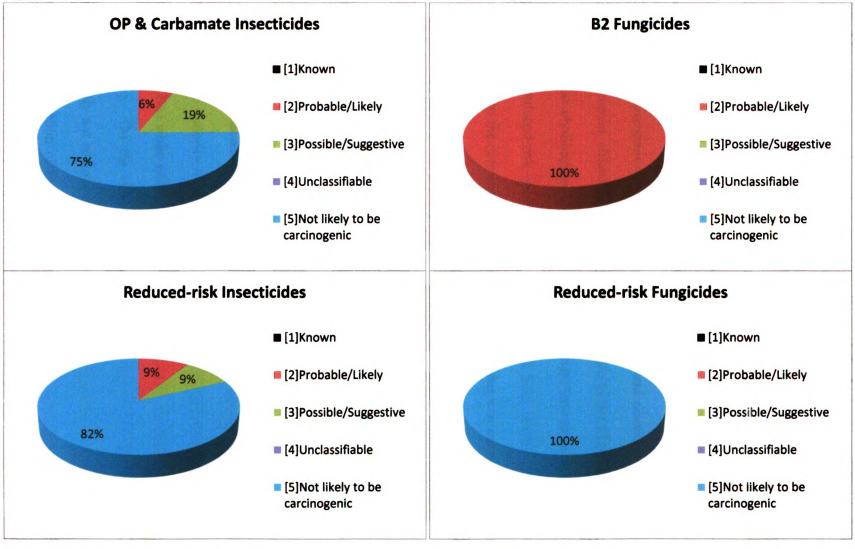
Cluster	Cancer Classification Guidelines		
	1986	1996	2005
[1] Known	A-human carcinogen	Known/Likely	Carcinogenic to humans
[2] Probable/Likely	B (B1 & B2)-probably human carcinogen		Likely to be carcinogenic to humans
[3] Possible/ Suggestive	C-possible human carcinogen		Suggestive evidence of carcinogenic potential
[4] Unclassifiable	D-not classifiable as to human carcinogenicity	Cannot be determined	Inadequate information to assess carcinogenic potential
[5] Not likely to be carcinogenic	E-evidence of non-carcinogenicity for humans	Not likely	Not likely to be carcinogenic to humans

Figure 4.8. Dietary acute toxicity categories[1] of the old and new insecticides and fungicides.



[1] *I=highly toxic, II=moderately toxic, III=slightly , IV=not acutely toxic*

Figure 4.9. Carcinogenic "clusters" of the old and new insecticides and fungicides.



Appendix B shows the differences in the toxicity properties of the old and the reduced-risk insecticides and fungicides. The OPs are generally cholinesterase inhibitors and exhibit neurological and, sometimes, developmental effects. They are all on the Endocrine Disruptor Screening Program (EDSP) draft list except for fenamiphos and fonofos, but most are not likely to be carcinogens. The NMCs are neurotoxic/cholinesterase inhibitors and are also included in the EDSP draft list but are not likely to be carcinogenic. Besides causing carcinogenic and developmental effects, the B2 fungicides captan, chlorothalonil and iprodione are also in the EDSP draft list but are not classified as cholinesterase inhibitors and tend to have low acute toxicities. By comparison, the reduced-risk insecticides raise fewer and less intense toxicological concerns compared to the conventional pesticides, often offering a much higher level of safety in standard animal tests. These insecticides are not cholinesterase inhibitors and are classified as OP alternatives by the EPA, most are "not likely" to be carcinogens, and they do not exhibit developmental or serious neurological toxicity. The reduced-risk fungicides have low acute toxicities, are non-cholinesterase inhibitors, non-carcinogenic and no evidence of developmental effects were shown from studies for most of them.

Figure 4.8 shows more specifically the dietary acute toxicity categories of the OP and NMC, and the reduced-risk insecticides, and the B2 carcinogenic and the reduced-risk fungicides. The majority of the OPs and the NMCs are classified as highly acutely toxic/category I (73%) while 64% of the reduced-risk insecticides belong to category IV (not acutely toxic). On the other hand, the B2 carcinogenic and the reduced-risk fungicides are mostly not acutely toxic (category IV) (80% and 83%, respectively). The carcinogenic classification of the old and the new pesticides are shown in Figure 4.9.

Most of the OPs and NMCs (75%) and the reduced-risk insecticides (82%) and all the reduced-risk fungicides belong to the "not likely to be carcinogenic" cluster.

From these comparisons it can be concluded that the differences between the toxicological properties of iprodione and fludioxonil are quite typical of the B2 carcinogenic fungicides and their replacements (Figures 4.8 and 4.9). The risks from the OPs and the NMCs are more closely related to their high acute toxicities and neurotoxic effects. However, the reduced-risk replacement compounds are much more selective in their toxicity to insects and very much safer to vertebrates (Appendix B). Although they are not entirely lacking in hazard, particularly environmentally, the decrease in acute toxicity is of such a magnitude and their residue levels low enough, that, in practice, they appear to present no realistic dietary risk. As the use of many of the most toxic OPs and NMCs has been eliminated or greatly reduced, and their residues in the food supply have declined, risk has declined accordingly as shown by the data on the reduction in risk from specific OPs in the diet presented in the EPA-OIG report using the DRI approach. At the same time, the use of the reduced-risk insecticides has correspondingly increased without introducing significant dietary risks, and, although the quantitative assessment of this trend would be very difficult if not impossible on a comprehensive basis, it is inevitable that these responses to FQPA have enhanced the safety of the U.S. food supply.

4.7 Conclusion

Establishing dietary risk trends requires comprehensive, consistent and continuous residue data. The publicly-available PDP database has national residue coverage while the CA-DPR database covers mostly California-based commodity residue data only. Both databases are used for several purposes but they are not primarily set up for use in dietary risk trend analysis. There is lack of continuity in the commodities sampled because they vary each year, and the analytical sensitivity changes with time, which makes establishing both residue and dietary risk trends difficult. This probably is a factor leading to the conclusion of EPA-OPP (U.S.EPA-OIG 2006a, b) that despite considerable effort, they have been unable to develop a scientifically sound method that uses available data to assess the public health impacts of their regulatory program. A database designed to serve this purpose is needed and would be very useful to analyze and determine how the dietary risks from pesticides have changed over the years and to provide a gauge on how the implementation of regulations such as FQPA has succeeded in its primary goal of changing dietary exposure, particularly for infants and children.

The tiered analysis of exposure is an integral part of the EPA's pesticide regulatory methodology. In this study, the exposure estimates at the different tier levels, both for acute and chronic assessments, vary and tend to decrease as the tier level gets higher wherein the input parameters become more realistic (i.e. residue monitoring data and adjustment factors). However the degree of decrease is very variable from case to case. Where the decrease in estimated risk is considerable as the tier level increases, the initial estimates provided by lower tier analysis, while clearly useful for the initial

evaluation of the need for regulation, do not accurately represent the actual risk and can be seriously misleading if presented publicly without further explanation.

The use of actual residue monitoring data and percent crop treated values from various years at the tier 3 level allowed for a comparison of the dietary risk estimates before and after the FQPA. The decrease in the acute risk estimates for iprodione at the tier 3 level before and after the FQPA, even though they were not at the level of concern even before the FQPA, denotes regulatory consequence of the FQPA. This is an indication of lower residues detected and regulatory actions to decrease the use of iprodione over time.

There were differences in the exposure estimates derived from the DEEM and LifeLine programs, but overall the results were closely comparable and it is unlikely that they would provide results that differ enough to create a regulatory dilemma. The differences were due to the significant variations in how these programs model exposure. In those situations where these programs utilize Monte Carlo methodology, the variability inherent in this method approaches that typically seen between the DEEM and Lifeline estimates.

The differences in the mechanism of toxicity of iprodione and fludioxonil did not allow comparison in the risk estimates between the two compounds. Although iprodione presents little realistic acute toxic risk, it is both a carcinogen that can present unacceptable levels of risk and has endocrine disruptor properties that have not yet been fully evaluated. These risks are eliminated through its replacement by fludioxonil. Fludioxonil is virtually devoid of acute toxic risk and the regulatory endpoint for its chronic toxicity is failure to gain weight without distinct pathology. Further, the actual

residue levels of fludioxonil in stone fruits are well below those calculated to be safe for lifetime consumption. These contrasting toxicological profiles are quite typical of the older and the reduced-risk replacement compounds, and in this respect, the case study here may have broader applicability. This analysis suggests that, although the results will not be numerically identical with other crops and chemicals, the general results obtained here with iprodione and fludioxonil may reasonably represent the kind of decrease in dietary risk associated with the broader replacement of the B2 carcinogens and anticholinesterases with other reduced-risk pesticides. This example illustrates the contribution that FQPA has made to enhancing the safer use of pesticides and to the significant role of the IR-4 program in ensuring that these reduced-risk materials are broadly available to the growers of many fruit, vegetable and nut crops.

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CHAPTER 5
SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

The passage of FQPA resulted in major regulatory changes for pesticides. Some of these changes include added requirements to reregister pesticides (with focus on older compounds-OPs, NMCs and B2s), requirement of aggregate and cumulative risk assessments, an additional safety factor for the protection of infants and children, and the expedited registration of uses of reduced-risk and OP replacement pesticides. These requirements effected significant changes in the use of both traditional and reduced-risk pesticides but only a few studies have been published to show these changes. In this study, the trends in use of these pesticides were assessed since the FQPA was passed in 1996 using data from the California Department of Pesticide (CA-DPR) and the CropLife Foundation (CLF) databases. These sources showed an overall substantial decrease in the use of the anticholinesterases, OPs (50%) and the NMCs (70-75%), the two pesticide groups that were the initial focus of regulatory action, over the years from 1992 to 2006. However, the use of some of the individual pesticides in these classes (eg. chlorpyrifos and oxamyl) remained high or showed less decline. Conversely, the reduced-risk insecticides showed a consistent increasing trend in use and are now a central part of pest management in fruit and vegetable production. This trend fits well with the declining use of the OPs in view of the fact that most of the reduced-risk insecticides are OP replacements. On the other hand, the use of the B2 fungicides declined by only 10-20% since the enactment of the FQPA. Despite their carcinogenic potential, their use and residues in most cases have not been found to be at levels of regulatory concern by the EPA. They also have the advantages of low cost, low resistance potential and broad

spectrum activity against pathogens. The reduced-risk fungicides have also shown a regular increase in use since the FQPA that can be attributed to very high efficacy compared to the older B2 pesticides and in some case their systemic action and more desirable spectrum of activity.

The application rates (lbs/application) of the reduced-risk pesticides were found to be significantly lower (5 to 10-fold) than the older pesticides. These lower application rates combined with the substantial decline in use of the anticholinesterases and, to a lesser degree, the B2 fungicides, have led to an overall decrease in the amount of pesticides applied in the production of fruits, vegetables and nut crops. In combination with the improved toxicological profiles of the reduced-risk compounds, this is likely to lead to lower environmental impacts. It was concluded that the USDA IR-4 minor use pest management program was responsible for obtaining approximately 50% of these reduced-risk registrations.

The changes in the residue detection since the passage of the FQPA were also examined for both the traditional and newer pesticides using the USDA Pesticide Data Program (PDP) and the California Department of Pesticide Regulation (CA-DPR) databases. The residue data for the OPs, NMCs and the B2s showed considerable year-to-year variability which tended to obscure trend analysis. The OPs, however, still showed an overall decline in residue detection frequency with individual OPs such as azinphos-methyl and methyl parathion having a more distinct downward trend since they have been subject to the most rigorous regulatory actions. The lack of an overall decline in the residue detection trend for the B2 fungicides corresponds to their modest decline in use. However, the lack of an obvious decrease in residue detections for the NMCs does

not correspond to the steep decline in their use. The reason for this is not clear. Some of the individual reduced-risk pesticides such as imidacloprid, acetamiprid and tebufenozide showed unexpectedly high percent detects. These higher detections can be due to applications that are made close to harvest, and in part, to the systemic properties of some of these pesticides, particularly those with substantial use on fruits and vegetables. However, the record for residue detections for the reduced-risk compounds is brief and several of the detection rates were low and variable, which make establishing a trend difficult.

Little has been published that examines the impact of the FQPA on pesticide exposure and dietary risks. The risk assessment process has evolved from the use of deterministic to probabilistic methods of analysis. The newer processes are more complex but are more realistic, give information regarding the distributions of exposures and risks, and now are widely employed. The following study used two probabilistic risk assessment programs, DEEM and Lifeline. The EPA's tiered approach in assessing dietary risk was employed to determine changes in a dietary risk from iprodione and fludioxonil on stone fruits using residue data from 1995 to 2006. The risks tend to be lower as the tier level gets higher because of more refined and realistic input parameters. In this study, the results from the use of the tiered approach showed that the dietary risk varies at different tier levels and proved that the use of more realistic inputs (i.e. residue monitoring data and residue adjustment factors) tend to result in lower risk estimates. For this reason, the tier 1 risk estimates should not be taken as actual risk estimates, but they are useful for initial regulatory evaluation. The dietary risk assessments were conducted

using the DEEM and LifeLine programs. The results using these different models for assessing exposure and risk were comparable with less than 5% difference in most cases.

The fludioxonil-iprodione case study was used to assess the changes in the dietary risk from replacing an older compound with an IR-4-registered pesticide and how risk has changed since the FQPA was enacted. Fludioxonil has replaced iprodione in its postharvest uses on the stone fruits group and for peaches as an individual crop, and the use of iprodione for preharvest treatment has also been restricted. The reference dose (RfD) was used as a gauge for the potential effects of pesticides at other doses but, as the EPA noted, it should not be "categorically concluded that all doses below the RfD are 'acceptable' or will be risk-free, and that all in excess of the RfD are 'unacceptable' or will result in adverse effects". Although limited, this is a reasonable and useful approach for now. However, the differences in the mechanism of toxicity between fludioxonil and iprodione do not allow for comparison of the risk estimates of these two compounds. But the significant contribution to food safety is the elimination of cancer risk from the replacement of iprodione with fludioxonil (which was registered by IR-4 for use on stone fruits group) for post harvest uses. The acute dietary risk estimates from iprodione have been shown to decrease after the passage of FQPA (15% of the RfD and 7% of the RfD, using 1995 and 2006 PDP residue data, respectively) even though they were not at the level of EPA concern even before the FQPA. The reduction in the dietary risk results from the post-FQPA decrease in use of iprodione which lowered residues. It is also representative of the kind of decreased dietary risk that comes from the use of reduced-risk pesticides as replacement for older compounds.

This study utilized the publicly-available databases such as the PDP, CA-DPR and the CLF databases for the use, residue and dietary risk trend analyses. Each of the databases follows a different protocol in their monitoring methods and thus, does not allow for cross-database analysis. Overall, these databases are not set up for trend analysis. There is a lack of continuous and comprehensive national use and residue data. The type and quantity of crops sampled vary each year and make the data discontinuous. These factors make establishing trends in use, residue and dietary risk difficult.

This study is a preliminary attempt at analyzing the changes in pesticide use, residue detection and dietary risk as a result of the enactment of the FQPA. However, the findings in this study can be further expanded through the following recommendations:

1. There is a need for a more comprehensive database for pesticide use with a national coverage that can be used for trend analysis. This would require use data to be gathered annually on a defined series of key food crops. The sampling method should be developed to give reasonable coverage of all significant growing areas in the U.S. For example, the expansion of the use data collection of the National Agricultural Statistics Service (NASS) database would be a significant source of data for assessing and establishing pesticide use trends and the resultant changes brought about by regulatory changes. In addition, the data provided by NASS is publicly-available compared with privately-owned databases such as the very expensive Doane Survey. Unfortunately previous attempts to expand the NASS database in this way have not been strongly supported by potential users.
2. There is also a need for residue databases with more consistent sampling size and more uniform types of crops sampled every year to parallel the more comprehensive

use data. The PDP database has a national coverage and maintains annual residue reports for various crops, but lacks consistency in the type and size of crops sampled each year that makes establishing trends difficult. Identifying the key crops grown in different parts of the U.S. and the consistent sampling of these commodities would greatly enhance the residue database and this could be utilized to more accurately assess the status of and changes in dietary risk with time and as a result of specific regulatory actions.

3. It is impossible to develop a single index to indicate the overall level of risk posed by dietary pesticide residues, and how this changes with time, because there are many different toxicological endpoints for these compounds so that estimated risks cannot be combined together to provide a single value. However, it should be possible to conduct such a continuing study for groups of compounds with a common mechanism of toxicity and to follow these compounds as a group using the relative potency factor approach to allow normalization of the data from different compounds. This approach is illustrated by the cumulative risk assessment for organophosphates conducted by EPA (2002) (Organophosphate Pesticides: Revised Cumulative Risk Assessment http://www.epa.gov/opp00001/cumulative/rra-op/). In the simplest case, this cumulative assessment would require an assumption of additivity for the normalized exposures to the several compounds, which may well be an approximation, but overall, this analysis conducted consistently and at regular intervals, would provide a better insight into the direction and magnitude of changes in dietary risk than any we now have available.

APPENDICES

APPENDIX A
Preliminary Selected Pesticides

List of Preliminary Selected Pesticides

B2 Carcinogens	OPs	NMCs	Reduced-risk Fungicides	Reduced-risk Insecticides
1. captan	1. acephate	1. aldicarb	1. azoxy-strobin	1. acetamiprid
2. chloro-thalonil	2. azinphos methyl	2. bendio-carb	2. cyprodinil	2. bifenazate
3. folpet	3. chlorpy-rifos	3. carbaryl	3. fenhexamid	3. buprofezin
4. iprodione	4. coumaphos	4. carbofuran	4. fludioxonil	4. cinnam-aldehyde
5. mancozeb	5. DDVP (dichlor-vos)	5. formet-anate HCl	5. mefenoxam	5. fipronil
6. maneb	6. demeton	6. methio-carb	6. trifloxy-strobin	6. hexaflum-uron
	7. diazinon	7. methomyl		7. imida-cloprid
	8. dicroto-phos	8. oxamyl		8. indoxacarb
	9. dimethoate	9. propoxur		9. novaluron
	10. disulfoton	10. thioben-carb		10. methoxy-fenozide
	11. ethion	11. thiodicarb		11. pymet-rozine
	12. ethoprop			12. pyripro-xifen
	13. fenamiphos			13. spinosad
	14. fenthion			14. tebufen-ozide
	15. fonofos			15. thiameth-oxam
	16. malathion			
	17. metham-idophos			
	18. methida-thion			
	19. methyl parathion			
	20. naled			
	21. oxydem-eton methyl			
	22. parathion			
	23. phorate			
	24. phosalone			
	25. phosmet			
	26. profenofos			
	27. sulfotep			
	28. sulprofos			
	29. tetrachlor-vinphos			
	30. trichlorfon			

APPENDIX B
Pesticide Toxicity Properties

Appendix B.1. Toxicity properties of the organophosphates insecticides

OPs	Acute Oral Toxicity[i]	Cholin-esterase Inhibitor[ii]	Carcin-ogen	Developmental or Reproductive Toxicity	EDSP Draft List[iii]	Other Toxicity[iv]	Top crops and sites in California[v]	FQPA Factor
1.Acephate	III; LD_{50} 1.4 g/kg (male rat) [1]	Yes	Possibl e [2]	No increased sensitivity to fetuses and pups [1]	Yes	↑H,B [1]	Head lettuce, cotton, celery, structural pest control, outdoor container nursery	1X [1]
2.Azinphos-methyl	I: LD_{50}= 4.6 mg/kg (rat) [3]	Yes	Not Likely [3]	No increased susceptibility in fetuses or pups-[3]	Yes	↑ B,M; W; Concerns for MF, FF, AI; [3]	almonds, apples, pistachios, pears, walnuts	1X [3]
3.Chlorpyrif os	II; LD_{50}= 223 mg/kg [4]	Yes	Not Likely [2]	Increased susceptibility and sensitivity among neonates [4]	Yes	W; ↑●F,AI [4]	Cotton, oranges, almonds, alfalfa for forage, walnuts	10X [4]

[i] Fact Sheet; I=highly toxic, II=moderately toxic, III=slightly toxic, IV=not acutely toxic

[ii] PAN. Pesticide Action Network.

[iii] Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the FFDCA. Endocrine Disruptor Screening Program (EDSP), U.S. EPA, 2007.

[iv] ↑=high toxicity; ●=moderate toxicity; ↓=low toxicity. FF=freshwater fish; FI=freshwater invertebrates; MF=marine fish; MI=marine invertebrates; AI=aquatic invertebrates; AO=aquatic organisms; TO=terrestrial organisms; M=mammals; F=fish; B-birds; H=honeybees; W=worker exposure/concern

[v] CA-DPR 2005 Use data

Appendix B.1...cont'd.

4.Diazinon	III; LD_{50}= 1250 mg/kg (rat) [5]	Yes	Not Likely [2]	No increased susceptibility to fetuses [5]	Yes	↑B,H,FF,FI [5]	Leaf lettuce, head lettuce, almonds, broccoli, spinach	1X [5]
5.Dimeth-oate	II; LD_{50}= 358 mg/kg(male rat), 414mg/kg (female rat) [6]	Yes	Possible human carcinogen [6]	Rat pup mortality observed at very low levels of exposure from a developmental neurotoxicity study [6]	Yes	↑FI,B •FF,M (RED,2006)	Alfalfa for forage, Tomatoes for processing, oranges, corn for forage, broccoli	1X (RED, 2006)
6.Disulfoton	I; LD_{50}= 6.2mg/kg (M,rat),1.9mg/kg(F, rat) [7]	Yes	Not Likely; E [2]		Yes	W [7]	Asparagus, outdoor propagation nursery, broccoli, bell peppers, cabbage	1X [7]
7.Fenami-phos	I; LD_{50}= 2.7mg/kg (M,rat), 3.0mg/kg (F, rat) [8]	Yes	Unlikely [8]		No	↑B,M,AO, H [8]	Table and raisin grapes, wine grapes, cherries, oranges, kiwis	1X [8]

Appendix B.1...cont'd.

8.Fonofos	I; LD_{50} = 6.8-18.5mg/kg (F,rat); 3.2-7.9mg/kg (M,rat) [9]	Yes	No evidence [10]		No	↑B, AO [10]	Bell peppers	NA [10]
9.Methamid-ophos	I; LD_{50}= 15.6mg/kg (rat) [11]	Yes	Unlikely [2]	Neuropathology reported in hens and humans in open scientific literature [11]	Yes	W; ●FF (IRED, 2002)	Alfalfa for forage, cotton, tomatoes for processing, potatoes, tomatoes	3X [11]
10. Methida-thion	I; LD_{50}= 25-54 mg/kg (rat) [12]	Yes	Possible [13]		Yes	↑B [13]	Artichokes, oranges, almonds, peaches, olives	1X [13]
11. Methyl parathion	I; LD_{50}= 4.5-24mg/kg (rat) [14]	Yes	Not Likely [2]	Neuropathology seen in experimental animals [14]	Yes	B, H, humans	Walnuts, onions, succulent beans, cherries	10X [14]

Appendix B.2. Toxicity properties of *N*-methylcarbamate insecticides

NMCs	Acute Oral Toxicity[i]	Cholin-esterase Inhibitor[ii]	Carcin-ogen	Developmental or Reproductive Toxicity	EDSP Draft List[iii]	Other Toxicity[iv]	Top crops and sites in California[v]	FQPA Factor
1.Aldicarb	I; LD_{50}= 0.5-1.5mg/kg (liquid; rats, mice,rabbit) [15]	Yes	Unlikely [2]	Brain cholinesterase inhibition approximately 2 times greater in young rat compared to adult rat at similar acute doses [16]	Yes	↑AO,TO [16]	Cottons, pecans, soil preplant, dried beans, sorghum	2X [16]
2.Carbaryl	II; 301 mg/kg (rat) [17]	Yes	Likely to be carcinogenic to humans [17]	Low level of concern for evidence of susceptibility in developmental neurotoxicity study [17]	Yes	↑H,MI,F [17]	Oranges, olives, apples, peaches, pistachios	1X[17]

[i] Fact Sheet; I=highly toxic, II=moderately toxic, III=slightly toxic, IV=not acutely toxic

[ii] PAN. Pesticide Action Nework.

[iii] Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the FFDCA. Endocrine Disruptor Screening Program (EDSP), U.S. EPA, 2007.

[iv] ↑=high toxicity; ●=moderate toxicity; ↓=low toxicity. FF=freshwater fish; FI=freshwater invertebrates; MF=marine fish; MI=marine invertebrates; AI=aquatic invertebrates; AO=aquatic organisms; TO=terrestrial organisms; M=mammals; F=fish; B-birds; H=honeybees; W=worker exposure/concern

[v] CA-DPR 2005 Use data

Appendix B.2...cont'd.

3.Carbo-furan	I; LD_{50}=7.8 mg/kg (rat) [18]	Yes	Not Likely [18]	Evidence of qualitative increased susceptibility in rat multi-generation reproduction study; No evidence of increased susceptibility of developmental fetuses in rat and rabbit studies [18]	Yes	↑M,FF,MI [18]	Alfalfa for forage, wine grapes, outdoor propagation nursery, oats, artichokes	5X [18]
4.Methomyl	I;LD_{50}= 34mg/kg (M, rat), 30mg/kg (F,rat); [19]	Yes	Not likely [19]	No evidence of developmental toxicity [19]	Yes		Alfalfa for forage, corn, head lettuce, leaf lettuce, sugarbeets	3X [19]
5.Oxamyl	I;LD_{50}=5.4 mg/kg (rat) [20]	Yes	Unlikely [2]		Yes	↑ B, M [21]	Celery, celery, bell pepper, tomatoes, onions	1X [21]

Appendix B.3. Toxicity properties of the B2 carcinogenic fungicides

B2 Carcinogenic Fungicides	Acute Oral Toxicity[i]	Cholin-esterase Inhibitor[ii]	Carcinogen	Develop-mental or Reproductive Toxicity	EDSP Draft List[iii]	Other Toxicity[iv]	Top crops and sites in California[v]	FQPA Factor
1.Captan	IV; LD_{50}=9g/kg (rat) [22]	No	$Q_1^* = 2.4x10^{-3}$ $(mg/kg/day)^{-1}$ [22]	Causes developmental effects at maternally toxic doses [22]	Yes		Strawberries, almonds, prunes, table and raisin grapes, outdoor propagation nursery	1X [22]
2.Chloro-thalonil	IV; LD_{50} > 10,000 mg/kg (rat) [23]	No	Q_1^*= $7.66x10^{-3}$ $(mg/kg/day)^{-1}$ [23]	Developmental effects occurred only in the presence of significant maternal toxicity [23]	Yes	↑F [23]	Tomatoes for processing, landscape, onions, almonds, potatoes	1X [23]

[i] Fact Sheet; I=highly toxic, II=moderately toxic, III=slightly toxic, IV=not acutely toxic

[ii] PAN. Pesticide Action Nework.

[iii] Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the FFDCA. Endocrine Disruptor Screening Program (EDSP), U.S. EPA, 2007.

[iv] ↑=high toxicity; ●=moderate toxicity; ↓=low toxicity. FF=freshwater fish; FI=freshwater invertebrates; MF=marine fish; MI=marine invertebrates; AI=aquatic invertebrates; AO=aquatic organisms; TO=terrestrial organisms; M=mammals; F=fish; B-birds; H=honeybees; W=worker exposure/concern

[v] CA-DPR 2005 Use data

Appendix B.3...cont'd.

3.Iprodione	III; LD_{50} = 4468 mg/kg (rat) [24]	No	Q_1^* = 4.39×10^{-2} [24]		Yes	↑● FI; ●MF, MI Invert-ebrates [24]	Almonds, head lettuce, leaf lettuce, carrots, peaches	3X for fe-males 13+ [24]
4.Mancozeb	IV; LD_{50} > 5000 mg/kg [25]	No	Q_1^*=0.0601 $(mg/kg/day)^{-1}$ (Q*is that of ETU) [25]	Concern for developmental neurotoxicity [25]	No	↑F,AI [25]	Onions, table raisins and grapes, wine grapes, tomatoes for processing, potatoes	1X [25]
5.Maneb	IV; LD_{50} > 5000 mg/kg (rat) [26]	No	Q_1^*=0.0601 $(mg/kg/day)^{-1}$ (Q*is that of ETU) [26]	Decreased fetal viability observed [26]	No	↑FF, MF, FI, MI	Walnuts, head lettuce, leaf lettuce, almonds, onions	1X [26]

Appendix B.4. Toxicity properties of reduced-risk insecticides

Reduced-risk Insecticides	Acute Oral Toxicity[i]	Cholin-esterase Inhibitor[ii]	Carcin-ogen	Developmental or Reproductive Toxicity	EDSP Draft List[iii]	Other Toxicity[iv]	Top crops and sites in California[v]	FQPA Factor	Reduced-risk/OP Alternative[vi]
1.Aceta-miprid	III (IV); [27]	No	Not likely [27]	No evidence of neurotoxicity; Increased susceptibility following pre-/postnatal exposure in rats [27]	No	↓ M [27]	Cotton, leaf lettuce, head lettuce, tomatoes for processing, apples	3X [27]	RR/OP alt.
2.Bifenazate	IV; LD_{50}> 5000 mg/kg (rats) [28]	No	Not likely [29]		No	Toxic to fish [28]	Table and raisin grapes, almonds, wine grapes, strawberries, cotton	1X [28]	RR/OP alt.

[i] Fact Sheet; I=highly toxic, II=moderately toxic, III=slightly toxic, IV=not acutely toxic

[ii] PAN. Pesticide Action Nework.

[iii] Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the FFDCA. Endocrine Disruptor Screening Program (EDSP), U.S. EPA, 2007.

[iv] ↑=high toxicity; ●=moderate toxicity; ↓=low toxicity. FF=freshwater fish; FI=freshwater invertebrates; MF=marine fish; MI=marine invertebrates; AI=aquatic invertebrates; AO=aquatic organisms; TO=terrestrial organisms; M=mammals; F=fish; B-birds; H=honeybees; W=worker exposure/concern

[v] CA-DPR 2005 Use data

[vi] U.S. EPA, 2008. Reduced Risk/Organophosphate Alternative Decisions for Conventional Pesticides.

Appendix B.4...cont'd.

3.Bupro-fezin	III; LD_{50}> 5000mg/kg (rat) [30]	No	Low carcin-ogenic potential [31]	No indication of neurotoxicity [31]	No	↓M [30]	Table and raisin grapes, oranges, wine grapes, cotton, pistachios	1X [32]	RR/OP alt.
4.Imida-cloprid	III; LD_{50}= 4687 mg/kg (rat) [33]	No	Not likely [34]		Yes	Acutely toxic to some bird species [35]	Structural pest control, landscape, head lettuce, leaf lettuce, table and raisin grapes	1X [36]	OP alt.
5.Indoxa-carb	III; LD_{50}= 1818 mg/kg (m&f, rat) [37]	No	Not likely [37]	Does not cause reproductive or defelopmental effects [37]	No	•B; ↑• FF,FI, MF, MI [37]	Cotton, alfalfa for forage, tomatoes for processing, broccoli, head lettuce	1X [37]	RR/OP alt.
6.Methoxy-fenozide	IV; LD_{50}> 5.0mg/kg [38]	No	Not likely [39]	No appropriate endpoint identified for acute neurotoxicity developmental toxicity [39]	No	•F,FI [38]	Almonds, wine grapes, table and raisin grapes, tomatoes for processing, cotton	1X [39]	RR/OP alt.

Appendix B.4...cont'd.

7.Pymet-rozine	IV; LD_{50}= 5820 mg/kg (m&f, rat) [40]	No	Likely human carcino-gen [40]	Produced developmental effects in pups, but at levels toxic to parents [40]	No	•AI [40]	Broccoli, leaf lettuce, head lettuce, tomatoes, celery	3X [40]	RR/OP alt.
8.Pyriproxy-fen	IV; LD_{50}> 5000mg/ kg [41]	No	No evidence of carcinoge nicity [42]	No indication of neurotoxicity and develop-mental effects [42]	No	•F [2]	Oranges, almonds, cotton, walnuts, strawberries	1X [42]	RR/OP alt.
9.Spinosad	IV; LD_{50}= 3738 mg/kg (m,rat), >5000 mg/kg(f, rat) [43]	No	Not likely [44]	No evidence of development-al and neurotoxic effects	No	↑ F [2]	Oranges, head lettuce, leaf lettuce, table and raisin grapes, strawberries	1X [44]	RR/OP alt.
10. Tebufen -ozide	IV; LD_{50}= 5 g/kg (rat) [45]	No	No evidence of carcinoge nicity [46]	No evidence of neurotoxicity reported [46]	No	• F [2]	Tomatoes for processing, cotton, alfalfa for forage, leaf lettuce, walnuts	1X [46]	RR/OP alt.

Appendix B.4...cont'd.

11. Thia-methoxam	IV; LD_{50}> 5000 mg/kg (f,rat) [47]	No	Not likely [48]	Signs of neurotoxicity in several studies; [48]	No	↑ F [2]	Cotton, commodity fumigation, tomatoes for processing, cantaloupe, bell pepper	1X [48]	OP alt.

Appendix B.5. Toxicity properties of the reduced-risk fungicides

Reduced-risk Fungicides	Acute Oral Tox-icity[i]	Cholin-esterase Inhibitor[ii]	Carcin-ogen	Develop-mental or Reproductive Toxicity	EDSP Draft List[iii]	Other Toxicity[iv]	Top crops and sites in California[v]	FQPA Factor	Reduced-risk/ OP Alter-native[vi]
1.Azoxy-strobin	IV; LD_{50}=> 5000mg/ kg (rat) [49]	No	Not likely		No	↑ FF,FI, MF, MI [49]	Almonds, rice, cotton, wine grapes, wheat	1X [50]	RR
2.Cypro-dinil	IV; LD_{50}=> 5000mg/ kg (rat) [51]	No	Not likely		No	↑ FF,MI • F [51]	Almonds, wine grapes, table and raisin grapes, strawberries, peaches	1X [51]	RR
3. Fenhex-amid	IV; LD_{50}> 5000mg/ kg (rat) [52]	No	Not likely	Evidence of reproductive effects -[52]	No	• FF, MF, FI, MI [52]	Strawberries, wine grapes, table & raisin grapes, cherries, kiwis	3X [52]	RR

[i] Fact Sheet; I=highly toxic, II=moderately toxic, III=slightly toxic, IV=not acutely toxic

[ii] PAN. Pesticide Action Nework.

[iii] Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the FFDCA. Endocrine Disruptor Screening Program (EDSP), U.S. EPA, 2007.

[iv] ↑=high toxicity; •=moderate toxicity; ↓=low toxicity. FF=freshwater fish; FI=freshwater invertebrates; MF=marine fish; MI=marine invertebrates; AI=aquatic invertebrates; AO=aquatic organisms; TO=terrestrial organisms; M=mammals; F=fish; B-birds; H=honeybees; W=worker exposure/concern

[v] CA-DPR 2005 Use data

[vi] U.S. EPA, 2008. Reduced Risk/Organophosphate Alternative Decisions for Conventional Pesticides.

Appendix B.5...cont'd.

4.Fludi-oxonil	IV (FR, 1998); LD_{50}> 5050mg/kg [53]	No	Not classifiable [54]	No evidence of developmental effects [54]	No		Strawberries, landscape, cotton, peaches, greenhouse plants	1X [54]	RR
5.Mefen-oxam	III; LD_{50}> 2965 mg/kg (F, rat) [55]	No	Not likely [56]		No		Carrots, spinach, onions, strawberries, sunflowers	1X [56]	RR
6.Trifloxy-strobin	IV; LD_{50}> 5g/kg (rat) [57]	No	Not likely [58]	No indication of developmental toxicity [57]	No	Affects aquatic organisms at low concentrations [57]	Wine grapes, table and raisin grapes, almonds, pears, apples	1X [57]	RR

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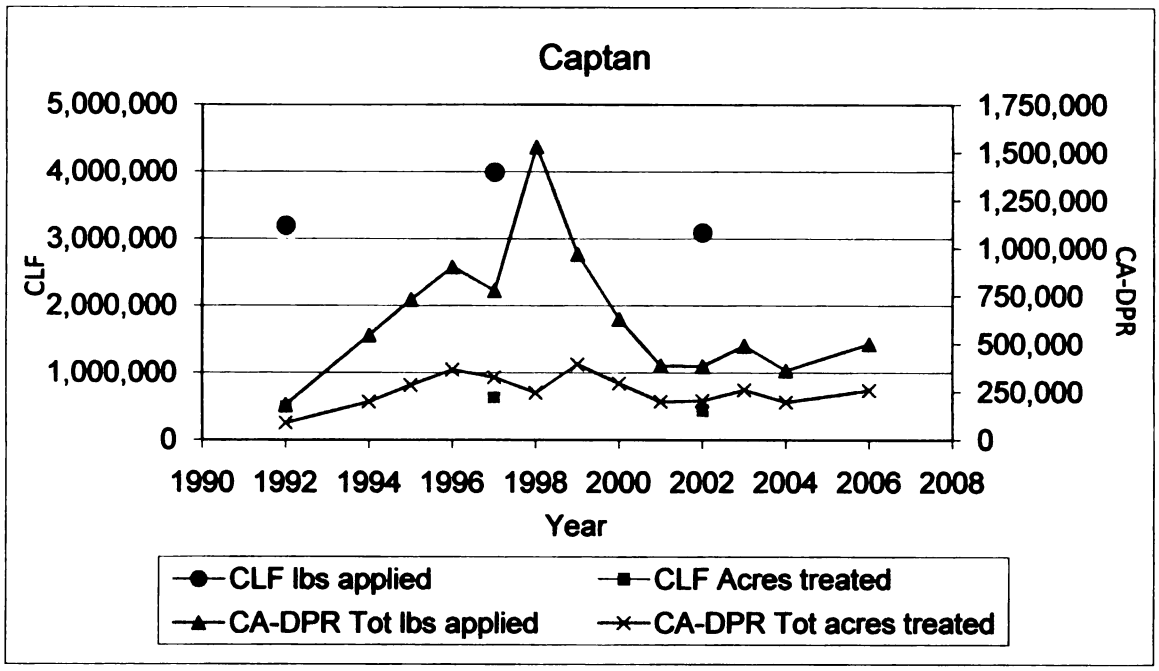
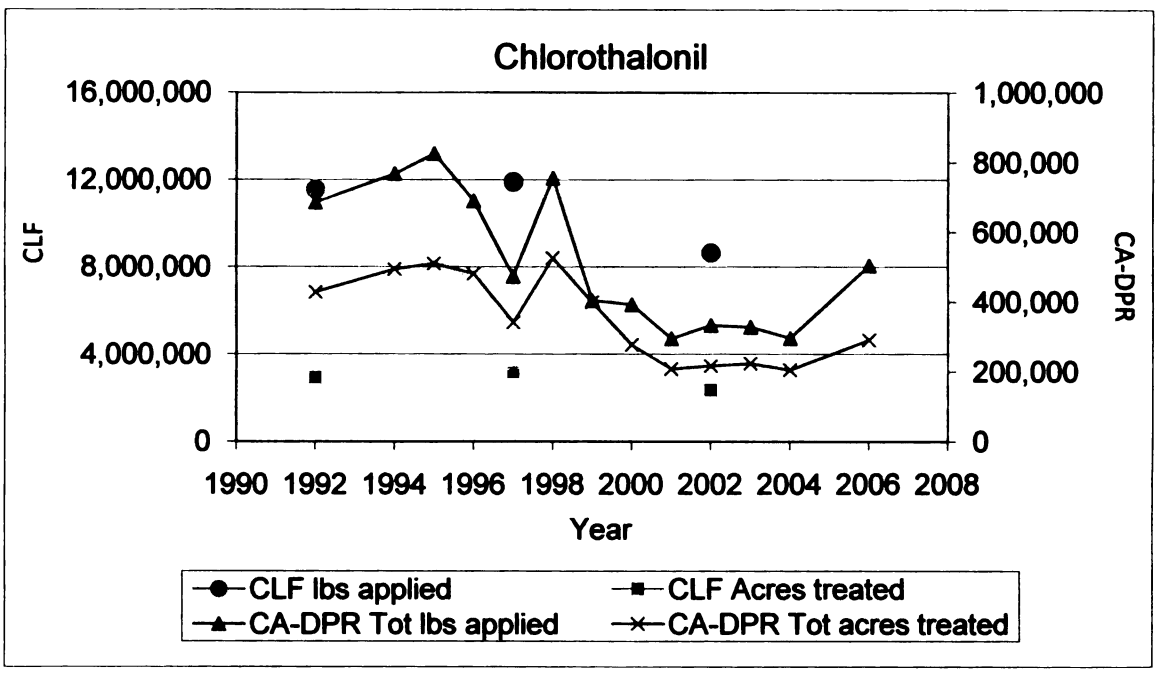
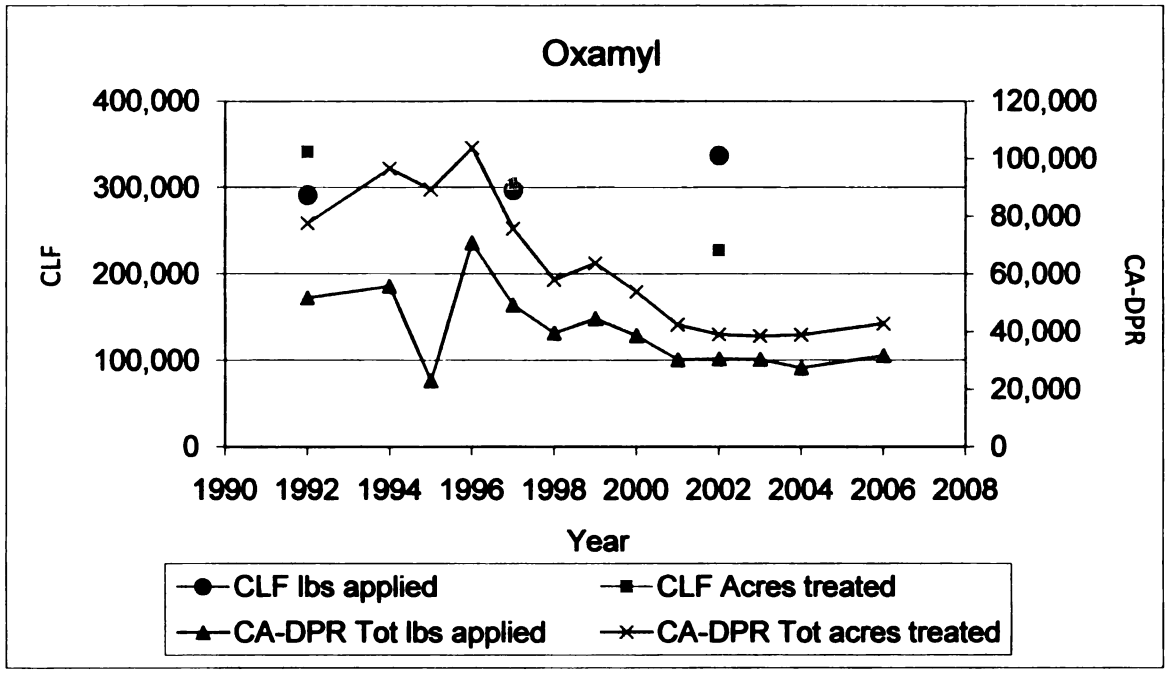
APPENDIX C
Individual Pesticide Use Charts

B2 carcinogenic fungicides



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CA-DPR
1990 1992 1994 1996 1998 2000 2002 2004 2006 2008
Year
CLF lbs applied
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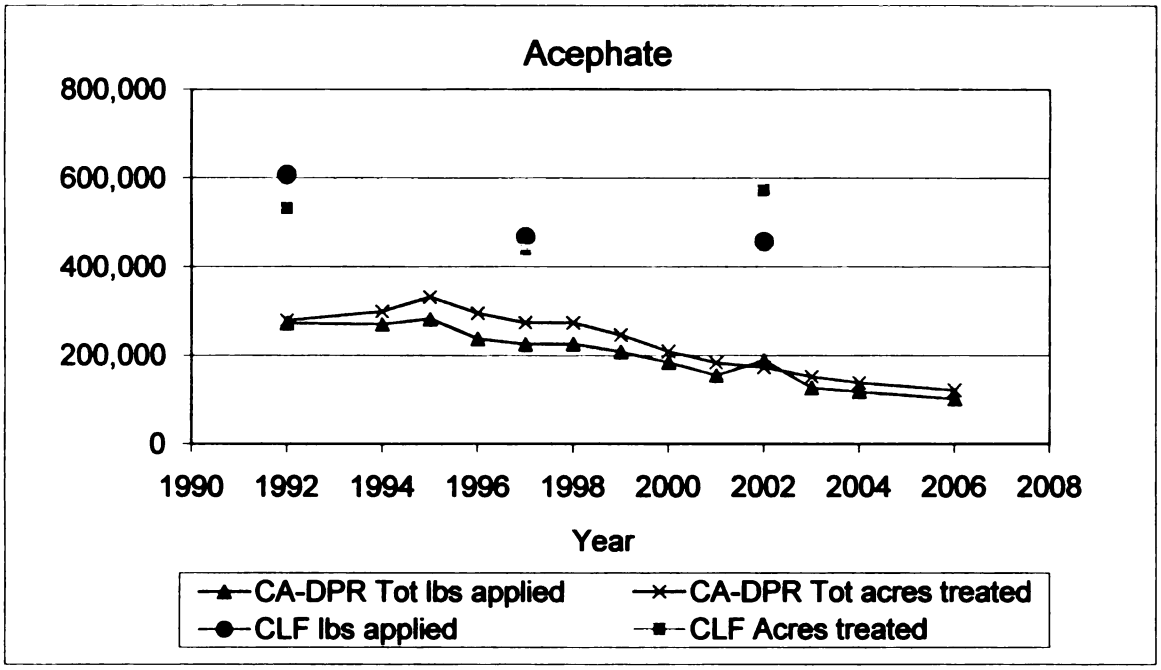
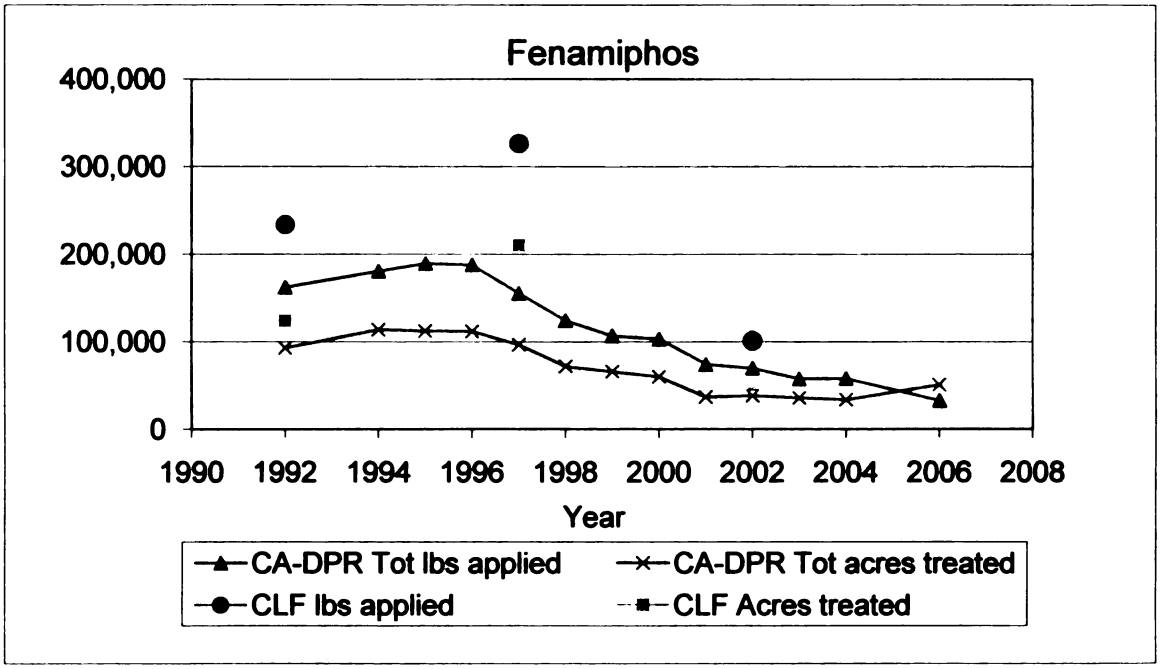
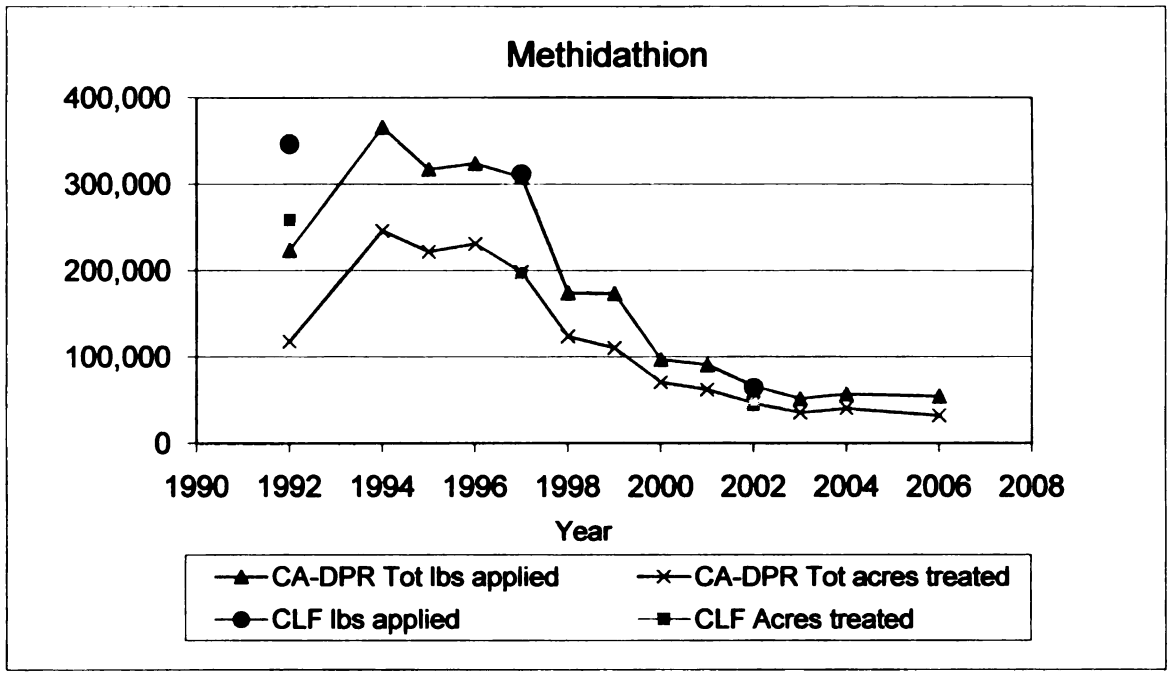
CA-DPR Tot lbs applied
CA-DPR Tot acres treated

Organophosphate insecticides



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1994
1996
1998
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2004
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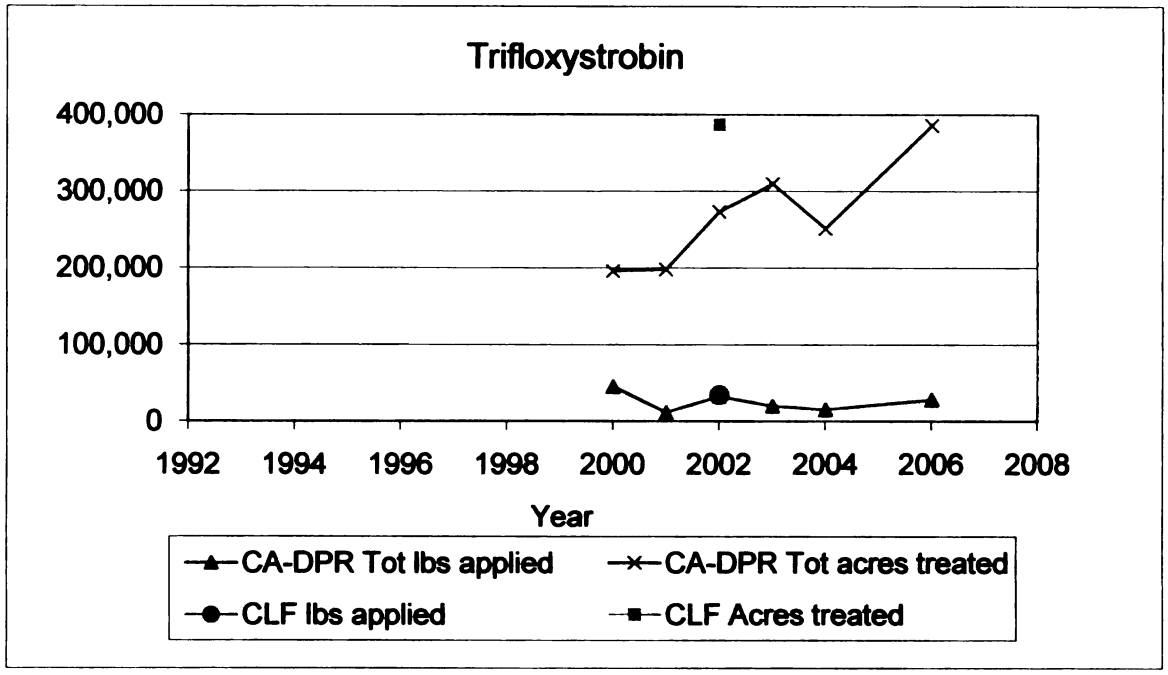
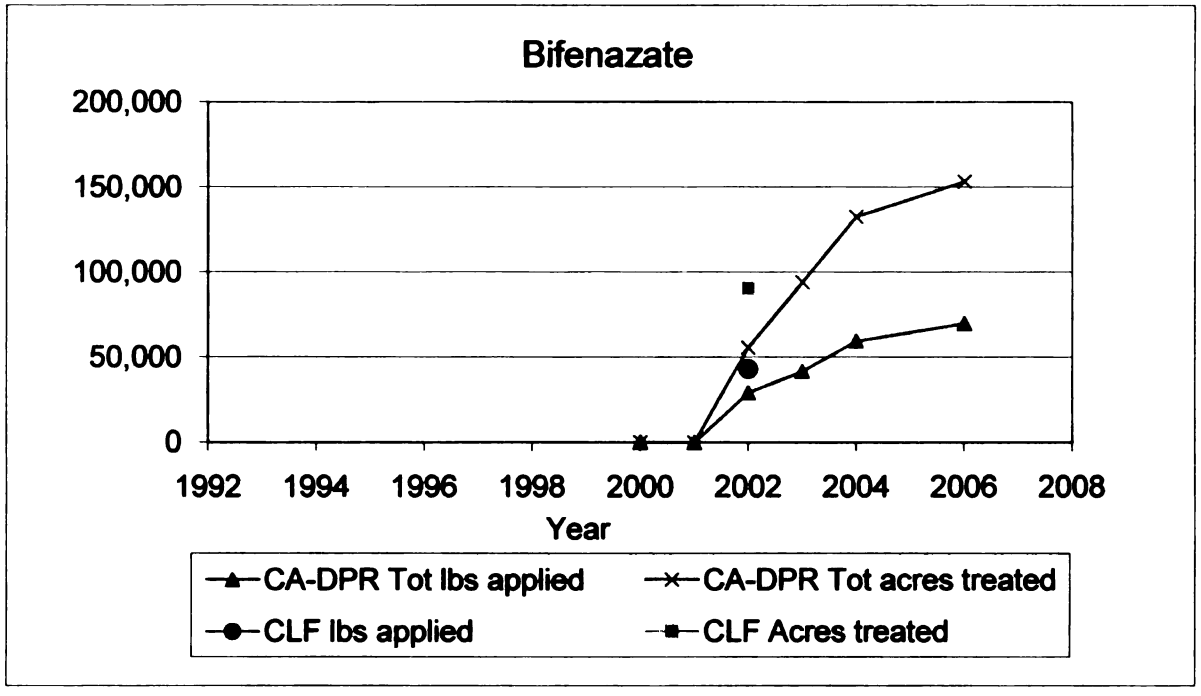
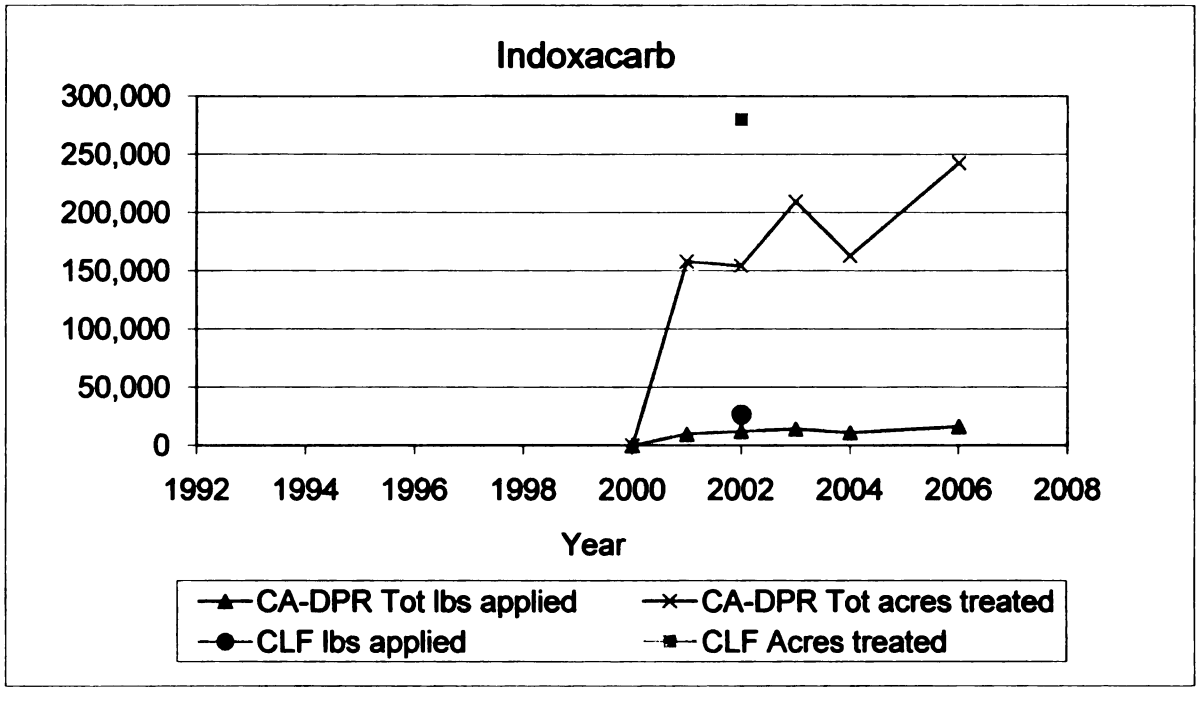
Year
CA-DPR Tot lbs applied
CA-DPR Tot acres treated
CLF lbs applied
CLF Acres treated

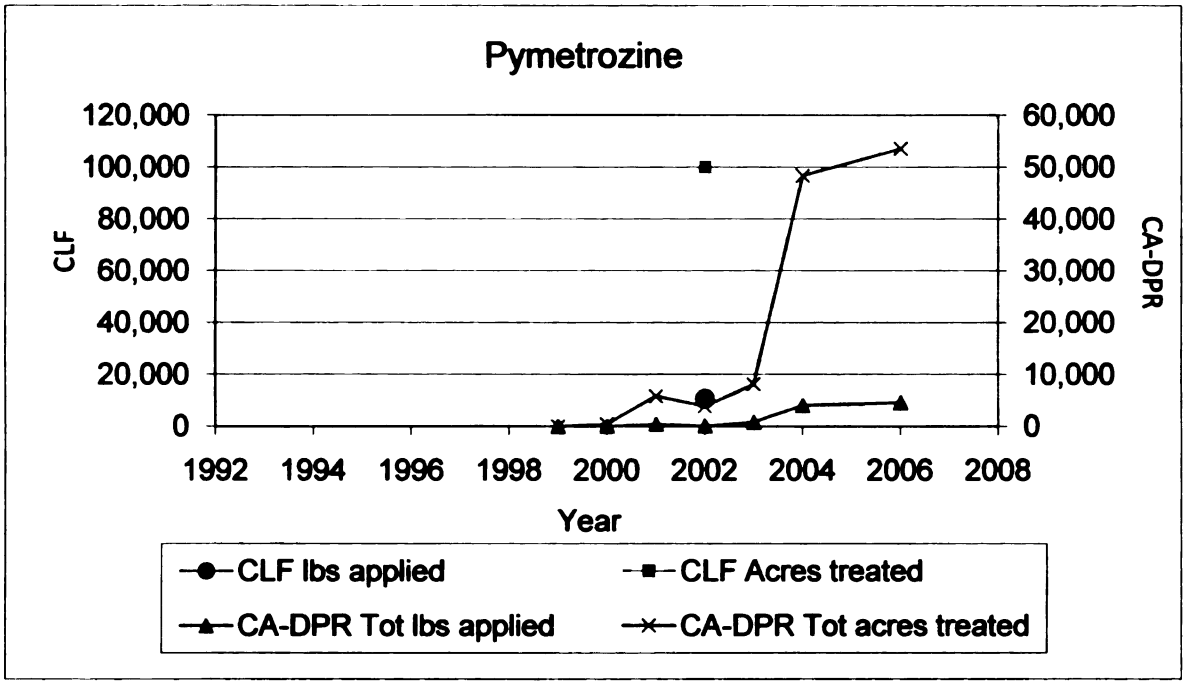
Reduced-risk fungicide



Reduced-risk insecticides






Pymetrozine
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80,000
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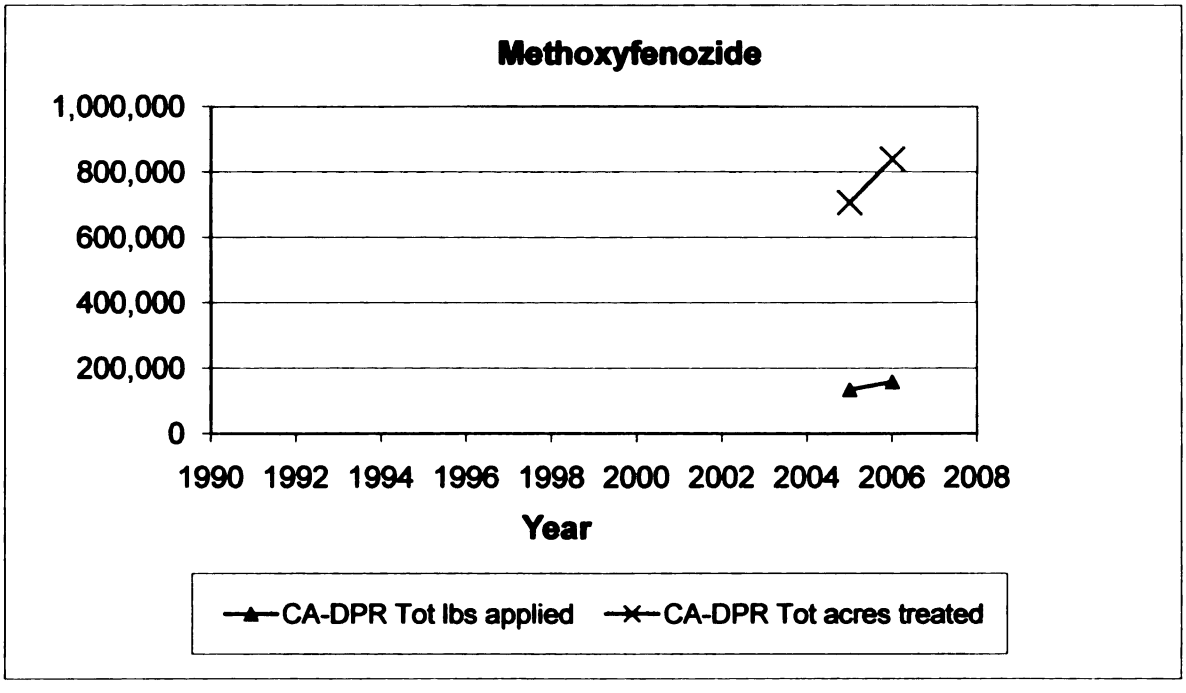
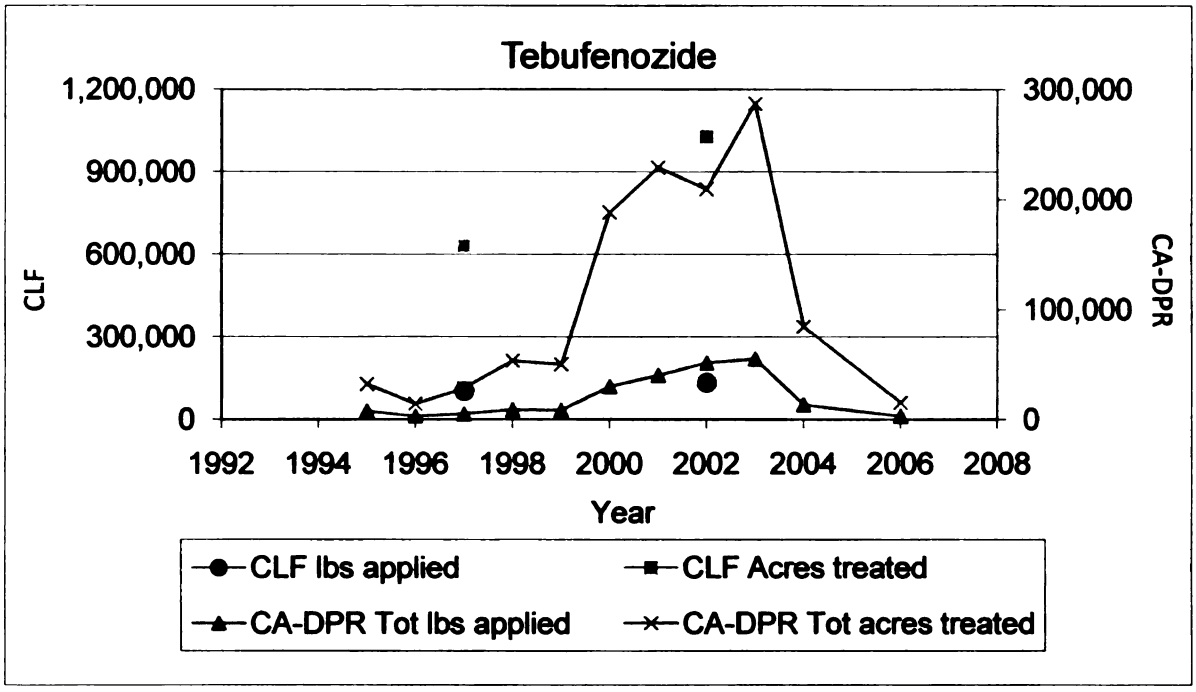
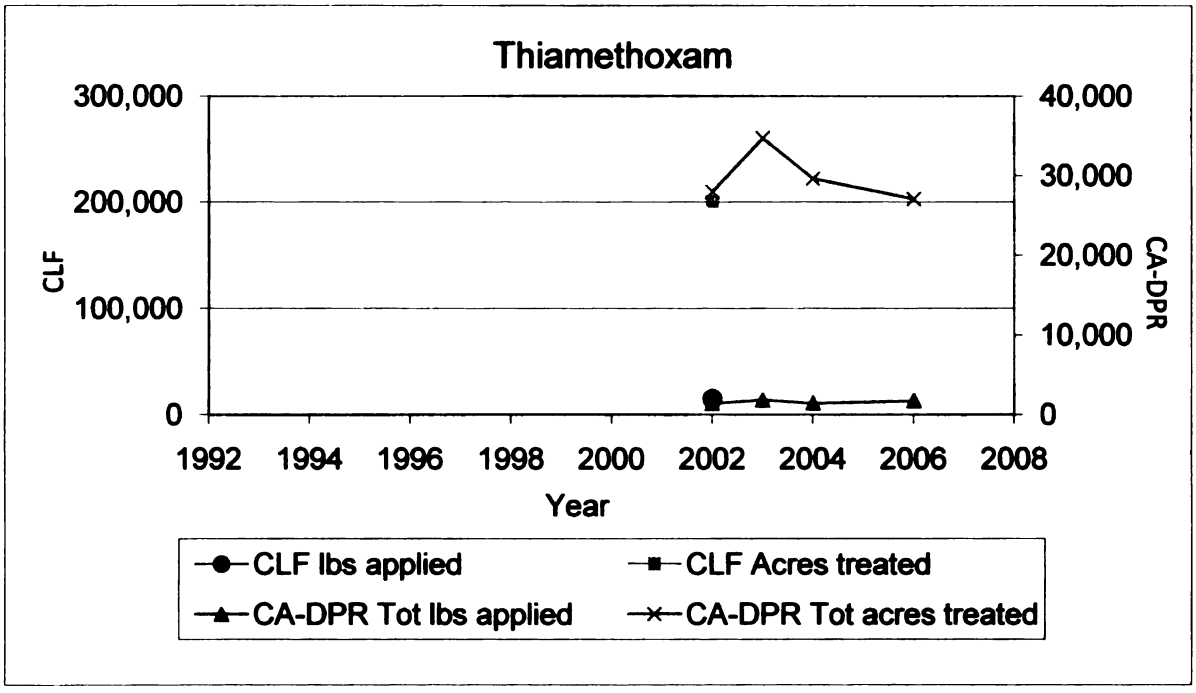
40,000
20,000
0
CLF
60,000
50,000
40,000
30,000
20,000
10,000
0
CA-DPR
1992 1994 1996 1998 2000 2002 2004 2006 2008
Year
CLF lbs applied
CLF Acres treated
CA-DPR Tot lbs applied
CA-DPR Tot acres treated

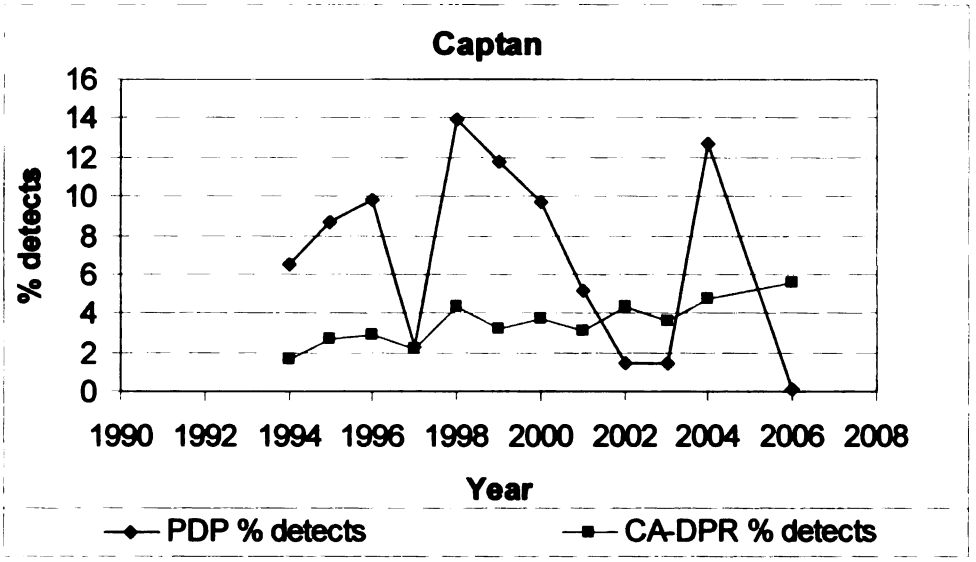

Methoxyfenozide
1,000,000
800,000
600,000
400,000
200,000
0
1990 1992 1994 1996 1998 2000 2002 2004 2006 2008
Year
CA-DPR Tot lbs applied
CA-DPR Tot acres treated

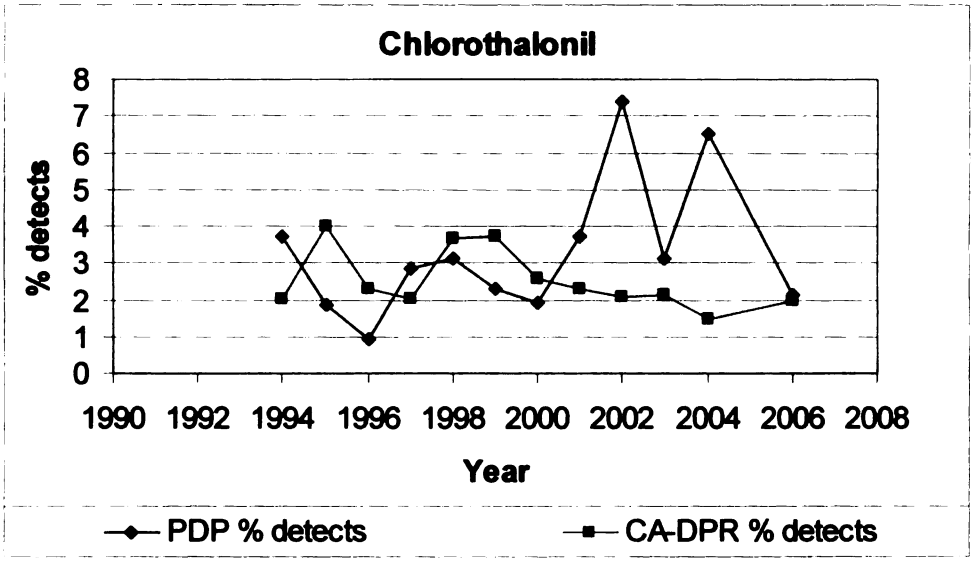

Tebufenozide
1,200,000
900,000
600,000
300,000
0
CLF
300,000
200,000
100,000
0
CA-DPR
1992 1994 1996 1998 2000 2002 2004 2006 2008
Year
CLF lbs applied
CLF Acres treated
CA-DPR Tot lbs applied
CA-DPR Tot acres treated

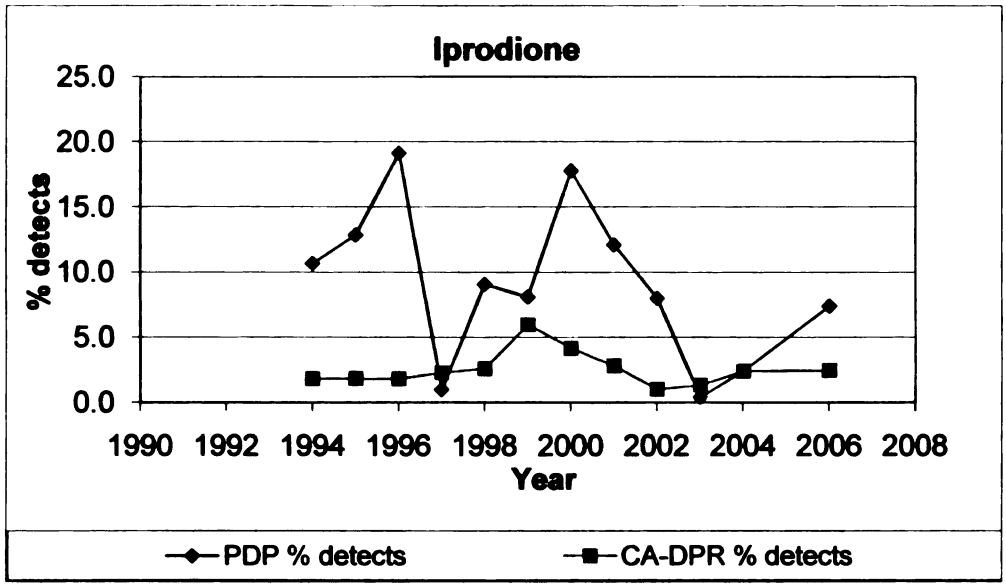

Thiamethoxam
300,000
200,000
100,000
0
CLF
40,000
30,000
20,000
10,000
0
CA-DPR
1992 1994 1996 1998 2000 2002 2004 2006 2008
Year
CLF lbs applied
CLF Acres treated
CA-DPR Tot lbs applied
CA-DPR Tot acres treated

APPENDIX D
Individual Pesticide Residue Detects Charts

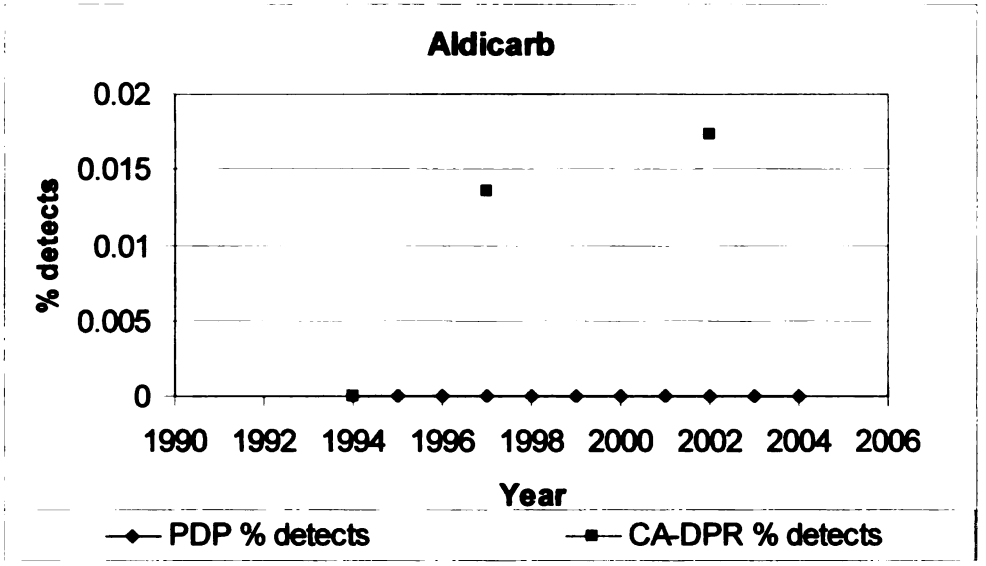
B2 carcinogenic fungicides

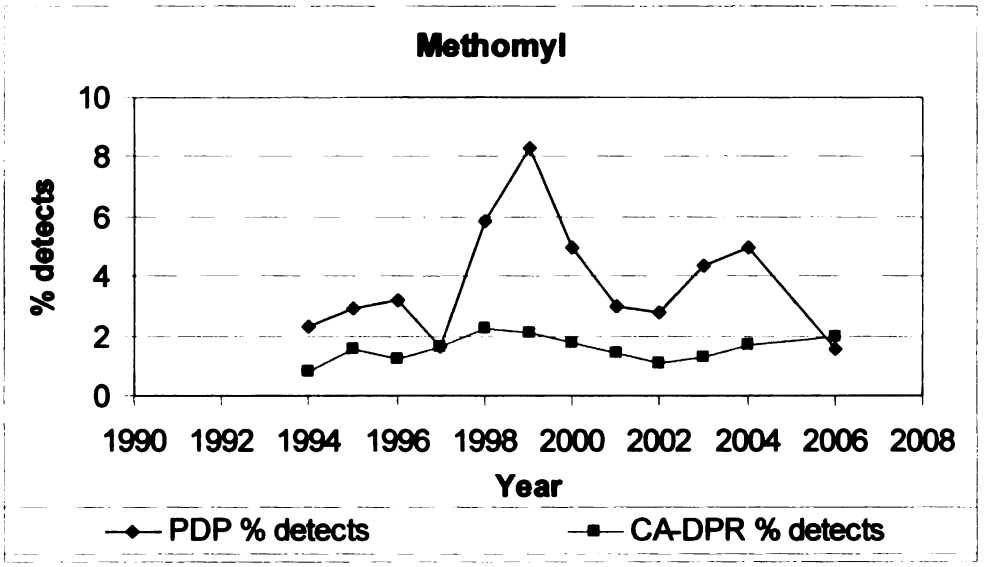


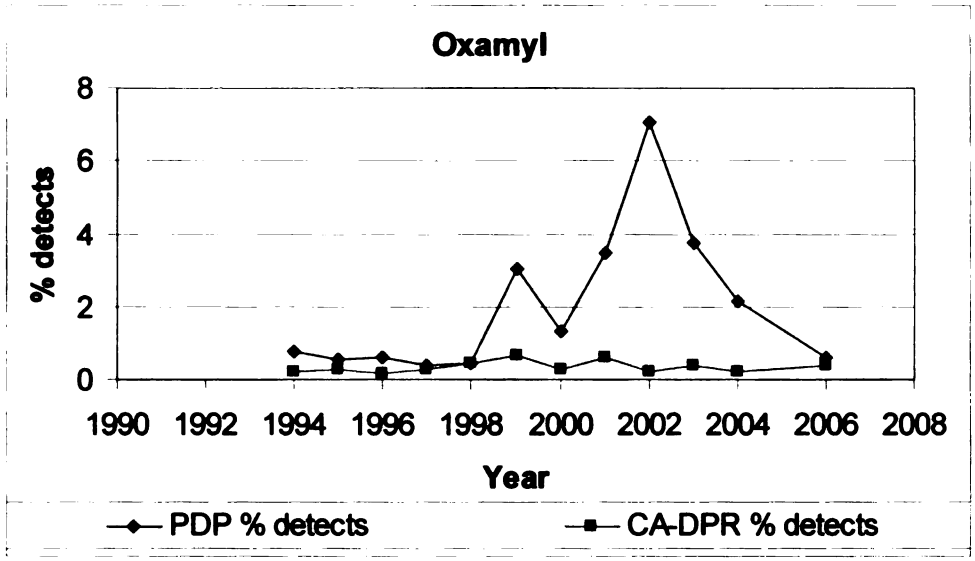



Iprodione
25.0
20.0
15.0
10.0
5.0
0.0
% detects
1990 1992 1994 1996 1998 2000 2002 2004 2006 2008
Year
PDP % detects
CA-DPR % detects

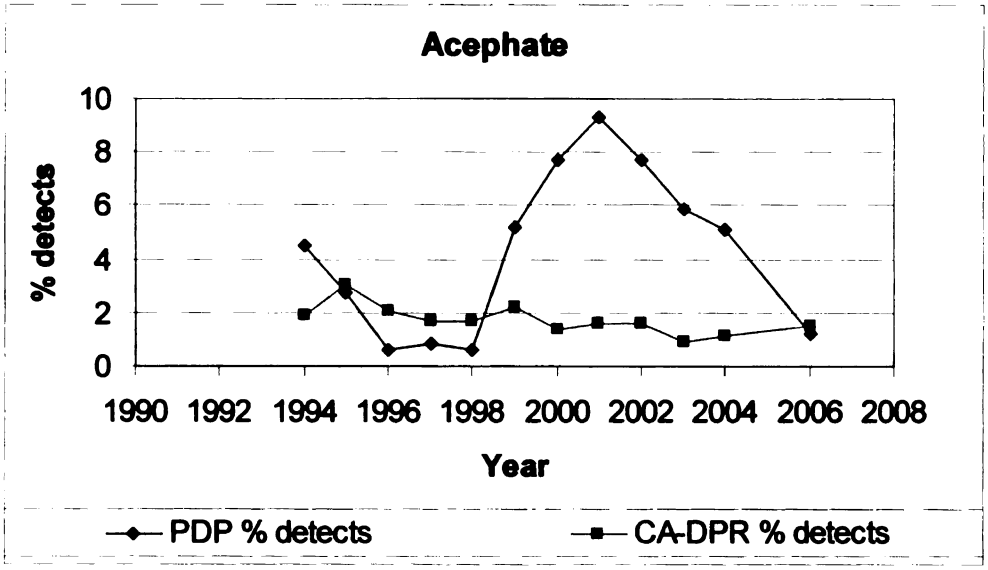
Carbamate insecticides

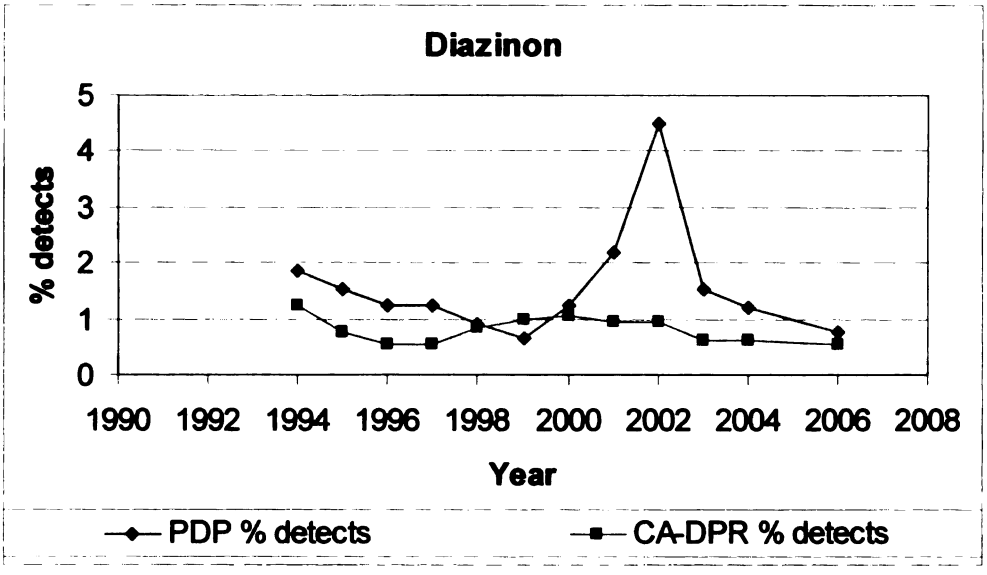


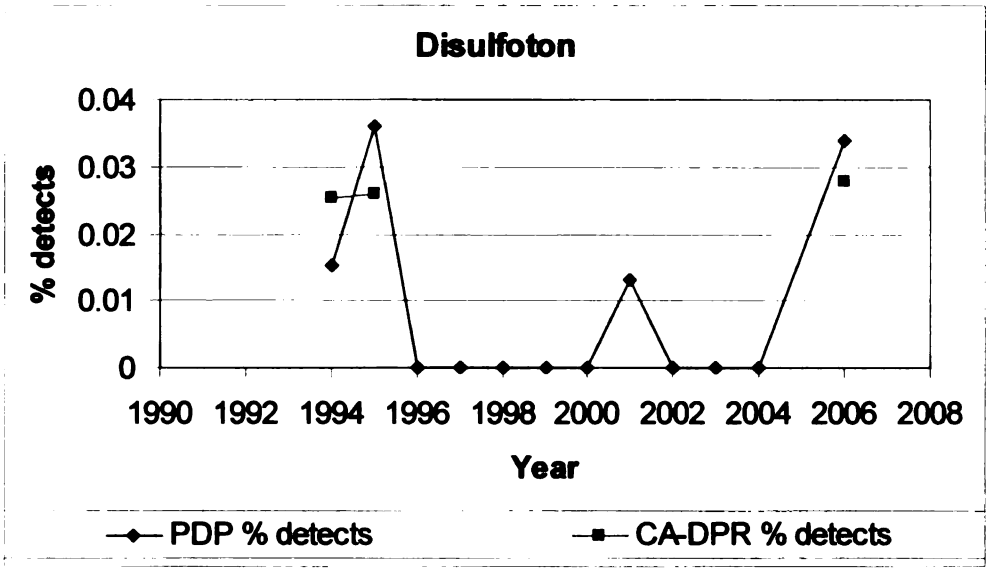


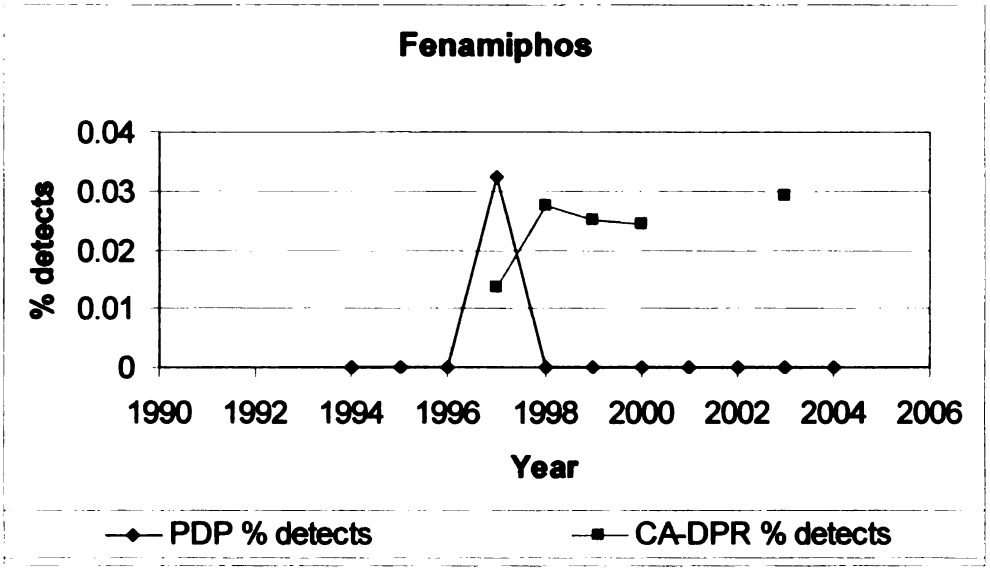

Oxamyl
8
6
4
2
0
% detects
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year
PDP % detects
CA-DPR % detects

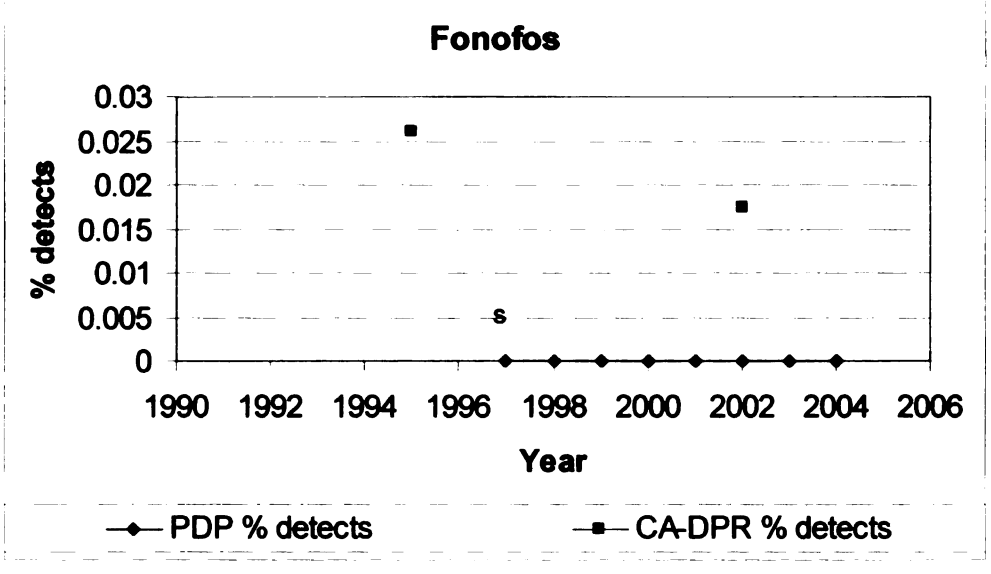
Organophosphate insecticides



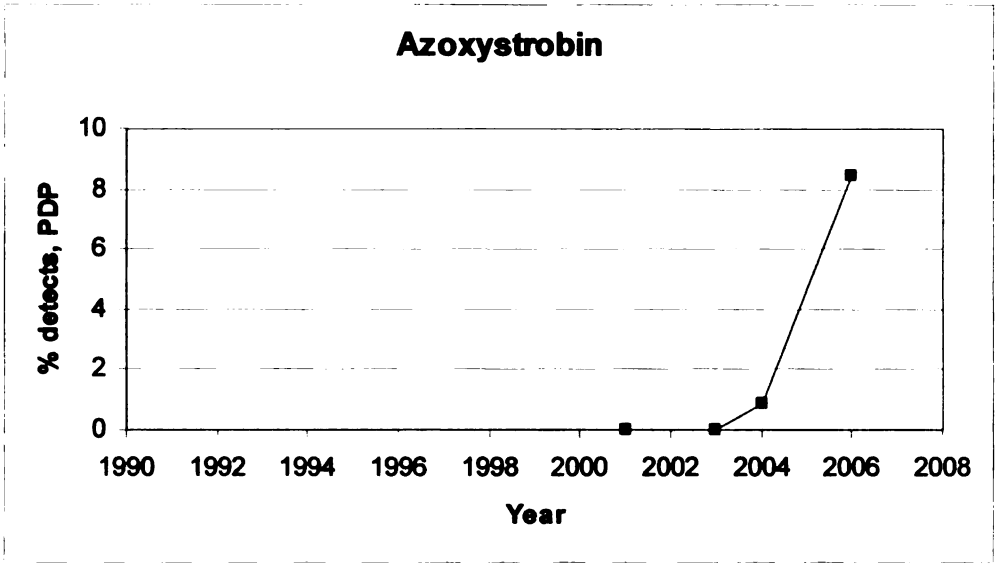


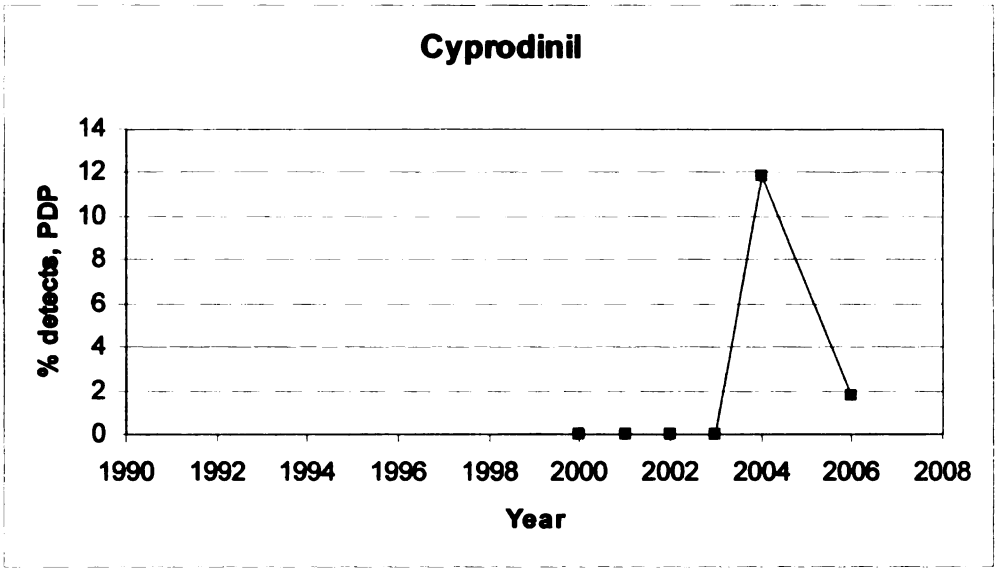

Disulfoton
0.04
0.03
0.02
0.01
0
% detects
1990 1992 1994 1996 1998 2000 2002 2004 2006 2008
Year
PDP % detects
CA-DPR % detects

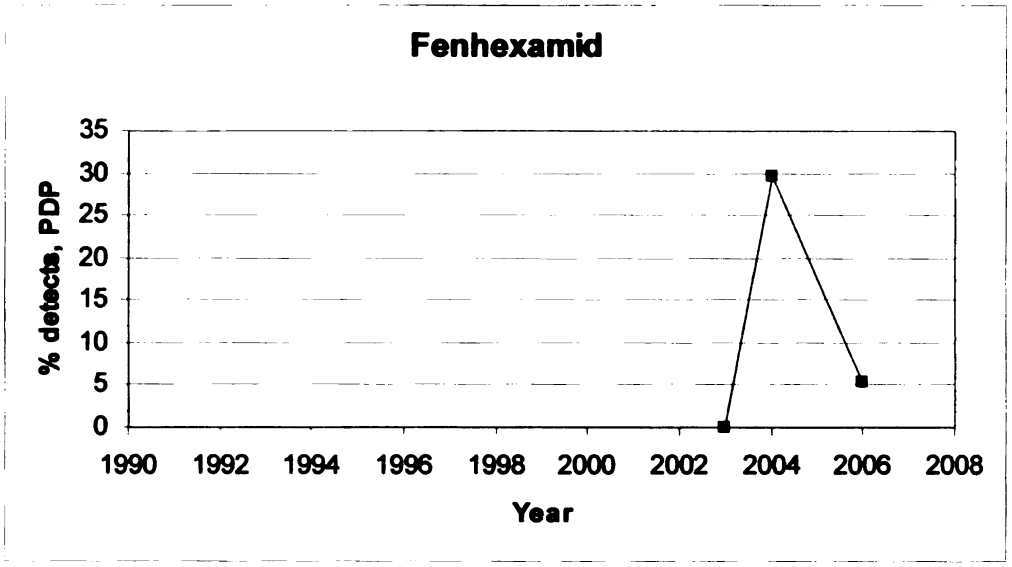

Fenamiphos
0.04
0.03
0.02
0.01
0
% detects
1990 1992 1994 1996 1998 2000 2002 2004 2006
Year
PDP % detects
CA-DPR % detects

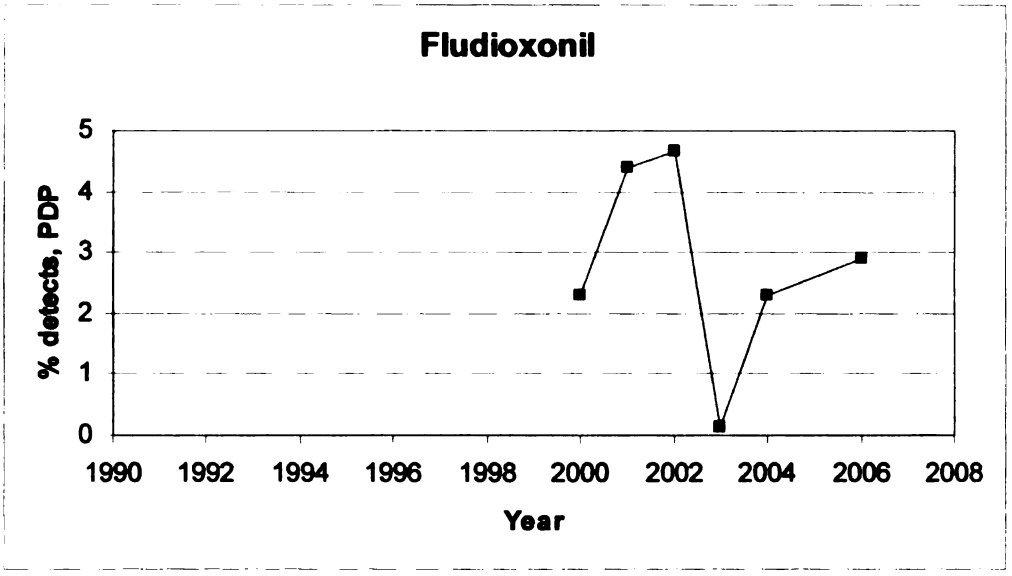

Fonofos
0.03
0.025
0.02
0.015
0.01
0.005
0
% detects
1990 1992 1994 1996 1998 2000 2002 2004 2006
Year
PDP % detects
CA-DPR % detects

Reduced-risk fungicides

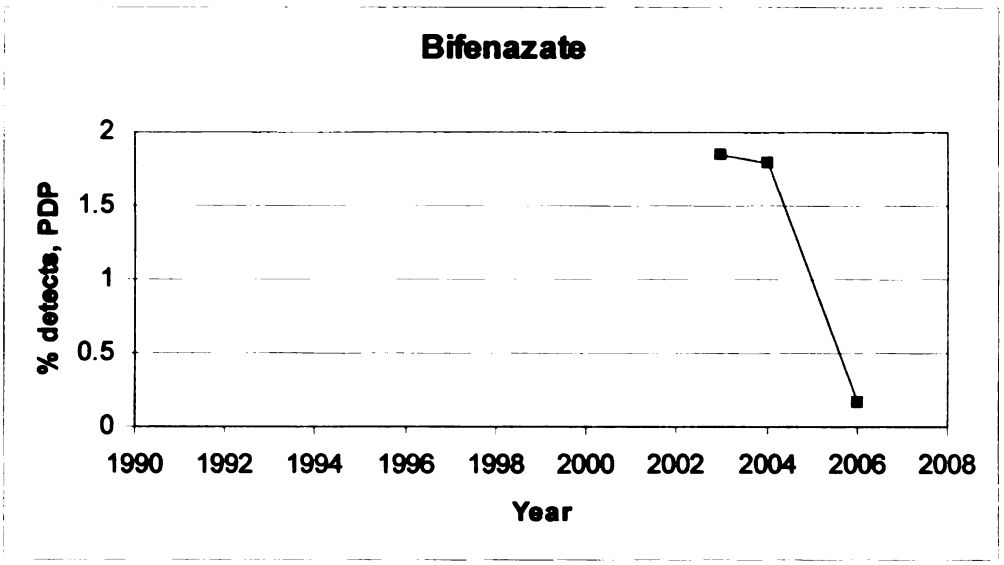


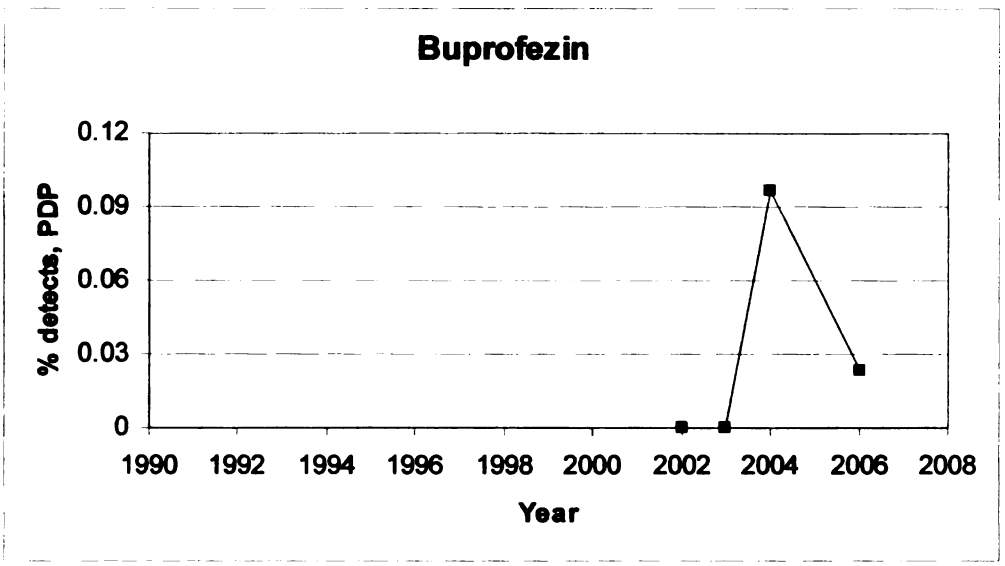


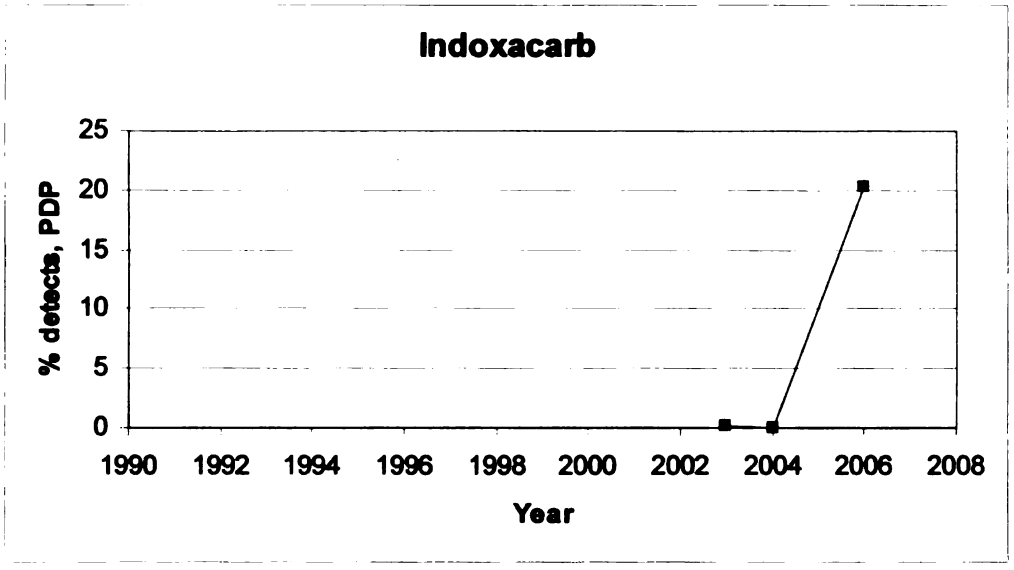

Fenhexamid
% detects, PDP
35
30
25
20
15
10
5
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year

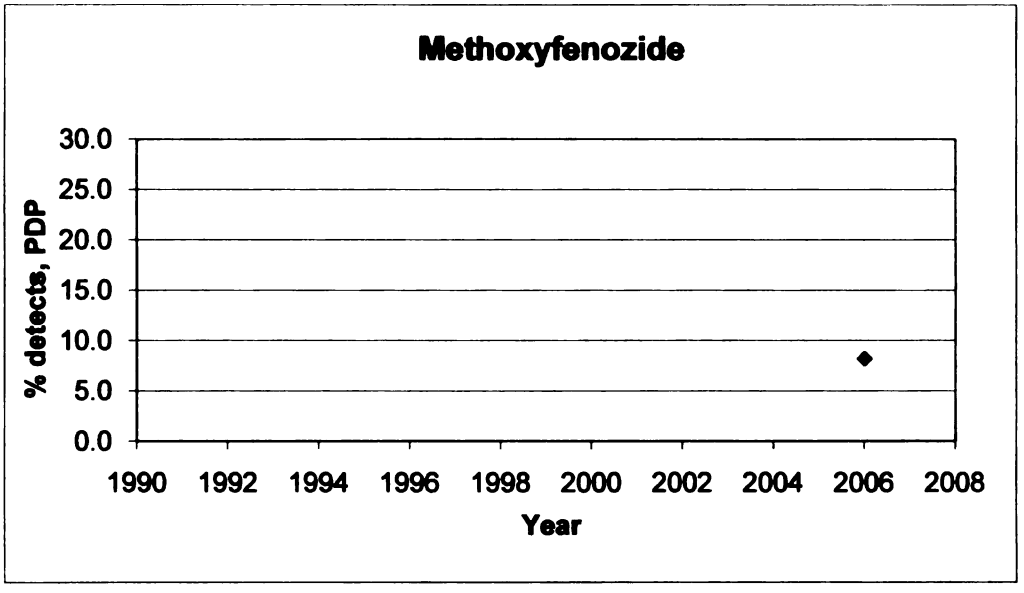

Fludioxonil
% detects, PDP
5
4
3
2
1
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year

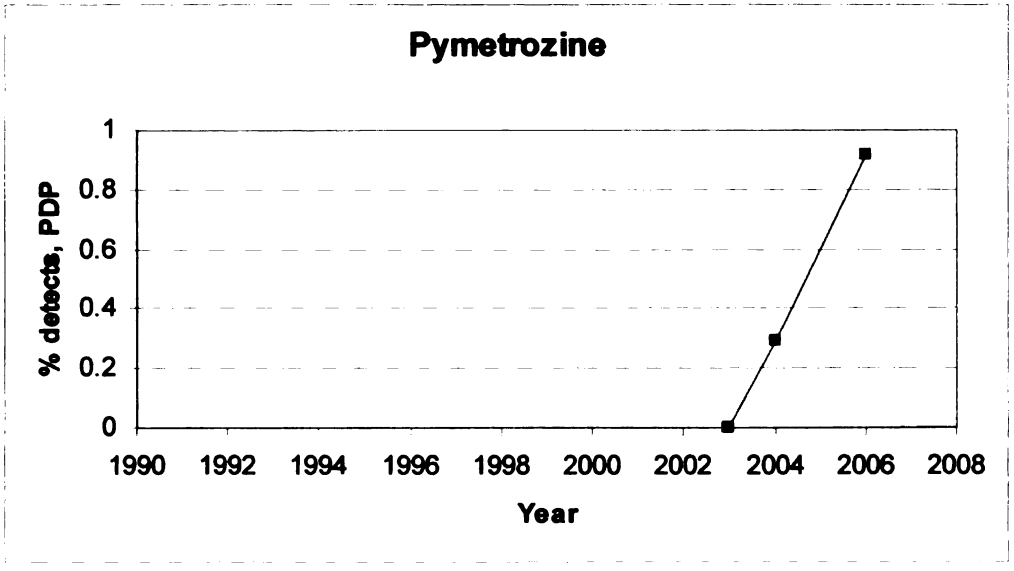
Reduced-risk insecticides

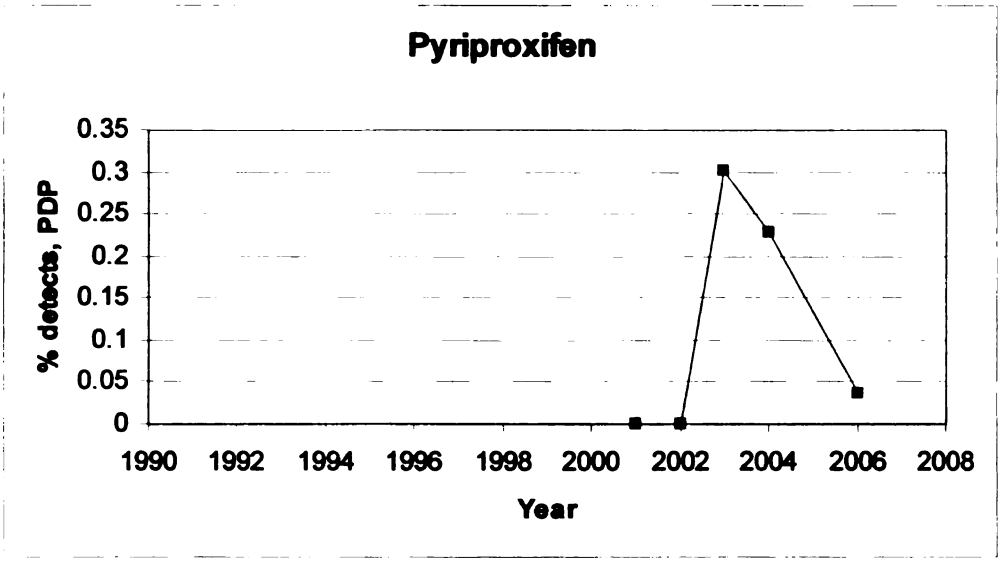


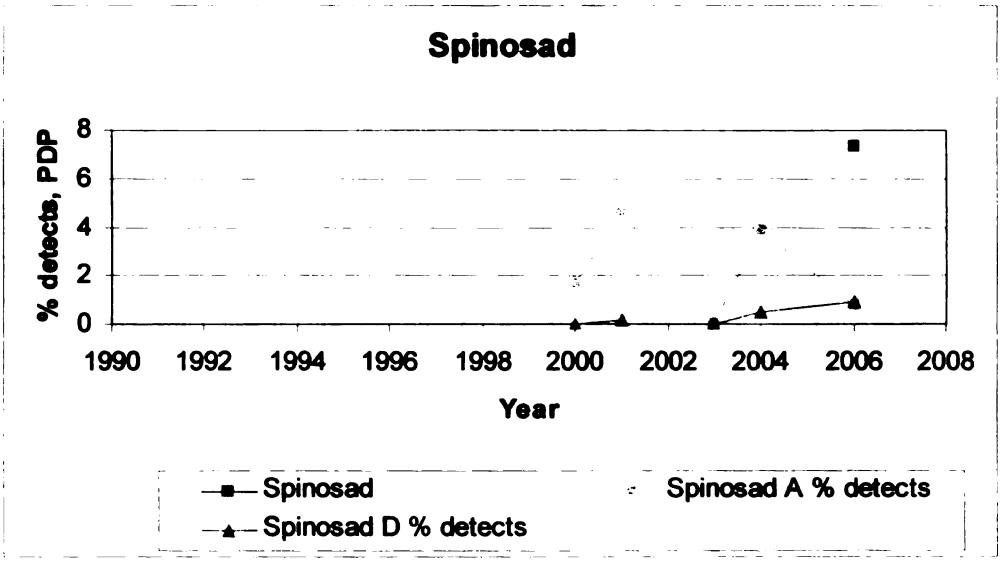


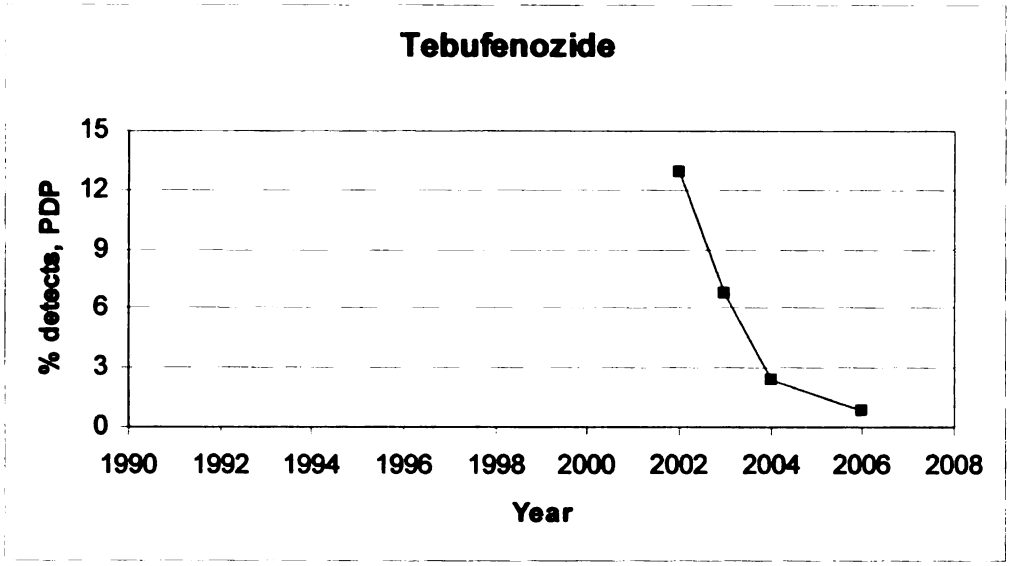

Indoxacarb
% detects, PDP
25
20
15
10
5
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year

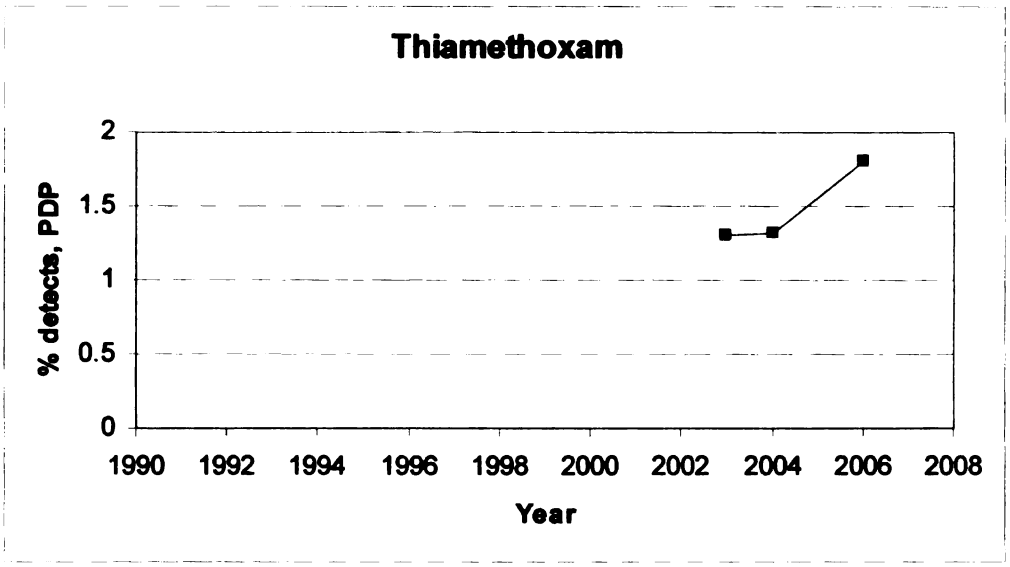

Methoxyfenozide
% detects, PDP
30.0
25.0
20.0
15.0
10.0
5.0
0.0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year


Pymetrozine
% detects, PDP
1
0.8
0.6
0.4
0.2
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year


Pyriproxifen
% detects, PDP
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year


Spinosad
% detects, PDP
8
6
4
2
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year
Spinosad
Spinosad A % detects
Spinosad D % detects


Tebufenozide
% detects, PDP
15
12
9
6
3
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year


Thiamethoxam
% detects, PDP
2
1.5
1
0.5
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year

APPENDIX E
Acute and Chronic Exposure and Risk Estimates for Iprodione

Appendix E.1. Iprodione acute exposure estimates for stone fruits

Population Group	DEEM or LifeLine	Tier 1 (PCT=100%, Tolerance)		Tier 2 (PCT=100%, HFT Residue)		Tier 3					
						PCT=1992 PCT, 1995 PDP Residue)		1997 PCT, 2000 PDP Residue		2002 PCT, 2006 PDP Residue	
		Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD
All Ages	DEEM	0.022842	11.42	0.000919	0.46	0.007768	3.88	0.003950	1.97	0.003221	1.61
	LifeLine	0.024800	12.40	0.000865	0.43	0.008500	4.25	0.005720	2.86	0.004920	2.46
Ages 1-2	DEEM	0.093014	46.51	0.003614	1.81	0.029729	14.86	0.014677	7.34	0.012762	6.38
	LifeLine	0.116000	57.80	0.003890	1.95	0.030500	15.20	0.014800	7.39	0.019000	9.52
Ages 3-5	DEEM	0.060515	30.26	0.002582	1.29	0.016950	8.47	0.009282	4.64	0.007586	3.79
	LifeLine	0.065000	32.50	0.002490	1.24	0.019600	9.81	0.010000	5.00	0.009390	4.69
Ages 6-12	DEEM	0.033671	16.84	0.001455	0.73	0.009901	4.95	0.005475	2.74	0.004239	2.12
	LifeLine	0.032600	16.30	0.001400	0.70	0.011400	5.69	0.007210	3.61	0.005060	2.53
Ages 13-19	DEEM	0.009493	4.75	0.000464	0.23	0.004641	2.32	0.002454	1.23	0.002068	1.03
	LifeLine	0.004930	2.47	0.000323	0.16	0.003760	1.88	0.002750	1.37	0.002420	1.21
Ages 20-49	DEEM	0.009419	4.71	0.000340	0.17	0.003851	1.93	0.002423	1.21	0.001843	0.92
	LifeLine	0.020300	10.20	0.000663	0.33	0.005850	2.92	0.004050	2.03	0.003530	1.76
Ages 50+	DEEM	0.026807	13.40	0.000884	0.44	0.006240	3.12	0.003305	1.65	0.002865	1.43
	LifeLine	0.024500	12.30	0.000753	0.38	0.007140	3.57	0.004860	2.43	0.004070	2.04

Tiers 1 and 2 exposure estimates, 95th percentile.
Tier 3 exposure estimates, 99.9th percentile.

Appendix E.2a. Iprodione chronic exposure estimates for stone fruits using DEEM

Population Group	Tier 1 (PCT=100%)		Tier 2				Tier 3			
			1992 PCT		2002 PCT,		1992 PCT		2002 PCT	
	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD
All Ages	0.003750	18.4	0.002134	10.5	0.000957	4.7	0.000055	0.3	0.000022	0.1
Ages 1-2	0.013251	65.2	0.007727	38.0	0.003637	17.9	0.000203	1.0	0.000088	0.4
Ages 3-5	0.008285	40.7	0.004817	23.7	0.002185	10.7	0.000141	0.7	0.000056	0.3
Ages 6-12	0.005073	24.9	0.002877	14.1	0.001273	6.3	0.000091	0.4	0.000034	0.2
Ages 13-19	0.001932	9.5	0.00106	5.2	0.000479	2.4	0.000034	0.2	0.000013	0.1
Ages 20-49	0.001935	9.5	0.001146	5.6	0.000503	2.5	0.000027	0.1	0.000011	0.1
Ages 50+	0.003849	18.9	0.002081	10.2	0.000914	4.5	0.000049	0.2	0.000020	0.1

Appendix E.2b. Iprodione chronic exposure estimates for stone fruits using LifeLine

Population Group	Tier 1 (PCT=100%)		Tier 2				Tier 3			
			1992 PCT		2002 PCT		1992 PCT		2002 PCT	
	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD
All Ages	0.003980	19.60	0.002270	11.20	0.001010	4.98	0.000057	0.28	0.000023	0.11
Ages 1-2	0.016100	79.00	0.009450	46.50	0.004500	22.10	0.000220	1.08	0.000097	0.48
Ages 3-5	0.008980	44.20	0.004810	23.70	0.002290	11.30	0.000150	0.74	0.000057	0.28
Ages 6-12	0.004940	24.30	0.003020	14.90	0.001280	6.29	0.000085	0.42	0.000034	0.17
Ages 13-19	0.001590	7.82	0.000981	4.82	0.000446	2.20	0.000028	0.14	0.000011	0.05
Ages 20-49	0.002960	14.60	0.001700	8.35	0.000725	3.57	0.000042	0.21	0.000017	0.08
Ages 50+	0.003430	16.80	0.001910	9.41	0.000849	4.18	0.000047	0.23	0.000018	0.09

Appendix E.3. Iprodione acute exposure estimates for peaches

Population Group	DEEM or LifeLine	Tier 1 (PCT=100%, Tolerance)		Tier 2 (PCT=100%, HFT Residue)		Tier 3					
						1992 PCT, 1995 PDP Residue		1997 PCT, 2000 PDP Residue		2002 PCT, 2006 PDP Residue	
		Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD
All Ages	DEEM	0.006733	3.370	0.000222	0.110	0.007768	3.88	0.010573	5.29	0.002972	1.49
	LifeLine	0.008860	4.430	0.000053	0.026	0.009070	4.53	0.005090	2.54	0.004330	2.16
Ages 1-2	DEEM	0.068762	34.380	0.002269	1.130	0.029729	14.86	0.018493	9.25	0.012591	6.30
	LifeLine	0.079500	39.800	0.002020	1.010	0.030400	15.20	0.021900	11.00	0.013600	6.79
Ages 3-5	DEEM	0.033384	16.690	0.001102	0.550	0.016950	8.47	0.011896	5.95	0.007430	3.72
	LifeLine	0.043000	21.500	0.000642	0.321	0.016300	8.13	0.011100	5.57	0.009470	4.74
Ages 6-12	DEEM	0.018061	9.030	0.000596	0.300	0.009901	4.95	0.009112	4.56	0.003927	1.96
	LifeLine	0.017200	8.610	0.000384	0.192	0.012600	6.28	0.006610	3.31	0.004410	2.20
Ages 13-19	DEEM	0.001355	0.680	0.000045	0.020	0.004641	2.32	0.004977	2.49	0.001973	0.99
	LifeLine	0.000958	0.479	0.000011	0.005	0.005000	2.50	0.002690	1.34	0.002110	1.06
Ages 20-49	DEEM	0.000877	0.440	0.000029	0.010	0.003851	1.93	0.003796	1.90	0.001718	0.86
	LifeLine	0.004930	2.470	0.000034	0.017	0.007100	3.55	0.003450	1.73	0.003170	1.58
Ages 50+	DEEM	0.015388	7.690	0.000508	0.250	0.006240	3.12	0.004979	2.49	0.002528	1.20
	LifeLine	0.008160	4.080	0.000043	0.022	0.006570	3.28	0.004120	2.06	0.003610	1.80

Tiers 1 and 2 exposure estimates, 95th percentile.
Tier 3 exposure estimates, 99.9th percentile.

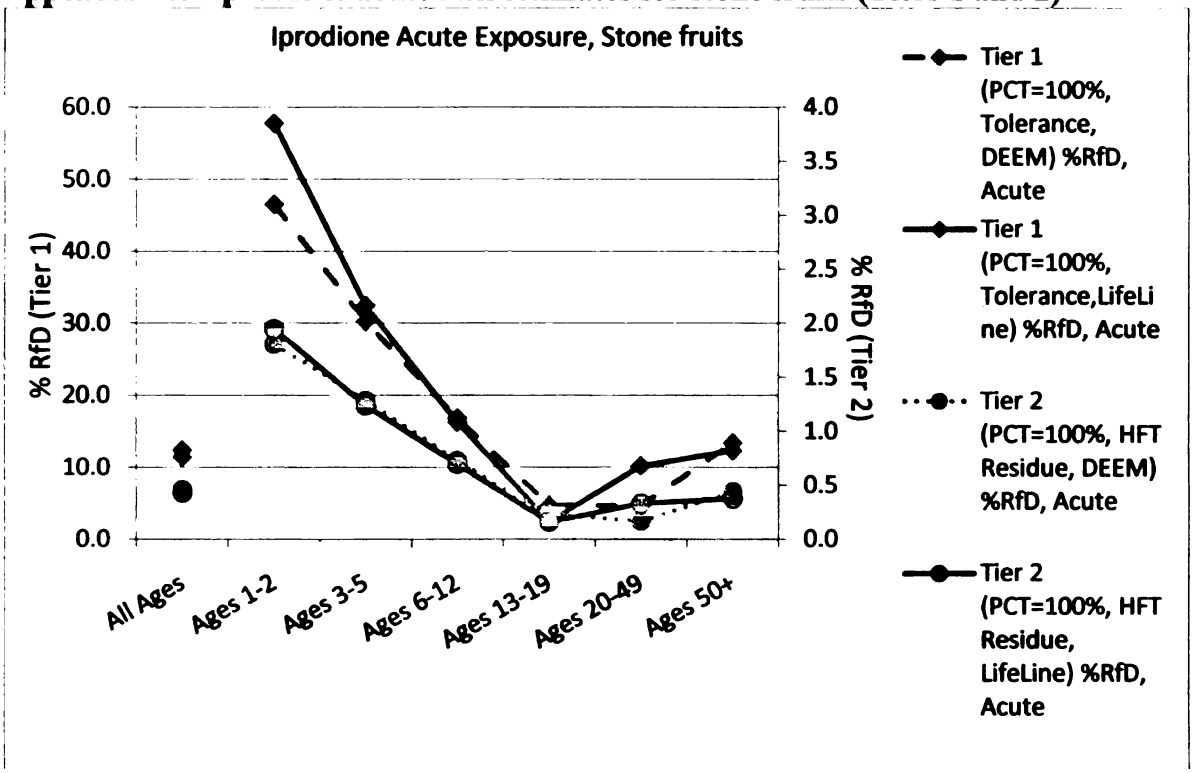
Appendix E.4. Iprodione chronic exposure estimates for peaches

Population Group	DEEM or LifeLine	Tier 1 (PCT=100%, Tolerance)		Tier 2				Tier 3			
				1992 PCT, Tolerance		2002 PCT, Tolerance		Ave. FT, 1992 PCT		Ave. FT, 2002 PCT	
		Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD	Exposure	%RfD
All Ages	DEEM	0.002218	10.90	0.001331	6.50	0.000665	3.30	0.000033	0.20	0.000016	0.10
	LifeLine	0.002330	11.50	0.001410	6.95	0.000709	3.49	0.000034	0.17	0.000017	0.08
Ages 1-2	DEEM	0.009712	47.80	0.005827	28.70	0.002914	14.30	0.000146	0.70	0.000073	0.40
	LifeLine	0.010900	53.60	0.006810	33.50	0.003440	16.90	0.000174	0.85	0.000082	0.40
Ages 3-5	DEEM	0.005409	26.60	0.003245	16.00	0.001623	8.00	0.000080	0.40	0.000040	0.20
	LifeLine	0.006330	31.10	0.003420	16.80	0.001720	8.45	0.000082	0.40	0.000043	0.21
Ages 6-12	DEEM	0.002980	14.70	0.001788	8.80	0.000894	4.40	0.000044	0.20	0.000022	0.10
	LifeLine	0.003070	15.10	0.001790	8.78	0.000925	4.55	0.000043	0.21	0.000022	0.11
Ages 13-19	DEEM	0.001246	6.10	0.000748	3.70	0.000374	1.80	0.000018	0.10	0.000009	0.00
	LifeLine	0.001070	5.29	0.000659	3.24	0.000333	1.64	0.000016	0.08	0.000008	0.04
Ages 20-49	DEEM	0.001038	5.10	0.000623	3.10	0.000312	1.50	0.000015	0.10	0.000008	0.00
	LifeLine	0.001670	8.20	0.001010	4.98	0.000493	2.43	0.000024	0.12	0.000012	0.06
Ages 50+	DEEM	0.002005	9.90	0.001203	5.90	0.000601	3.00	0.000030	0.10	0.000015	0.10
	LifeLine	0.001780	8.77	0.001100	5.42	0.000560	2.76	0.000027	0.13	0.000014	0.07

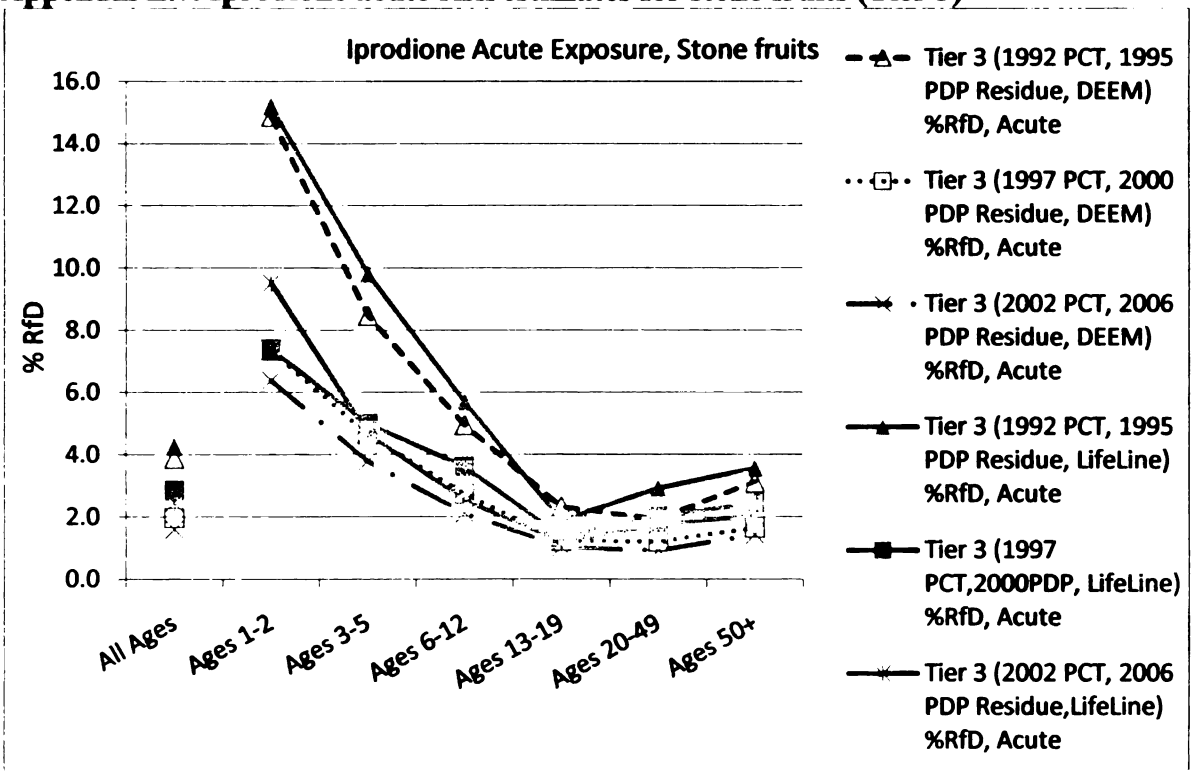
Appendix E.5. Iprodione cancer risk estimates for peaches and stone fruits

Commodity	DEEM or LifeLine	Tier 1 (PCT=100)	Tier 2		Tier 3	
			1992 PCT	2002 PCT	1992 PCT	2002 PCT
Peaches	DEEM	9.74E-05	5.84E-05	2.92E-05	1.44E-06	7.22E-07
	LifeLine	1.03E-04	6.22E-05	3.12E-05	1.51E-06	7.51E-07
Stone fruits	DEEM	1.65E-04	9.37E-05	4.20E-05	2.40E-06	9.81E-07
	LifeLine	1.75E-04	1.00E-04	4.45E-05	2.50E-06	1.01E-06

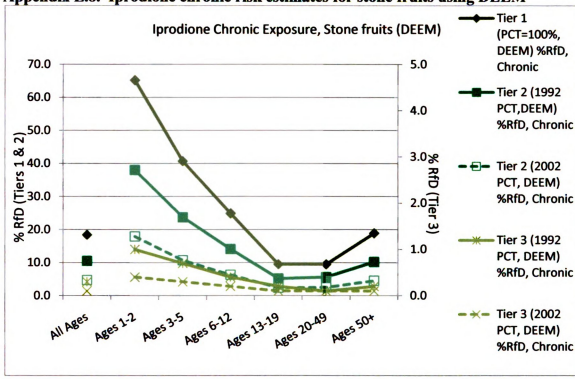
Appendix E.6. Iprodione acute risk estimates for stone fruits (Tiers 1 and 2)



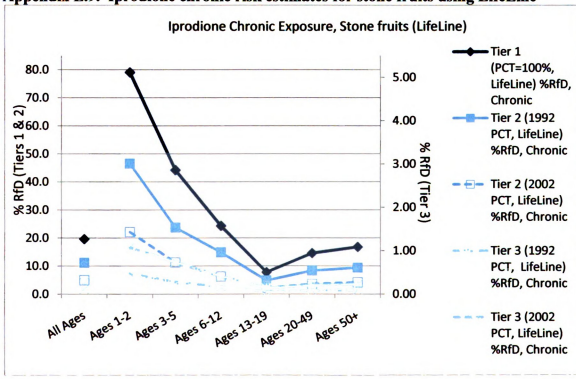
Appendix E.7. Iprodione acute risk estimates for stone fruits (Tier 3)



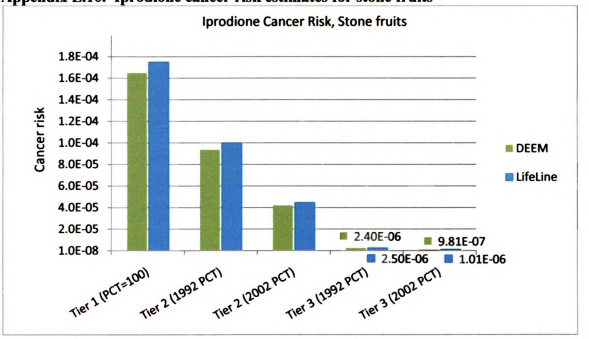
Appendix E.8. Iprodione chronic risk estimates for stone fruits using DEEM



Appendix E.9. Iprodione chronic risk estimates for stone fruits using LifeLine



Appendix E.10. Iprodione cancer risk estimates for stone fruits



APPENDIX F
Acute and Chronic Exposure and Risk Estimates for Fludioxonil

Appendix F.1. Fludioxonil acute exposure estimates for stone fruits

Population Group	DEEM or LifeLine	Acute					
		Tier 1 95th		Tier 2 95th		Tier 3 (2006) 99.9th	
		Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD
All Ages/ US Population	DEEM	0.005710	0.57	0.002140	0.21	0.002187	0.22
	LifeLine	0.006010	0.60	0.002530	0.25	0.003120	0.31
Ages 1-2	DEEM	0.023253	2.33	0.013569	1.36	0.008732	0.87
	LifeLine	0.027500	2.75	0.017800	1.78	0.011000	1.10
Ages 3-5	DEEM	0.015129	1.51	0.007139	0.71	0.005317	0.53
	LifeLine	0.015000	1.50	0.008290	0.83	0.007910	0.79
Ages 6-12	DEEM	0.008418	0.84	0.003930	0.30	0.002798	0.28
	LifeLine	0.007980	0.80	0.003760	0.38	0.004010	0.40
Ages 13-19	DEEM	0.002373	0.24	0.000839	0.08	0.001417	0.14
	LifeLine	0.001470	0.15	0.000353	0.04	0.001780	0.18
Ages 20-49	DEEM	0.002355	0.24	0.000439	0.04	0.001215	0.12
	LifeLine	0.005010	0.50	0.001840	0.18	0.002420	0.24
Ages 50+	DEEM	0.006702	0.67	0.003342	0.33	0.001973	0.20
	LifeLine	0.005870	0.59	0.002510	0.25	0.002460	0.25

Appendix F.1. Fludioxonil acute exposure estimates for stone fruits

Population Group	DEEM or LifeLine	Acute					
		Tier 1 95th		Tier 2 95th		Tier 3 (2006) 99.9th	
		Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD
All Ages/ US Population	DEEM	0.005710	0.57	0.002140	0.21	0.002187	0.22
	LifeLine	0.006010	0.60	0.002530	0.25	0.003120	0.31
Ages 1-2	DEEM	0.023253	2.33	0.013569	1.36	0.008732	0.87
	LifeLine	0.027500	2.75	0.017800	1.78	0.011000	1.10
Ages 3-5	DEEM	0.015129	1.51	0.007139	0.71	0.005317	0.53
	LifeLine	0.015000	1.50	0.008290	0.83	0.007910	0.79
Ages 6-12	DEEM	0.008418	0.84	0.003930	0.30	0.002798	0.28
	LifeLine	0.007980	0.80	0.003760	0.38	0.004010	0.40
Ages 13-19	DEEM	0.002373	0.24	0.000839	0.08	0.001417	0.14
	LifeLine	0.001470	0.15	0.000353	0.04	0.001780	0.18
Ages 20-49	DEEM	0.002355	0.24	0.000439	0.04	0.001215	0.12
	LifeLine	0.005010	0.50	0.001840	0.18	0.002420	0.24
Ages 50+	DEEM	0.006702	0.67	0.003342	0.33	0.001973	0.20
	LifeLine	0.005870	0.59	0.002510	0.25	0.002460	0.25

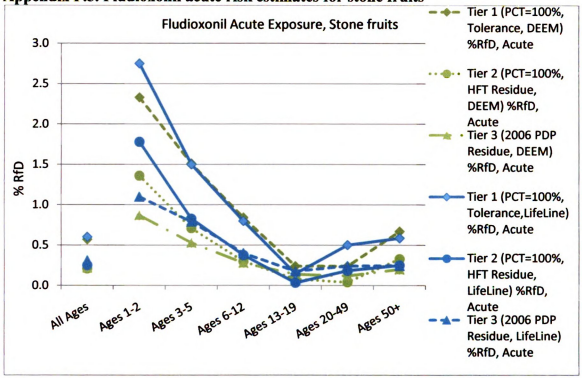
Appendix F.3. Fludioxonil acute exposure estimates for peaches

Population Group	DEEM or LifeLine	Acute					
		Tier 1 95th		Tier 2 95th		Tier 3 (2006) 99.9th	
		Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD
All Ages/ US Population	DEEM	0.001683	0.170	0.001279	0.13	0.002045	0.20
	LifeLine	0.002090	0.209	0.001650	0.17	0.002990	0.30
Ages 1-2	DEEM	0.017191	1.720	0.013065	1.31	0.008669	0.87
	LifeLine	0.019900	1.990	0.016100	1.61	0.013500	1.35
Ages 3-5	DEEM	0.008346	0.830	0.006343	0.63	0.005176	0.52
	LifeLine	0.009140	0.914	0.006520	0.65	0.008150	0.82
Ages 6-12	DEEM	0.004515	0.450	0.003432	0.34	0.002702	0.27
	LifeLine	0.004330	0.433	0.003330	0.33	0.004480	0.45
Ages 13-19	DEEM	0.000339	0.030	0.000257	0.03	0.001378	0.14
	LifeLine	0.000205	0.021	0.000155	0.02	0.001200	0.12
Ages 20-49	DEEM	0.000219	0.020	0.000167	0.02	0.001143	0.11
	LifeLine	0.001180	0.118	0.000781	0.08	0.002230	0.22
Ages 50+	DEEM	0.003847	0.380	0.002924	0.29	0.001787	0.18
	LifeLine	0.001930	0.193	0.001700	0.17	0.002320	0.23

Appendix F.4. Fludioxonil chronic exposure estimates for peaches

Population Group	DEEM or LifeLine	Chronic					
		Tier 1		Tier 2		Tier 3	
		Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD	Exposure (mg/kg/day)	% RfD
All Ages/ US Population	DEEM	0.000554	1.70	0.000122	0.40	0.000038	0.10
	LifeLine	0.000565	1.71	0.000130	0.40	0.000040	0.12
Ages 1-2	DEEM	0.002428	7.40	0.000534	1.60	0.000169	0.50
	LifeLine	0.002710	8.21	0.000624	1.89	0.000192	0.58
Ages 3-5	DEEM	0.001352	4.10	0.000298	0.90	0.000093	0.30
	LifeLine	0.001410	4.26	0.000321	0.97	0.000097	0.30
Ages 6-12	DEEM	0.000745	2.30	0.000164	0.50	0.000051	0.20
	LifeLine	0.000743	2.25	0.000171	0.52	0.000053	0.16
Ages 13-19	DEEM	0.000312	0.90	0.000069	0.20	0.000021	0.10
	LifeLine	0.000251	0.76	0.000062	0.19	0.000019	0.06
Ages 20-49	DEEM	0.000260	0.80	0.000057	0.20	0.000018	0.10
	LifeLine	0.000410	1.24	0.000090	0.27	0.000028	0.08
Ages 50+	DEEM	0.000501	1.50	0.000110	0.30	0.000035	0.10
	LifeLine	0.000442	1.34	0.000103	0.31	0.000032	0.10

Appendix F.5. Fludioxonil acute risk estimates for stone fruits



Appendix F.6. Fludioxonil chronic risk estimates for stone fruits