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A DATABASE OF ARTHROPODS RESISTANT TO
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A DATABASE OF ARTHROPODS RESISTANT TO INSECTICIDES AND MITICIDES

By

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ABSTRACT

A DATABASE OF ARTHROPODS RESISTANT TO INSECTICIDES AND MITICIDES

By

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The resistance of pest organisms to the toxic effects of pesticide is a world-wide phenomenon defined as "the microevolutionary process of genetic adaptation through the selection of biocides." The severe consequences of resistance have led governments to recommend the development of a central and permanent 'data bank' of resistance information. We designed and constructed a computerized database using relational database theory to meet this need. Our measurement of this dynamic, genetic phenomenon was a 'case' of resistance: the first documented and peer-reviewed occurrence of a species resistant to a specific pesticide formulation in a country or region. The information was drawn from previous authors and a search of the literature for cases of resistance since the last published tallies. As of 2002, there were 543 arthropod species resistant to one or more of 315 pesticide formulations in at least one part of the world.

Taking advantage of the relational data model, the resistance database was linked with the US EPA Pesticide Product Information System to compare resistance occurrence in the United States with Pesticide Registration events. The results show a strong correlation between the exponential rise of resistance cases in the 1960s and 1970s with pesticide registration patterns, as well as the more recent decline in the rate of new resistance cases.

To Terri

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PREFACE

World-wide sales for insecticides exceeded $9B in 1999 (Donaldson, 2002 #10), and in the year 2000 insecticide and acaricide (miticide) applications amounted to over 79 thousand metric tons (WAICENT, 2003). Estimates for all pesticides are substantially higher. The FAO estimates 1.5 billion hectares of the world's land were used for agriculture 1994-1996 (Fischer, 2002 #7). Resistance is the genetic based, evolutionary response of insects and mites to the pesticide suppression strategy. Arthropods are without rival in published documentation of their evolutionary ability to develop resistance with over 543 species resistant to one or more pesticides reported by 2002.(Table 1, Chapter 2, page 40)

This thesis documents the construction of, output, and analysis of a computerized database of historical reports of arthropods resistance to pesticides. The goal was not only to update the work of previous researchers who've compiled lists of resistance cases but also to deliver this updated information in a form more useful to a larger, modern audience. The desire was to openly and freely share information about resistance with the world via the Internet.

This thesis is presented in three chapters and one appendix. The first is an overview of pesticide resistance definitions, policy related to pesticide resistance, and definition of a "resistance case," the unit upon which database of pesticide resistance is based. Chapter two describes the database: it details the aspects of pesticide resistance therein, the database construction, pesticide resistance summaries, and several caveats on its use. The third chapter presents a unique analysis comparing insecticide resistance, insecticide application statistics and historical pesticide registration records in the United States. This analysis combined three distinct databases: the arthropod resistance database, the USEPA's registration database (Office of Pesticide Programs 2000) and a pesticide use database from the National Center for Food and Agriculture Policy (Gianessi and Marcelli 2000). The appendix provides the computer code to re-create the database. There was not space to print the full contents of the database: a printed table representing all data had nearly 5,800 rows and 33 columns. As of May 9, 2003 the data was available and searchable on the Internet at the website http://whalonlab.msu.edu

Work on this project was supported in part by the Center for Integrated Plant Systems of Michigan State University, the USDA CSREES, the Insecticide Resistance Action Committee (IRAC) of the international agrochemical industry, and Michigan's Project GREEEN.

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CHAPTER 1. DEFINING A MEASUREMENT OF RESISTANCE

Introduction

In the early part of the 20th century, the first pesticide-resistant arthropod species, the San Jose scale, *Aspidiotus perniciosus* (Comstock) was discovered to "resist" the toxic effects of lime sulfur in deciduous fruits in the state of Washington (Melander 1914). Since that time, the phenomenon of arthropods resisting the effects of pesticides is well documented and intensively studied, producing hundreds of articles per year (Booth et al 1983). By the year 2002, there were 543 arthropod species reported to be resistant to one or more of 315 pesticide compounds (Table 1, page 39) One species of phytophagous mite, *Tetranycus urticae* (Koch), is resistant or cross-resistant to over 75 pesticide active ingredients formulations from eight chemical classes (Table 4, page 46). The magnitude of the resistance problem, having grown in less than a century, would have us believe that the appearance of pesticide resistant populations seems to be a common result from the use of pesticides. Few, if any, pest suppression tactics known have not elicited some form of resistance response in the target pest. Biological pesticides are no exception-including pesticides derived from *Bacillus thuringiensis* ((McGaughy and Whalon 1992), viruses (Fuxa et al. 1988), and parasitoids (Messenger and Bosch. 1971).

The consequences of pesticide resistance problems are dire enough that resistance management is an accepted part of any integrated pest management (IPM) program. The extent of pesticide resistance is too large to be easily enumerated. There is a need to determine the large-scale status of pesticide resistance, as "what gets measured, gets managed" (attributed to Peter Drucker).

History of Counting Pesticide Resistant Arthropods

To appreciate the magnitude of the resistance problem, it is crucial to enumerate when and where resistance has occurred. Early reviews of pesticide resistance included Metcalf (1955) and Busvine (1956, 1957), who published lists of resistant mosquitoes for the World Health Organization (WHO).
A. W. A. Brown also published tables of resistance cases for the WHO and other agencies in the 1950s until the early 1970s (Brown 1958)(Brown 1971). These early reviews focused on human and animal disease vectors, which were the initial targets of worldwide pesticide application (Brown 1951). In the mid-1970s Brown and Croft (1975) introduced the novel concept of using pesticide resistance to improve IPM by determining systems of compatible natural enemies and pesticides. Compatible natural enemies are species that would be resistant enough to survive the application of pesticides to manage pests within an agro-ecosystem. This culminated in a database (SELECTV) of pesticide resistant or pesticide tolerant biocontrol agents such entomophagous or parasitoid arthropods names (Croft 1990), (Theiling and Croft 1988). The SELECTV database has been subsequently updated and portions are available from Oregon State University (Jepsen and Hennigan 2000).

The penultimate publication to the current database, initiated at the request of the United Nations Food and Agriculture Organization (UN FAO), is a thorough review of resistant arthropod research (Georghiou and Lagunes-Tejeda 1991). This text documented 511 species that are resistant to one or more compounds in one or more regions (states, provinces, and countries), covering over 200 pesticide compounds based on 1,263 cited references (Table 1, page 39).

Definitions of Resistance

To enumerate occurrences of pesticide resistance, resistance must be clearly defined. Today the debate over resistance definitions rages on stronger than ever, perhaps exacerbated by our increasing technical ability to detect the alleles of an organism that confers resistance to, or increased tolerance for, a particular pesticide or class of pesticides. A working definition must be chosen to set the criteria for inclusion of a resistance report into the database.

The term "resistance" comes from the title of the first modern article documenting this phenomenon by A. Melander: "Can insects become resistant to sprays?" (Melander 1914) One of the first explicit definitions came from a panel of WHO - experts who defined resistance as "the development of an ability in a strain of insects to tolerate doses of toxicants which would prove lethal to the majority of individuals in a normal population of the same species" (World Health Organization 1957). However, it may be very difficult to find the "normal population" required by this definition, after more than 60 years of selection pressure from synthetic insecticide applications around the world ((Otto et al. 1992). In addition, the WHO definition says nothing about individuals resistant to pesticides – resistance in their definition is treated strictly as a population-level phenomena. This distinction has significance today because new techniques can detect the presence of resistant alleles in individuals (ffrench-Constant and Roush 1990). Screening for a very low frequency of resistance alleles, crucial for resistance management in genetically engineered plant pesticides such as *Bacillus thuringiensis* (Bt) toxin producing crops (Zhao et al. 2002a), would not fit the WHO definition.

J. F. Crow (1960) presented a more inclusive definition of resistance that considers single individuals as well as populations. He proposed "resistance marks a genetic change in response to selection" (Crow 1960). This definition is not restricted to high resistance levels: incipient resistance was included. However, the most significant consequence of pesticide resistance was missing: field-failure. While Crow's definition gets to the genetic cause of resistance, it does not identify the selecting agent, direction or result of selected genetic change. While Crow's statement is true, it falls short of a modern understanding of resistance management because it's possible to use selection to both increase and decrease resistant allele frequencies in a population along a continuum from resistance to susceptibility (McKenzie, 1996 #75, pp 89-121).

In 1987, R. M. Sawicki focused Crow's definition closer to an operational sense of resistance by re-incorporating the notion of field-failure present in the WHO definition, "Resistance marks a genetic change in response to selection by toxicants that may impair control in the field" (Sawicki 1987). That is, a genetic change that leads to increased frequency of resistant individuals that results in a control problem. Note, however, that Sawicki was careful to consider the possibility that resistance may or may not reduce the level of pests controlled. By this definition, therefore, strains of organisms that are selected for pesticide resistance in the laboratory are considered resistant.

In 1986, the introduction to a classic publication on resistance from the National Academy of Sciences states: “resistance is a consequence of basic evolutionary processes” (Glass 1986b). This definition mirrors Crow's statement above, but adds that resistance is simply an extension of existing natural processes. That is, it should come as no surprise that insects and other herbivorous arthropods have become adapted to synthetic or natural toxins when many of these same species feed unaffected on plants defended by secondary defense chemistry deadly to most other organisms (Croft and Brown 1975).

Whalon and McGaughy defined resistance as “the microevolutionary process of genetic adaptation through the selection of biocides” (Whalon and McGaughy 1988). This clearly indicates the type of change, the agent of change, and the direction. Toxicants and “biocides” are essentially equivalent, however the term “biocides” is more closely related to our notion of a deliberately applied pesticide, whereas toxicants might be thought of as naturally occurring plant secondary defensive compounds. By mentioning 'selection', they imply reduced action of the biocide, but as with Crow (1960), no mention of the conditions under which the selection process is made. Clearly this definition includes both lab-selected populations and field populations among pesticide resistant species.

The agrochemical industry has not been idle in the effort to understand, define, monitor, and manage pesticide resistance. The exponential increase in the world-wide cases of resistance during the first three-quarters of this century, combined with scientific and public pressure, led the pesticide industry to form various “Resistance Action Committees” including one for insecticides (IRAC), fungicides (FRAC), and herbicides (HRAC). These resistance action committees focus on various aspects of resistance management, especially monitoring resistance. IRAC's own definition of pesticide resistance, quoted directly is (IRAC 1997):

> An insect should only be viewed as resistant when:
>
> - The product for which resistance is being claimed carries a use recommendation against the particular pest mentioned, and has a history of successful performance.
> - Product failure is not a consequence of incorrect storage, dilution or application, and is not due to unusual climatic or environmental conditions.
> - The recommended dosages fail to suppress the pest population below the level of economic threshold.
> - Failure to control is due to a heritable change in susceptibility of the pest population to the product.
>
> Note: Sensitivity to an insect or mite control agent must decrease significantly before field failure is experienced. The term "resistance" should only be used once field failure has occurred and been confirmed.

The Committee's definition stressed that the term "resistance" applies only when field failure is confirmed. Although the IRAC criteria were sufficient to ensure that a pest population had truly developed resistance, the definition is still problematic for the early detection of resistance, setting the stage for a system of anecdotal reporting and resistance crisis rather than prevention and management. The implication here is that detection of low frequencies of resistant alleles in a population does not warrant a resistance outcry. The IRAC definition emphasizes the disagreement of whether "field failure" is a necessary condition for the definition and hence discovery of a case of resistance. One implication of a declaration of resistance is that the pesticide will no longer kill enough of the pest population below the integrated pest management (IPM) economic threshold, and henceforward that pesticide, and perhaps all others in with the same mode of action, should be avoided, as it no longer works. On the other hand, if it continues to be effective, it likely will work poorly, which is very undesirable in agricultural production or human and animal health protection systems with very low tolerance for pest damage.

The converse of the requirement for field failure is that lab selected resistance would fit into the definition. Since the transition from anecdotal reporting to resistance management would require resistance detection, monitoring efforts can now include the detection of resistant alleles in a sufficient amount of time to change management, and avert or ameliorate resistance evolution. Consider a case in which resistant individuals are present in small numbers and the recommended dose suppresses the pest population below the economic threshold. In this instance, there is no detected "field failure" and by the IRAC definition there is no resistance. But the genetic potential is present for the frequency of resistant individuals to increase in future generations, leading to control failure. On the other hand, it would be argued, that even with an increase in resistant allele frequency, a correct insecticide application would guarantee reduction of pest populations below an economic threshold. Further more, there are additional factors aside from pesticide application that may affect reduction of pest population levels. These factors could include the pest-mediating impacts of predators and parasites, pest movement and spatial distribution, crop phenology and susceptibility, weather, pest life-stage (e.g. larval instar), and frequency of resistant individuals (Roush and McKenzie 1991). That said, it is obvious that special care has to be taken in resistance definition and it's interpretation.

However, by the time field applications fail to control a pest population and it is declared 'resistant,' it may be too late to implement resistance management strategies for the pesticide in question. Once the resistant allele frequencies exceed just 1%, no resistance management tactic will suppress resistance from overtaking the population (Roush and Miller 1986). This resistance scenario could also be exacerbated by cross-resistance in the pest to other chemicals with a similar mode of action. Therefore, early detection of resistance is an important aspect missing in the IRAC definition.

Finally, a change in allele frequencies may also be a product of deliberate manipulation, as opposed to a by-product of human inputs into the environment. Examples include the populations of insects select for resistance to crystals of *Bacillus thuringiensis* that have been developed in the laboratory (Bolin et al. 1999); (Zhao et al. 2000). While several of these definitions mention the 'field' indicating the agroecological environment, none explicitly mention such lab-selected populations which can be useful in understanding some field-resistance cases.

Behavioristic Resistance

Most documented resistance studies document physiological adaptation as the resistance mechanism. However, behavior has played a role in resistance since the phenomeon was first studied (Busvine 1956). The term behavioral (or "behavioristic") resistance describes the development of the ability of individuals within a population to avoid a dose of pesticide that would otherwise prove lethal (WHO 1957). There are, however, limited examples of behavioral resistance. In at least one case, behavioral resistance was confounded with an unidentified and undifferentiated sibling species. Initially, resistance workers believed that a species of *Anopheles* mosquito in Africa avoided residues inside houses by remaining outdoors (Brown 1958). Later, this "behaviorally resistant" population was demonstrated to be a complex of sibling species (Colluzzi et al. 1977). One example of true behavioral resistance can be seen in the Australian sheep blowfly, *Lucillia cuprina* (Wiedemann), in which the oviposition of the fly was selected for behavioral resistance to cycloprothrin (Mariath et al. 1990). By essentially all of the definitions above, for a pest to be declared resistant by a behavioral mechanism, genetic differences must be shown, rather than present only observations of insects avoiding pesticides (Roush and Daly 1990). For physiological resistance, this is assumed, even when the gene conferring the trait remains unidentified, while for behavior it must be explicitly shown. In this case, genetic studies have shown that this behavioristic resistance is partially dominant and that the origin is polygenic (McKenzie et al. 1992).

A more recent case of putative behavioral resistance to a pest management strategy was observed in the corn root worm, *Diabrotica vigifera vigifera* (LeConte) (O'Neal 1999), which over-winters as larvae, and lays eggs which hatch and feed on corn roots. In Illinois, by laying eggs in soybean fields that require two years to hatch, this insect appears to have overcome alternative corn/soybean rotation, the dominant strategy of managing *D. virgifera* population levels. In the season following soybean, fields with *D. vigifera* eggs hatch and larvae attack the corn. If this oviposition behavior is a result of a genetic change in the population, selected for by the pest management strategy, then perhaps this case meets Whalon and McGaughey's (1998) definition. However, there is some debate about the cause of this newly observed behavior, and the possibility exists that it is not a change in the organism itself, but that the agro-ecological landscape has changed. Perhaps the overwhelming majority of acreage devoted to corn-soybean rotation has given *D. vigifera* no other choices for ovipositional sites within its dispersal range and females for lack of readily-available corn-acreage are overwhelmed by their oviposition drive and simply oviposit indiscriminately in soybean (O'Neal et al. 1999).

Due to the limited cases of behavioral resistance, the myriad factors affecting insect behavior, the lack of acceptable documentation, and other issues making genetic proof extremely difficult, the current database does not include these cases of resistance unless there is scientific, peer-reviewed acceptance of a genetic basis for behavioral resistance. However, the development of bioassays to discriminate between what might be termed behavioral susceptibility and behavioral resistance, together with genetic studies, certainly could be important for future resistance development. This will be increasingly important for pesticides that require the pest to ingest toxins to be effective, such as foliar Bt, Bt plant-pesticides, or insect growth regulators (IGR).

Definition of the unit case of resistance

Resistance workers may disagree as to whether or not pesticide resistance is a property of a population or an individual, or even if failure to control a field population is a requirement for resistance. Yet there is general agreement that resistance occurs in finite units of time and space. To track the global phenomena of pesticide resistance it is necessary to identify a unit of pesticide resistance, and the origin and need to declare "case" of resistance for a catalog of resistance. For our purposes we define a case of resistance as a population (species per location) with significant alleles conferring resistance to a particular pesticide formulation. A pesticide, as applied, is often a formulation of multiple active pesticide compounds and several other ingredients such as synergists, adjuvants, so-called inert ingredients, and other additional pesticide compounds. Due the complexity of resistance and the importance of the presence of synergists for an applied formulation, a case must be distinct for each formulation that a pest population is tested against. For example, testing with a compound alone or together with a synergist such as Piperonyl Butoxide.

Identifying the edges of these units may very well be impossible but the function here again to elucidate the scope of the resistance cases, not necessarily to delineate them. While evidence points to some cases where an allele conferring resistance is spread globally (ffrench-Constant et al, 2000), others may be more isolated, such as Hawaiian Diamondback Moth (*Plutella xylostella*) populations resistant to Spinosad (Zhao et al. 2002b). In the latter example, it was clear when the resistance was selected for: within specific valleys on the island of Oahu between 1999 and 2001 when careful monitoring was done. Where global or continent-wide resistant populations exist, it may be difficult to identify a temporally and spatially explicit case. If the resistant population was selected from rare alleles present in wild-type populations, one might expect the genotype to be similar enough to consider all locations equal. However, in many cases resistance workers are only report the phenotype. This is because of the complex and costly research necessary to investigate the genetic basis for resistance. Given only the phenotype, one cannot say with certainty that a resistant population from the same species is distinct, and/or 'isolated' in a region. Nor can one infer that two different resistant populations share the same genotype because there is no delineation between a resistant and susceptible phenotype. Therefore one can only consider populations from distinct regions as distinct cases of resistance. However, the spatial scale as which we measure will greatly affect the number of cases that are counted. Geo-political boundaries are often used to identify regions containing pesticide resistant populations, in spite of the range of sizes of countries. In many cases this is all the information that is provided in a report of resistance (see chapter 2). Merging all cases from the continental US would result in a much-reduced count versus using individual states.

Therefore resistance may be delineated as the first occurrence of a species discovered to be resistant to a pesticide formulation (of one or more ingredients) collect from a defined region. These five elements (time, species, pesticide, place, and document) define a unit, or case, of resistance for inclusion in a database of resistance.

Measuring the Consequences of Resistance

David Pimentel of Cornell University published one widely cited estimate of the impact of pesticide resistance at production loss of US$1.4 billion for all major crops in the United States (Pimentel et al. 1992a). To arrive at this figure, he started with an estimate of yield loss in California cotton production in 1984 and applied this proportion the the entire cropping system of the US. However, the logic of this estimate is flawed. First, cotton is not a good example crop as cotton has heavier pest pressure, more insecticide use and much higher incidence of resistance. In 1997, cotton fields around the country received applications from one or more of 40 distinct insecticides active ingredients (Gianessi and Marcelli 2000). Second, levels of resistance vary across agro-ecosystems, and vary across regions. Third, the impact of resistance changes over time within an agro-ecosystem. Costs from resistance since 1984 must certainly have changed as pest populations change and as new pesticides are registered to address resistance issues. Certainly the introduction of transgenic cotton has made dramatic changes to pest management practices for cotton growers.

Pesticide Resistance Policy: a call for a database

Resistance drives not only IPM decisions, but also pesticide policy in the US and Europe and other parts of the world. In fact, the UN declared pesticide resistance as one of the top priorities (UNEP 1979). In the US, a 1984 study initiated by the US Board on Agriculture of the National Research Council made

16 recommendations, one of which stated, "Federal agencies should support and participate in the establishment and maintenance of a permanent repository of clearly documented cases of resistance" (Dover and Croft 1986). This recommendation was made law by the Food, Agriculture, and Trade Act in 1990, which called for a "national pesticide resistance monitoring program."

The Food Quality Protection Act of 1996 (FQPA) made dramatic changes to US pesticide policy by amending the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Among the FQPA amendments is an invocation of resistance as one of the four conditions designating "minor use" status for a pesticide registration. 'Minor uses' are defined as application sites in the US where the crop has less than 300,000 acres nationally. "Minor use" registrations have waived some registration fees (section (4)(i), paragraph (4)) and fewer data requirements (FIFRA section (3)(c) paragraph (2) subparagraph (A)). Minor use status therefore is an incentive to pesticide registrants to pursue EPA approval of their products in markets with otherwise little or no profit to the registrant. Minor uses of pesticides are given special status in many parts of section 3 (registration) and section 4 (re-registration) of FIFRA. Specifically, a pesticide registration may be declared a "minor use" when the US EPA, USDA, and the pesticide registrant determine that profits from sales of the pesticide for a specific use "does not provide significant economic incentive to support the initial registration or continuing registration" and that the use "plays or will play a significant part in managing pest resistance." A "minor use" pesticide is given special provisions that reduces the pesticide registration burden for otherwise the registrant had little to gain economically despite the fact that the pesticide may be important for the continued production of specific crops. (FIFRA section (3)(c) paragraph (2) subparagraph (A)). FQPA also added two new sections to the FIFRA establishing 'minor use programs' in both the USEPA (section 32) and the USDA (section 33).

In the European Union (EU), data eliminating the possibility of cross-resistance in the target pests is a requirement for every pesticide registration (EPPO 2002). To help determine which pesticide are useful for resistance management programs, both US and EU rules require that such pesticides be identified and cataloged. The FIFRA mentions resistance in that the mandated USDA minor use program (FIFRA96 section 23) will "carry out…the national pesticide resistance monitoring program established under section 1651 of the Food, Agriculture, Conservation and Trade Act (FACTA) of 1990 (7 U.S.C. 5882).

In fact a call for such a monitoring program came earlier when a 1984 study initiated by the Board on Agriculture of the US National Research Council (NRC) made 16 recommendations, one of which stated that "Federal agencies should support and participate in the establishment and maintenance of a permanent repository of clearly documented cases of resistance" (Glass 1986a).

CHAPTER 2. DESIGN AND SUMMARY OF A RELATIONAL DATABASE OF PESTICIDE RESISTANT ARTHROPODS.

Introduction

Pest management is challenging enough, and pest resistance to pesticides significantly increases the complexity, expense and perhaps the environmental impact of pesticides in the agroecosystem (Metcalf 1983). For those pesticide uses with even low frequency for resistance developing in the target pest population, resistance management must play a part in any Integrated Pest Management (IPM) plan (Glass 1986a). If pesticide resistance alleles are present in a pest population, or soon likely, alternative pesticides must be selected because the pesticide will not be effective (field failure) if resistance is not delayed. However, in almost every instance it is difficult to detect resistance in a local population before field failure occurs. In many of these cases, the genetic basis for resistance is already fixed in the population (>1% allelic frequency) and development many not be slowed with any strategy (ffrench-Constant and Roush 1990). Successful integrated pest management, which incorporates resistance management, requires diverse and accurate knowledge about the nature of the pesticide resistant population.

One way to address this problem is to determine what the status of resistance may be for each pest and pesticide combination in the environment for each pesticide that is available for use. While it may be overly simplistic or even specious to reduce the complexity of resistance to a binary state (resistance/not resistant), some indication whether pesticide resistance (or the potential) is present is one of the first insights necessary for wise pest management.

Information related to pesticide resistance is scattered throughout the agricultural research literature. Publications detailing insecticide resistance were frequent and diverse, with 100s annually, covering every imaginable aspect of resistance. Which of these aspects of resistance could or should contribute to a "permanent repository" as called for by the US Board on Agriculture (Glass 1986a)? How would these publications be used to define the status of resistance to address both the needs of pest management and of policy makers (see Chapter 1)?

Some of these resistance information needs in insects and mites (arthropods) were met in part by the work of George Georghiou at University of California, Riverside (Georghiou 1972, 1983, 1986, Georghiou and Lagunes-Tejeda 1991). The approach is straightforward: the authors measure resistance by listing pesticide resistance "cases" (see chapter 1, pg. 11) by the year the cases were published. A "case" is the first report of resistance on record, described by five elements:

1. cited reference,
2. arthropod species,
3. pesticide formulation it is reported to be resistant to,
4. region where the resistant population is found, and
5. the year of the report.

Georghiou (1983) noted that this information was computerized (Georghiou

1983), but to the public it was available in book form (Georghiou and Lagunes-Tejeda 1991) and unfortunately in a very limited printing by the Food and Agriculture Organization of the United Nations.

Clearly the need existed for a computerized database of arthropod resistance information, publicly available and amenable for summary and analysis. To address this need, a computerized database of resistance cases was designed and constructed using relational database theory.

Materials and Methods

Relational database theory was employed as the methodology for designing the data model to capture the resistance case concept (Codd 1970) (Date 1995). Nearly every modern commercial DBM software system is based upon this well-understood theory (Elmarsi and Navathe 1994). The relational database model is a formal theory of information modeling, defining highly structured data elements (relations or tables) that consist of sets of tuples (rows), well-defined mathematical operations on sets of tuples, the results of which also defined as sets of tuples. Each relation (table) must have one or more attributes (columns) that unique identify each tuple, designated the primary key (PK). Related information from two separate tables may be joined by inclusion of the primary key from one table in another table as a foreign key (FK). This technique was used extensively for the resistance database.

It was clear that data gathering would be the most costly process for resistance information given the sheer numbers of resistance research papers. Just as Georghiou 1991 incorporated A. W. A. Brown's work, we began the system with resistance records contained in Georghiou and Lagunes-Tejeda (1991). To maintain comparability with reported resistance figures prior to 1991, we modeled a portion of the database to completely cover the information included in this text. Timelines previously published in Georghiou and Melon (1983), Georghiou (1986), and Georghiou and Lagunes-Tejeda (1991) could therefore be extended.

There were several considerations necessary to arrive at a database structure given (1) design goals, (2) data and (3) a description of the semantic relationships within the data itself (Date 1995). While algorithmic procedures exist for modeling information for construction of a database (Halpin 1996), in this instance a functional design was clearly evident based upon the inherent structure of Georghiou and Lagunes-Tejeda (1991). The columnar form of this text presented the data directly to a relational database model. The format of this compilation of resistance cases was much more amenable to mapping into a relational database design than data from at least one previous author {e.g. Brown, 1971 #6}, who aggregated key information by reporting chemical class rather than detail resistance cases by individual compounds.

Entity-relationship techniques (Chen 1981) (Date 1995) were used to design the semantic model of Georghiou and Lagunes-Tejeda (1991) dataset with the dual goals of preserving the inherent structure for compatibility and to allow the expansion the information for more detailed analysis (Figure 1). The core of the model is the entity 'resistance' (cross-hatch shading), corresponding to a list of the cases of reported resistance, made up of five attributes discussed previously (page 17). These five attributes uniquely identify a case of resistance; the four related entities were joined with common attributes indicated by arrows. All of these relationships have one-to-many cardinality. In Figure 1, arrows point from the primary key table to the table containing the foreign key. All but the year attribute was determined to be complex enough to warrant expansion into separate entities, during the normalization process of the semantic model.

This model, as is standard practice, includes entity attributes with no semantic meaning that were used to form relationships between entities (Date 1992). These unique identification codes, typically numeric, were used in practice by join operations during data analysis. Such codes provide the advantage that text identifiers may be corrected or changed without a cascade of corresponding changes in the database. For example, updating genus or species names in the arthropods table as they change in the literature (*Heliothis zea* to *Helicoverpa zea*.) would not break the relationship between the arthropods table and related resistance records since the numeric key relates them. Similar examples can be made for location (e.g.country names) as they change in time. While several other variations on this semantic model were possible that would capture the information in the text, all would essentially contain a central entity for a resistance case.

While this parsimonious model captures the data in Georghiou and Lagunes-Tajeda 1991, to achieve the design goals for further manipulation required extending the model through additional attributes and entities. First, a linkage to external databases, which requires mapping records in the local database with external standardized codes, was built. This innovation was used to make standard codes such as pesticide active ingredient list compatible with existing USEPA codes (Office of Pesticide Programs 2000). These codes provided crucial linkage to the standardized identifiers for pesticides. The relationship between a chemical structure, a compound common name, the legal term "active ingredient," and a commercially available pesticide formulation is much more complex than a single chemical name. To perform analysis that summarized counts of core entities for groups of arthropods species, pesticides based upon chemical classes, and several other operational factors.

Based on this model, instructions were coded to build a relational database using a variant of standard Structured Query Language (SQL)(ISO 1992). Few relational database management systems (RDBMS) implement this standard completely, and many add proprietary extensions that negate the advantage of wide compatibility. All, however, implement some form of this relational databases *lingua franca*. This project used the MySQL RDMBS , which is freely available, closely adheres to the SQL standard, and is compatible with many existing computer systems (see program code listed in Appendix 1, page **Error! Bookmark not defined.**).

Data and references from Georghiou and Legunes-Tajeda (1991) were entered into the database system using forms developed in Microsoft Access version 7. Resistance cases based upon the review of that covered 50 journals from 15 countries in four languages, over refereed journal articles were entered into the database. Like previous efforts, the source data is the result of a review of published resistance accounts, obtained through a series of library and publication database searches. Only cases published in the peer-reviewed literature were selected for input. As has been stated previously, a report from the field of insecticide failure is not a sufficient indication of the presence of resistant individuals without scientific peer reviewed bioassay data. Obviously, scientists, resistance workers, and members of the agrochemical industry requiring empirical proof may view an undocumented claim of resistance with skepticism, even when such claims may in fact be true.

Significant variation exists in the resistance documenting methods in published reports. Standardized methods for resistance detection do exist. The UN FAO has been publishing standardized resistance bioassay methods for species affecting human health since 1969 (FAO reference). Nevertheless, lab techniques are constantly improving, and authors often interpret and report results of standardized tests differently (Croft 1986). Even within these established standards there are many factors that might cause misunderstanding, and it is difficult for any reviewer to determine the veracity of such diverse data. Therefore, part of the data input strategy was to rely upon the expertise of the reviewers of manuscripts and the editorial boards of publications as well as upon our own review of the values of the median lethal doses (LD_{50}), median lethal concentration (LC_{50}), median lethal time (LT_{50}), median knockdown (KD_{50}) and discriminating doses as the final criteria in determining a resistance case. The primary objective was to a statistical difference between resistant and susceptible populations for previously unreported species, compounds, and/or regions before the citation qualified for a new resistance case.

A very commonly reported measure of resistance was the resistance ratio (RR), which is the ratio of dose-mortality of the bioassayed strain (defined by the morbidity statistic used, e.g. LD_{50}, LC_{50}, KD_{50} or TL_{50}) to a known susceptible strain. We used reports of RR greater than or equal to ten, a traditional point of departure as a general rule for declaring a resistance case. However, in some instances we also included reports with RR smaller than 10 fold when the authors clearly made a case the resistance was sufficiently high to cause significant field resistance. No specific RR will predict field failure for all cases. However, this approach allowed consistency between records from Georghiou and Lagunes-Tejeda 1991. Factors involved in deciphering a resistance report included the Whalon and McGaughey (1998) definition of resistance, several intrinsic and extrinsic factors of the test itself and the type of statistic used to report the resistance level. Published reports of resistance cases developed in the laboratory were also included as a warning of potential or impending field failure. This is consistent with the working definition of resistance, which states that the genetic change conferring resistance may or may not lead to field failure.

Confounding this categorization of resistance literature was the observed variability among definitions of a pest 'population.' The catalog of resistance would not be complete without a spatial definition of pesticide resistant populations. Researchers often reported collecting individuals from multiple, reproductively isolated locations, but unfortunately reported aggregate bioassay results. Populations were described with vague spatial definition or overlapping boundaries. This was not surprising as the sampling and bioassay requirements to map the boundaries of a population are expensive. We used a coarse geographic resolution to circumvent these problems and thus limited distinction of regional cases to the national, state, or provincial level. Again, this design was comparable to Georghiou and Lagunes-Tajeda (1991).

It is presumptuous to say that all new resistance cases since 1991 were uncovered by this effort given the scope of this world-wide phenomena, the diversity of reporting mechanisms and the language challenge. Journals reviewed were published in English and a few in Spanish, French and Italian. In addition, several cases not included in previous resistance compendiums were contributed by a resistance researcher and former citizen of the Soviet Union (Il'Ichev, 2000). While the coverage of other languages was spare, the enumeration of pesticide resistance in arthropods is a dynamic process, not only as new populations develop resistance, but also as past reports from around the world are illuminated. One major benefit of a computerized repository for this information is that it may be updated and analyzed continually. To that end our database is available, as of May 9, 2003, via the Internet (http://whalonlab.msu.edu).

The Insecticide Resistance Action Committee (IRAC), an affiliation of agrochemical industry representatives, conducted an international survey to determine the status of resistance in many areas of the world. The result was a spreadsheet indicating which insects (or class of insects) have resistance to particular chemical classes together with the type of information source (field, confirmed, publication or rumor). Although this survey does not always indicate which specific pesticide the resistance is to, the data were incorporated it into the database, using the chemical class as the formulation, and, if no compound of this class was currently entered into the database for this species, the case was entered. The justification for including these data was the evaluation rigor and expert peer review process IRAC employed (IRAC, 2002). Unfortunately, however, the majority of cases in this document could not be included in the database because of lack of specificity either for the pesticide as described above or because only the genus was provided.

Results

Five hundred and forty three species of arthropods were reported to be resistant to one or more pesticides: 499 pest species (agricultural, urban or human health pests), and 44 species that were not pests (natural enemies and others) (Table 1). Two hundred seventy three genera, one hundred three families and sixteen orders represented species. Three hundred and five pesticide compounds were reported with many cases, species were resistant to more than one compound, either multiply-resistance (simultaneously carrying the resistance factors for multiple compounds), cross-resistant (having never been previously exposed yet resistant to that pesticide), or simply resistant to different compounds at different locations in time and space. Since 1989, 38 previously undocumented arthropod species were reported to be pesticide resistant in some capacity, just over 6% under increase in twelve years. However, there was a much larger proportional increase in the number of pesticide active ingredients to which arthropods have developed resistance.

Resistance Summary by class

The overwhelming majority of reported resistance cases related to organophosphate (44%) and organochlorine (32%) insecticides (Table 2). This was not surprising as these classes of compounds include the most popular pesticides to date, and many have been in use for over half a century (Osteen and Padgitt 2002). Pyrethroids and carbamates together constitute only about 16% of resistance cases. Bacterial pesticides, primarily those produced from species of *Bacillus thuringiensis* (Berliner) (Bt), represent a mere 2% of cases, and all other remaining chemical classes combined have led to the development of less than 2% of resistance cases, as reported in the literature.

Top Twenty Resistant Arthropods

Arthropods were ranked based upon the number of unique compounds to which documented resistance was reported at least once. Table 4 (page 46). reports the twenty most resistant arthropods according to this ranking. While not a ranking of pest importance or severity, many of the world's most destructive pests were included. It should be stressed that exclusion of a particular pest from this ranking does not reflect the lack of importance of an arthropod's economic importance (e.g. pest status). Indeed, every case of resistance is important and should be observed in the context of the system of production, human health protection, geographic area, and other factors. While many of these reports were decades old, new resistance reports surfaced steadily in the past ten years. Inclusion on this list may have been indicative not just resistance development from intense selection pressure, but also sheer numbers of pesticide against which these species was bioassayed. Combination of diversity pesticides used in the field, world distribution, and scientific interest reporting results of testing against a wide variety of compounds. Nonetheless, documentation of resistance to multiple pesticides is a strong indicator of heavy reliance on pesticides for pest management.

Genetic, biological, and operational factors significantly influence the development of resistance (Georghiou and Taylor 1986). Members of this list share worldwide distribution, severe crop damage or human health implications, and a large body of research. While many of the species listed also share similar biological and ecological characteristics including high generation turnover, great mobility and migration, and large numbers of offspring per generation as well as operational factors.

There were four pests of human health importance and sixteen agricultural pests in this ranking, a different ratio between these classes of pests than is of counts of species in the entire database (approximately 2:3 human health pest species to agricultural pest species in the database overall). In fact, no anopholene mosquito breached the top twenty. Poor representation by serious human disease vectors may have been indicative of the fact that the developing countries were most affected the diseases vectored by these pests, and the economic reality that many still use cheap organochlorines such as DDT for human health protection.

A spider mite (*Tetranychus urticae* (Koch),) for the greatest number of reported cases at 76, just 6 more compounds than the insect which placed second, the diamond back moth, *Plutella xylostella*. These species were closely followed by the green peach aphid, *Myzus persicae* (Sulzer), with 68 reported. There were four other homopteran species that have developed resistance to many conventional and novel compounds: *M. persicae Aphis gossypii, Phorodon humuli,* and *Bemisia tabaci.*(Gennadius) Beside common biological and ecological characteristics distinctive to this order, some homopterans were responsible for virus transmission driving economic thresholds very low. The response by growers is frequent application of pesticides, especially in *M. persicae* and *B. tabaci.* (whitefly) It was reported that Isreali tomato growers resorted to two insecticide applications per day to reduce the spread of Tomato Yellow Leaf Curl Virus by whitefly (Berlinger et al. 1993). In addition, frequent treatments in multiple hosts often cause a great deal of selection of individuals for resistance. Conversely the damson-hop aphid, *Phorodon humuli* remains during the summer only in hops and wild hops and stays close to the crop. But in this instance monophagy, when combined with high fecundy and primary pest importance (hops), make this a "the worst case scenario" for the development of resistance (Denholm et al. 1998).

Consumer demands for perfect cosmetic standards and a stricter restriction of "insect parts" present in food force producers to lower economic thresholds (Pimentel et al. 1992b). On crucifers the diamondback moth causes qualitative damage in addition to quantitative both of which growers use lots of insecticide. The use of Bt has reduced the proliferation of conventional insecticides in crucifers. However, intense use of this alternative pesticide has led to the development of field resistance to Bt (Tabashnik et al. 1990, Shelton et al. 1993).

Four Lepidopteran species were included in our top twenty including *Heliothis virescens*, *Spodoptera littoralis*, and *Helicoverpa armigera*, all of which have been exposed to heavy insecticide treatments in cotton. These species treatments in other hosts have increased the selection pressure. In the past, industrial cotton had been the recipient of more than 40% of the applied insecticides produced in the world making it a significant source of pesticide resistant species (National Research Council 2000).

Distinctive aspects of phytophagous mites, including very high fecundity, many generations per year (16 generations per year), and high selection pressure, often leads to pesticide resistance (Kennedy and Smitley 1985). It is not surprising that the spider mite *Tetranychus urticae* (Koch), a serious pest of fruit crops, tops our list. Two others, *Panonychus ulmi* and *Rhizoglyphus robin* are in the top ten.

Conversely the Colorado potato beetle (CPB), *Leptinotarsa decemlineata* typically has only from one to three generations per year, fewer than the majority in Table 4. However, this insect has a tremendous capacity to colonize a wide range of hosts including many species of the Solanacea family. Adaptation to defensive secondary metabolites produced by solanaceaous species family may have allowed the Colorado potato beetle to increase its range of hosts from the original wild hosts to those of the cultivated potato. Adaptation through thousands of years has made this insect a formidable species to breakdown xenobiotics, a trait which may have extended to insecticides. Another important factor in the development of resistance for CPB is reduced migration where "local selection" plays an important role (Grafius 1995). In local selection, individuals in a population do not disperse or immigrate, reducing gene flow and elevating the frequency of individuals with resistant alleles.

Similarly, the appearance of the high ranking (fourth) cattle tick, *Boophilus microplus*, was related to the method of application and host specificity. Total coverage of cattle by immersion in insecticide solutions increases the resistant selection and individuals with resistant alleles were rapidly screened. Given the limited host range of this insect, in terrestrial agriculture this would correspond to 100% acreage treated.

Insecticide resistance is also a problem in urban areas. For example, the housefly (*Musca domestica*) is a significant pest in veterinarian circles. In most farms, high selection pressures for resistance resulting from insecticide treatments occur in areas where the treatments were concentrated, the residuality of the insecticides is long, and the populations were relatively isolated (Keiding 1977). In addition, the common practice of screening windows and doors to avoid immigration also has led to rapid selection and an increase in resistant individuals (Georghiou and Taylor 1986).

Protection of human health has led to an intense use of insecticides. As a result, there were two species of mosquito: *Culex pipens* (ranked 9th), *Culex quinquefasciatus* (ranked 13). Anophelene mosquitoes did not make this list. However, there are far and away more resistant species from that genus than any other genus (63) . In fact there are more mosquitoes than any other arthropods on this list. *Anopheles albimanus,* that have developed resistance to many insecticides and have become vectors of diseases. In the year 2000, billions of people in the world's tropics were at risk of contracting malaria from such vectors (Marshall, 2000). Malaria infects 300 to 500 million people per year and every year 1.5 to 2.7 million individuals die from the disease (Danis and Gentilis 1998). *A. albimanus* is one vector of this disease that has developed resistance to insecticides used to curb the spread of Malaria. Other species in the genus *Anopheles* have developed resistance to insecticides as well, yet *A. albimanus* has maintained the greatest resistance in comparison with these other Malaria vectors. One reason for this higher resistance of *A. albimanus* to multiple compounds is the intense insecticide selection pressure exerted over the complex of insect pests in cotton (Georghiou, 1984, Georghiou, 1990) that also indirectly selected immature stages in breeding sites and adult stages in resting sites.

Tribolium castaneum, red flour beetle, is a principal pest of stored grains where complete coverage by insecticide treatment is a common practice to control insects. High selection pressure and low migration were some of the causes that have led this insect resistant to many insecticides.

Pesticide Resistance Timeline

Since 1983 published timelines of resistance. The first results, published from data up to 1979, demonstrated an exponential increase in new resistant species since the first in 1914 {Georghiou, 1983}. By 1986 that trend had begun to taper off (Georghiou 1986). We see a continuation of that trend in the new species, compounds and total new cases (species and compound combinations) from 1989 onwards that we have entered into the database (, page). The frequency of resistant species discovery has declined since the 1960s (, page), when it shot to the highest level in history. In the 70s and 80s many non-pest species, such as natural enemies, were added from researchers seeking bio-control agents compatible with spray programs (Theiling and Croft 1988) (Croft and Brown 1975).

Previous authors attributed this trend to the limit of pest species. Introduction of Integrated Pest Management (IPM) in the 1970s has probably slowed insecticide selection pressure and reduced the trends in resistance development that we have seen in our results. In addition many of the insecticides to which these pests have developed resistance have been canceled due to environmental and human health effects (see Chapter 3). However, one of the collateral effects of multiple-resistance is the presence of a diversity of mechanisms employed by the species with reported resistance that could be cross-resistant to existent and new compounds.

Resistance by Chemical Class

Most of the cases of resistance that have occurred with so-called conventional insecticides were classified in either the organochlorine (OC), organophosphate (OP), carbamate (CB) or pyrethroid (PY) chemical groupings (Table 2).

Conventional pesticides were those that have controlled a broad spectrum of species, have worked as contact nerve toxins, were easy to use, and have been in use for many decades. Few cases of resistance had been detected outside of conventional pesticides such as agonists and antagonists of GABA receptors, insect growth regulators, *Bacillus thuringiensis* (Bt) protoxins, and neonicotinoid compounds. Yet the appearance of insecticide resistance has followed a loose chronological pattern following the deployment of most insecticides. Generally, the first cases of resistance have been reported within three to five years after the compound was extensively used. A specific example comes from Danish Housefly research (Keiding 1977). Before the organochlorines were introduced, fifteen cases of resistance were to one of seven inorganic pesticides. From the time of the first case of DDT resistance in 1947 up until the 1980s the majority of resistance cases have resulted from the use of organochlorines, followed by organophosphates, carbamates, and pyrethroids – broad spectrum conventional pesticides with many formulations available from each chemical class. Adverse human health effects and negative environmental impacts from organochlorine compounds led to the cancellation of almost all of the insecticides in this class after the USEPA was created in 1970, paving the way for the organophosphates to be the most widely pesticide used. Many of the other classes were introduced solely to control pests resistant to compounds in the other classes (e.g formmidines) (Ware 1989). In the last two decades of the 20th century, four groups of pesticides saw resistance develop for the first time: compounds from the classes organotin (miticides), avermectin, and pheylpyrazoles, a the group of compounds that act as insect growth regulators.

Reduced registration and use reflects the decline in the rate of newly reported resistance cases in the organochlorine compounds in the last three decades; only 0.7% of the total known cases were reported between 1990 and the present (Table 5). In 2003, the only organochlorine compounds with remaining uses (worldwide) were DDT, endosulfan, lindane, and dicofol, and these uses are severely curtailed. In the United States, only endosulfan and dicofol have registrations remaining. Without organochlorines in the environment, and one would expect to see a much-declined rate of new species or new cases of resistance to them. However, species with no exposure to OCLs may be discovered in the lab to exhibit cross-resistance to them, as many pests with organoclorine resistance were shown to have cross-resistance to pyrethroids when they were introduced with little or no exposure to the pyrethroids (Miller, Salgado and Irving, 1983). It was discovered that the same gene (*kdr*) was facilitating resistance to both classes of compounds, which had similar target sites, many organochlorine-resistant pests developed resistance to pyrethroids quickly. When organochlorines were replaced by organophosphates, carbamates, and pyrethroids, more cases of resistance to these replacement compounds ensued. Although some uses of organophosphates and carbamates have been cancelled because of adverse human health effects, pesticides from these classes are still very widely used (Gianessi and Anderson 1995, NASS 1997, 1998, 1999, Gianessi and Marcelli 2000, NASS 2000).

Discussion

It should be noted that these totals represent reported resistance discoveries. The true status of R, the allele frequency per population, was rarely known for any time period after discovery for any but intensively studied agro-ecosystems. In some species, when the pesticide was no longer applied and hence the selection pressure relaxed, any non-dominant resistance alleles decline to pre-resistance frequencies. However, there is clear evidence that these will quickly return in the population (Georghiou 1986). A cumulative count is a snapshot of a phenomenon that varies over time.

To date, the appearance of species resistant to compounds with newly discovered modes of action has not been as dramatic as in conventional pesticides (chlorinated hydrocarbons, organophosphates, carbamates, pyrethroids, etc.). We cannot say that this will be true in the future. This trend may be due to the limited use of these (often costly) novel compounds, especially in developing countries where profits are low and regulation of cheaper alternatives is less stringent than in Europe and the United States. An increasing emphasis on integrated pest management a key component of sustainable agro-ecosystems will also increase the use of the compounds that fit with this strategy: those with characteristics of rapid degradation, narrow spectrum of pest species, and minimal toxic effects (acute or chronic) to humans and other non-target organisms. Government restrictions of conventional pesticides, such as through risk assessment mandated by the US FQPA, will very likely increase the use of these compounds as alternatives. Increased use of, and hence intensified selection pressure exerted by, these novel compounds on pest populations will almost certainly result in additional cases of resistant arthropods. The latest deployment of compounds to combat pest resistance looks promising, but we should be extremely cautious. It has been suggest early as 1961 that insecticide resistance is a natural outcome of our use of pesticides, given a 350 million year history of herbivorous arthropods evolving mechanisms to defeat toxins the defensive secondary plant chemistry of their hosts (Georghiou 1972). It is not surprising that, in the last one hundred years, 307 phytophagous arthropod pest species have evolved resistance to pesticides from selection by humans. A similar co-evolutionary case may be made for entomophagous arthropods (e.g. parisitoids) whose hosts sequester secondary compounds from plants. Whether the toxin is synthesized and applied by humans protecting a host plant, or synthesized and delivered by the host plant itself, the evolutionary endpoint is the same: resistance.

The development of resistance to pesticides is an incredibly complex process crossing biological and social disciplines. However, even with our simple modeling of resistance as a case, and limiting citations to the first appearance of a significant resistant population, several trends are apparent. However, there are several important aspects of resistance missing from this model. One attribute that is present in nearly all discussions of resistance cases is the cropping system in which the resistance occurs. There are at least two reasons for this omission in our database. First, selection of resistance alleles may take place wherever the population encounters pesticide residues. This may from a different crop farmed next door or thousands of miles away from the field where resistance was detected, such as *Empoasca fabae* (Carlson et al. 1991). There are worldwide examples of documented resistance to organochlorines and organophosphates in mosquitoes that may have been caused or aggravated by agrochemicals in the same regions (Georghiou 1990b). Secondly, generalist pest species whose host range include several difference crops may have been exposed to pesticide quite some distance from the field in which it was collected.

Databases have been used for some time in agriculture to detail and analyze broad aspects of pest management that would otherwise be intractable (Whalon et al. 1984). This project is one more example of how utilizing the relational data model can help will effective management of large sets of data.

Figure 1. Entity-relationship diagram of our semantic data model of the listing in Georghiou and Lagunes-Tajeda, 1991 (PK: Primary Key, Fk: Foreign Key)

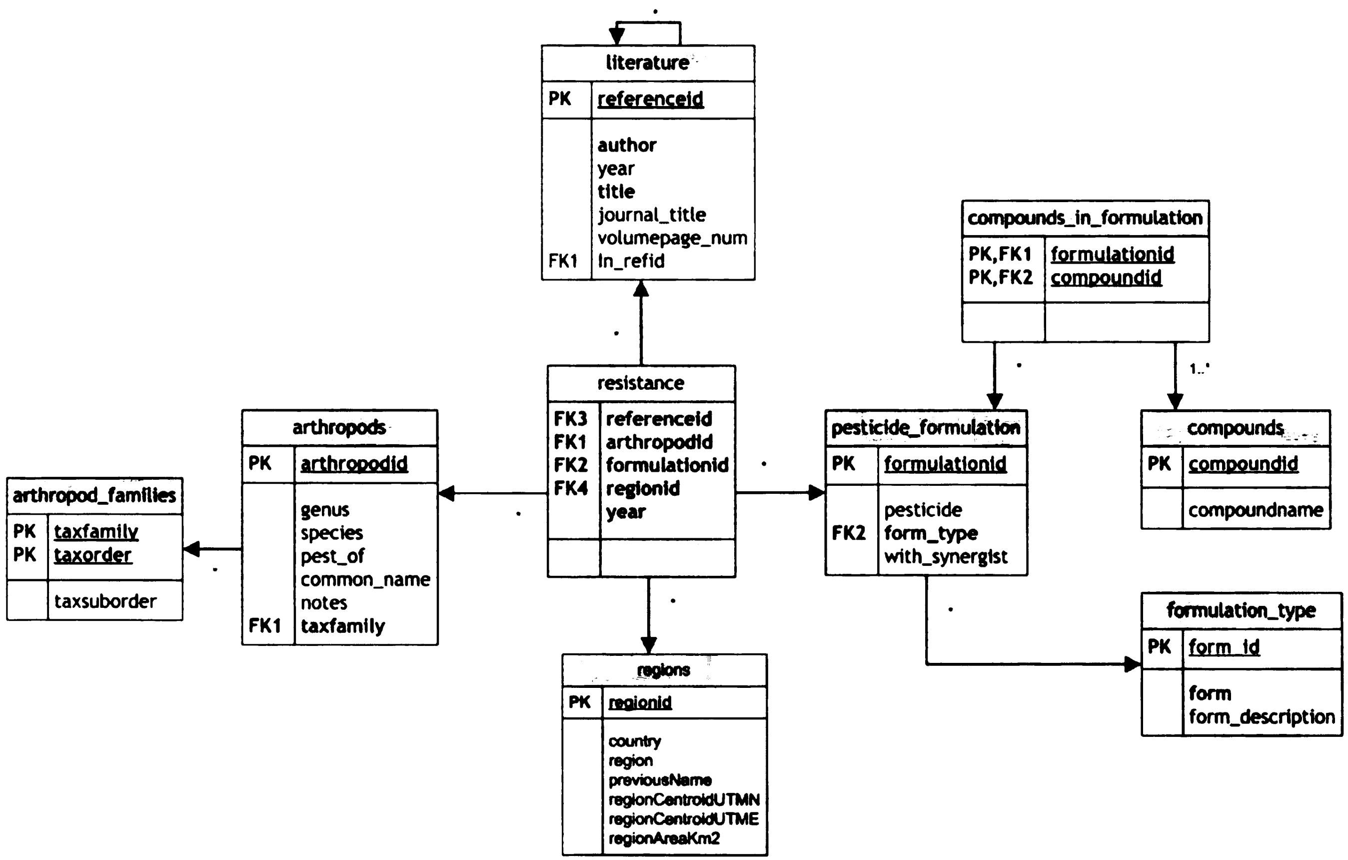

Figure 2. *Entity-relationship model of enhanced database. PK = primary key, FK=foreign key; arrows point in direction of unity*

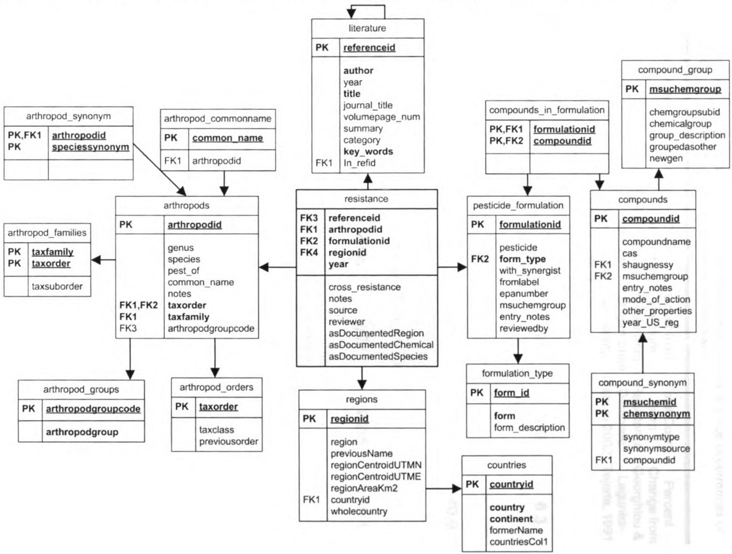

Table 1. Summary of Cases of Reported Pesticide Resistance; counts of uniqe occurrences of species, compounds, and cases along with publications reviewed

Aspect of a Resistance Case: description	Count published in Georghiou & Lagunes-Tejeda, 1991 (data to 1989)	Count from literature review from Michigan State University	Total Count from Resistance Database (data to 2002)	Percent Change from Georghiou & Lagunes-Tejeda, 1991
Species: arthropod species which were resistance to one or more pesticides	511	38	543	6.3
Compounds: a unique pesticide active ingredient to which one or more arthropod species is resistant	225	167	315	40.0
Unique Cases: a case of a unique species resistant to a unique compound, eg unique (species, compound) pairs	2286	502	2655	16.1
National Cases: a case of resistance unique to any one country, e.g, unique (species, compound, country)	4292	598	4793	11.7
Regional Cases: Species, Compound, Country, Region. May include multiple, identical cases from the same country (e.g. different states or provinces)	5053	732	5785	14.5
Referenced Documents: Number of citations of reports of new regional cases	1,263	205	1,468	16.2%

Table 2. Summary of Insecticide and Acaracide Resistance

Compound Mode of Action / Chemical Class	**# of Com-pounds with Resist-ance**	**Category of Resistant Arthropods**					***Total Cases by Chemical Class***	
		Agricultural, Forest and Ornamenal Plant Pests	Medical, Veterinary, and Urban Pests	Predators / Parasites	Other / Miscellaneous Arthropods	Pollin-ators		
Organo-phosphates	112	715	358	52	10		1135	44.1 %
Organochlorines	26	484	329	10	15	2	840	32.6 %
Pyrethroids	33	133	74	11	1		219	8.5%
Carbamates	35	132	57	14	1		204	7.9%
Bacterials	38	42	4				46	1.8%
Miscellaneous	30	37	8	1			46	1.8%
Fumigants	6	21					21	0.8%
Insect Growth Regulators	10	16	2		3		21	0.8%
Organotins	3	8					8	0.3%
Formamidines	2	4	2				6	0.2%
Arsenicals	2	2	11				13	0.5%
Avermectins	2	2	3	1			6	0.2%
Chloronicotinoid	1	2	1				3	0.1%
Rotenone	1	2					2	0.1%
Dinitrofenols	1	1					1	0.0%
Sulfur Compounds	2	1		1			2	0.1%
Phenylpyrazoles	1		1				1	0.04 %
Total Cases by Arthropod Category		**1602**	**850**	**90**	**30**	**2**	***2574***	
		62.2%	33.0%	3.5%	1.2%	0.1%		

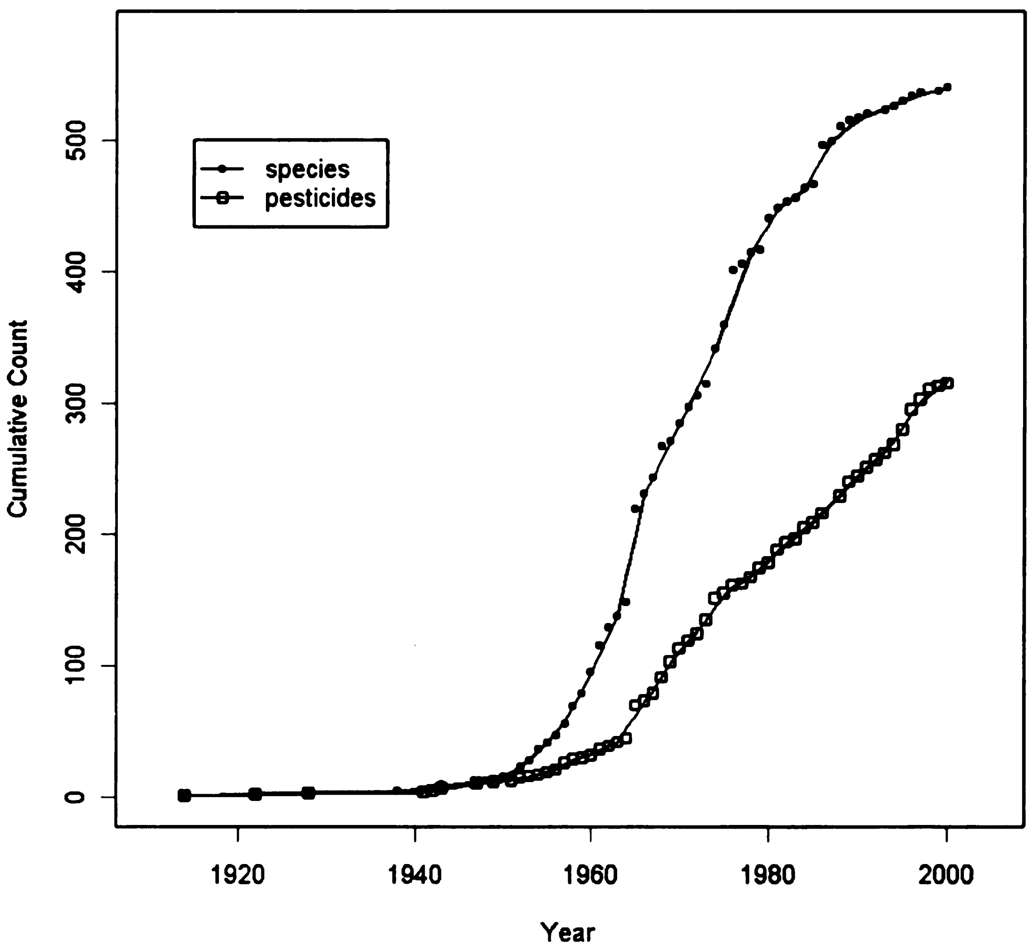

Figure 3. Accumulation of Arthropod Resistance, 1914-2001: Number of First Reports of Resistance ifor a Species per Year, (fit with Loess curve to emphasize discontinuities)

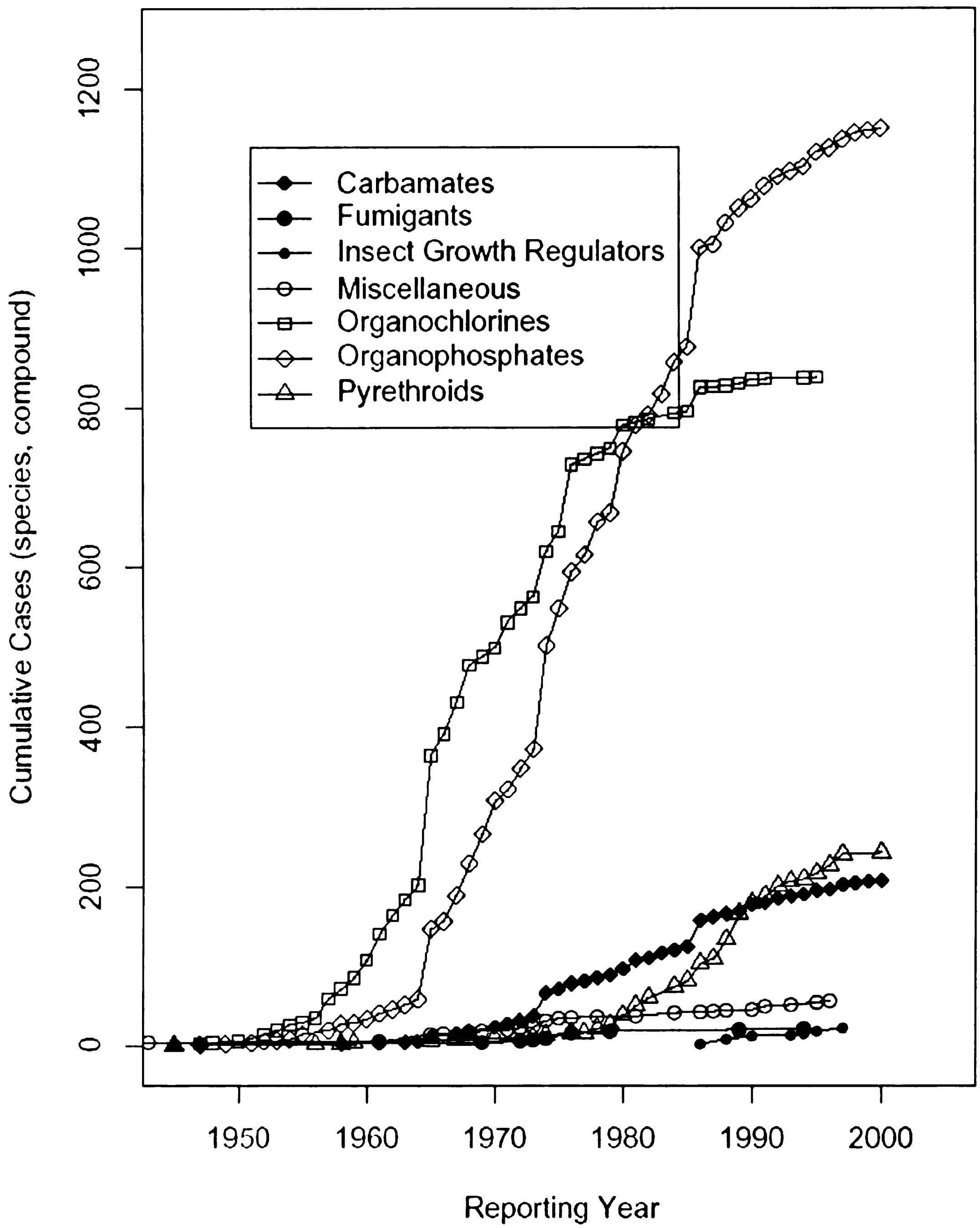

Figure 4. Time series of resistance case discover by chemical class for those classes with > 25 cases of resistance. A case is the first discovery of a species and pesticide.combination.

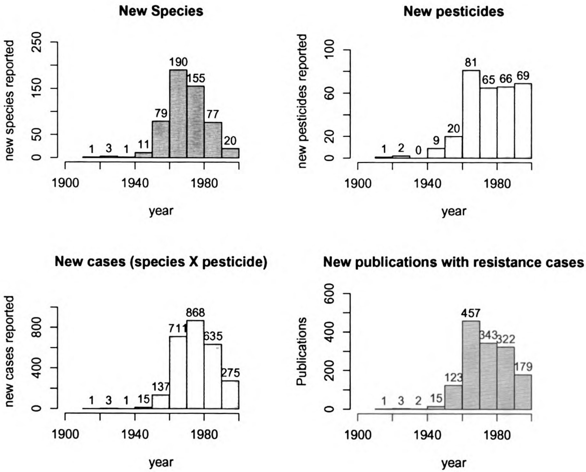

Figure 5. Frequency of new species with no prior resistance, new pesticides, reports and new cases by decade.

Table 3. Cases of Insecticide and Acaricide Resistance by Chemical Class

Rank by # of cases of resistance	**prior to 1980**		**prior to 1990**		**prior to 2000**	
1	Organochlorines	757	Organophosphates	1050	Organophosphates	1136
2	Organophosphates	669	Organochlorines	838	Organochlorines	844
3	Carbamates	89	Carbamates	169	Pyrethroids	224
4	Miscellaneous	31	Pyrethroids	166	Carbamates	202
5	Pyrethroids	26	Miscellaneous	39	Bacterials	46
6	Fumigants	18	Fumigants	20	Miscellaneous	46
7	Arsenicals	13	Arsenicals	13	Fumigants	21
8	Nicotinoids	3	Insect Growth Regulators	7	Insect Growth Regulators	21
9	Bacterials	2	Formamidines	6	Arsenicals	13
10	Formamidines	2	Organotins	5	Organotins	8
11	Dinitrofenols	1	Bacterials	4	Avermectins	6
12	Rotenone	1	Nicotinoids	3	Formamidines	6
13	Sulfur Compounds	1	Sulfur Compounds	2	Nicotinoids	6
14			Avermectins	1	Rotenone	2
15			Dinitrofenols	1	Sulfur Compounds	2
16			Rotenone	1	Dinitrofenols	1
17					Phenylpyrazoles	1

Table 4. Top Twenty Resistant Arthropods, ranked by number of unique compounds reportedly resistant

Rank	Species	Family-Order	Number of Pesticides with Reported Resistance	Number of references in the database	year of first report	most recent report	hosts	Common Name
1	*Tetranychus urticae*	tetranychidae-acari	76	104	1943	1999	cotton, fruits, vegetables, walnut, ornamentals	Two-spotted spider mite
2	*Plutella xylostella*	plutellidae-lepidoptera	70	58	1953	2000	crucifers, nasturtium	Diamond-back moth
3	*Myzus persicae*	aphididae-homoptera	68	76	1955	1986	flower, crops, fruit, trees, grains, tobacco, vegetables	Peach-potato aphid
4	*Boophilus microplus*	ixodidae-acari	41	25	1947	1988	cattle	southern/tropical cattle tick
5	*Leptinotarsa decemlineata*	chrysomelidae-coleoptera	40	37	1955	2000	eggplant, pepper, potato, tomato	Colorado potato beetle
6	*Panonychus ulmi*	tetranychidae-acari	40	70	1951	1991	fruit trees	Fruit tree red spider mite
7	*Blattella germanica*	blattellidae-orthoptera	39	60	1956	1997	urban environments	German cockroach
8	*Heliothis virescens*	noctuidae-lepidoptera	37	39	1961	1997	chickpea, corn, cotton, tobacco	Tobacco budworm
9	*Musca domestica*	muscidae-diptera	36	25	1947	1999	urban environments, livestock	House fly
10	*Tribolium castaneum*	tenebrionidae-coleoptera	34	34	1962	1999	stored grain, peanuts, sorghum	Rust-red flour beetle

Table 4. (continued) Top Twenty Resistant Arthropods, ranked by number of unique compounds reportedly resistant

Rank	**species**	**Family-Order**	**Number of Pesticides with Reported Resistance**	**Number of references in the database**	**year of first report**	**most recent report**	**hosts**	**Common Name**
11	*Culex pipiens pipiens*	culicidae-diptera	33	26	1961	1987	Humans	House mosquito
12	*Bemisia tabaci*	aleyrodidae-homoptera	33	21	1981	1998	cotton	Sweetpotato whitefly
13	*Phorodon humuli*	aphididae-homoptera	32	18	1965	1986	hop, plum	Hop aphid
14	*Spodoptera littoralis*	noctuidae-lepidoptera	32	21	1962	1997	alfalfa, cotton, potato, vegetables	Egyptian cotton leafworm, Army worm
15	*Aphis gossypii*	aphididae-homoptera	30	21	1965	1995	cotton, vegetables	Melon and cotton aphid
16	*Culex quinquefasciatus*	culicidae-diptera	27	39	1952	1997	human health (vector transmission)	mosquito
17	*Helicoverpa armigera*	noctuidae-lepidoptera	25	27	1969	1997	cotton, corn, sorghum, tomato	Old world bollworm
18	*Lucilia cuprina*	calliphoridae-diptera	25	11	1958	1998	cattle, sheep	Australian sheep blowfly
19	*Spodoptera exigua*	noctuidae-lepidoptera	23	21	1960	2000	cotton, tomato, celery, lettuce, cabbage and alfalfa	Beet army worm, Lesser army worm
20	*Rhizoglyphus robini*	acaridae-acari	22	2	1986	1988	Ornamentals	Bulb mite

CHAPTER 3. ANALYSIS: RESISTANCE AND REGISTRATION IN THE US

Introduction

The first case of pesticide resistance was reported in the United States in 1908 and resistance has had dire consequences in the US ever since (see Chapter 1). From that first case of resistance until 2002, the US had over 1,500 new cases reported (see Chapter 2), ranking it as the number one country in the world. Given these sheer numbers of cases, it is crucial to have some notion of what drives resistance development in the US. This chapter exploits a number of databases to explore how pesticide resistance, use, and implementation trends are drivers of resistance cases.

Arthropod pesticide resistance is not a new phenomenon, contrary to the opinion some authors (Horowitz and Denholm 2001), resistance populations appeared in the 40s just years after DDT was introduced in the US (Brown 1951). For example, in eastern Florida, resistance occurred after less than 3 years of DDT use to control Salt Marsh Flies. Certainly some arthropod pest species did not develop pesticide resistant populations. For example, no pesticide resistance report existed by 2003 for potato aphid, *Macrosiphum euphorbiae* (Thomas), a Potato-Y virus (PYV) vector, although the US potato crop received intense pesticide application (National Research Council 2000) for defense of one of the most resistant defoliating insects known, the Colorado Potato Beetle (CPB), *Leptinotarsa decimlineata* (**Error! Reference source not found.**,Chapter 2). However, when pesticide resistance does develop in any species, it may do so within a few seasons. It has been claimed, for those species with reported resistance, that resistance develops within 3-5 yrs after pesticide implementation (Mota-Sanchez, Bills, and Whalon 2001).

Since the first DDT-resistant *Musca domestica* population was discovered in 1947, pesticide resistance discoveries have accumulated steadily over time (Georghiou 1983 and see Chapter 2). The 1960s witnessed the discovery of 19 newly resistant species per year and 15 per year in the 1970s. (Figure 4). However, in the 1990s that rate declined to an average of just over 2 species annually (see chapter 2). Georghiou speculated on the cause of this decreased rate (Georghiou, 1986 #62) , however he did not correlate this decline with historical records of these causes.

The declining trend may well have resulted from reduced pesticide use more rapid introduction of new modes of action or IPM. A complex confluence of an arthropod's agroecosystem, genetic potential, life history traits, and other factors select pesticide-resistant populations (see chapter 4). However, without the pesticide application there would be no selection for a resistant population. Therefore, when seeking a causal agent, the first step is to review a pesticide's history in the pest host-range.

Many aspects described pesticide usage, but typical reports included averages of annual sales (lbs), seasonal applications (lbs, number), in which crop it was applied, area applied (acres), rate per unit area (lbs/acre) (e.g. (NASS 1996, 1997, 1998, 1999, 2000, Donaldson et al. 2002), etc).

Assuming all pesticide sold is applied, pesticide sales indicate a measure of the total pesticide load in the environment. No federal agency collects pesticide sales data or comprehensive pesticideuse quantities. However, the USEPA produces annual estimates. Donaldson (2002) reported sales as total lbs active ingredient for fungicides, herbicides, insecticides (including acaricides), and 'other' pesticides. Yet, using these statistics as indicators of resistance selection pressure may be problematic as the weight of a substance has little bearing on its toxicity (Graham-Bryce 1987).

Insecticides and acaricides were incredibly diverse. By the end of the century, there were at least 17 classes of insecticides and acaricides in existance, more depending on one's classification scheme. In the US in 1997, over 67 insecticides and acaricides were applied (>1% crop acreage per state, 81 crops on 307 million acres) . Excluding oils, this meant active ingredient application rates ranged from 0.3to 30 lbs per acre for the season. Over two hundred insecticides and acaricides were available worldwide in the year 2000 (Tomlin 2000). Toxicity varies among all pesticides more than one-thousand fold (Copplestone 1977). Indeed, the mix of pesticides available has changed over time, since recent dramatic pesticide policy changes (see below). Overall tonnage of active ingredients sold gave little indication of the selection pressure. More active ingredient details would be needed before conclusions about resistance are drawn. However, in many specific agro-ecosystems, pesticide application histories are well known and use and resistance may be correlated on a case-by-case bases.

Long-term and consistent use measurements for specific active ingredients were largely not available in the public literature. Proprietary data were available but cost prohibitive. National pesticide usage information was not systematically collected by any federal agency until 1990 when the National Agricultural Statistics Service (NASS) began a complex of chemical use surveys. In addition, while evolution of resistance is a phenomenon of a population's exposure to pesticides over time and space, pesticide use reporting has rarely been spatially or temporally explicit. Data are typically annual aggregates for the entire US or specific US states. Some exceptions are data collected by the California Department of Pesticide Regulation (Federighi 2001) and infrequent, detailed grower surveys from NASS (NASS 1996). In Michigan, a pilot survey administered by NASS in 1998 (vegetables) and 1999 (fruit) that was temporally but not spatially definite (Harris 2000). Prior to 1990 when NASS began their surveys, pesticide use data was sparse or overly summarized. Pesticide use details are critical for understanding pest management practices, however existing pesticide use statistics as anything but a general guide would be challenged as indicators of resistance development (Osteen 1992).

Agrochemical use is often reported per crop. The US Pesticide Impact assessment program produced several detailed assessment of pesticide use and benefits for individual crops, but these were not persistent over time. However, while the crop in which resistance discovery was made may have been documented, it is not recorded in the MSU database as many population cross farm-boundaries and population structure influence by exposure in any crop.

To correlate Ps and R, at minimum it should be known when the pesticide was first used anywhere. Pesticide use is not a good indicator of that fact, as survey does not necessarily coincide with a compound's introduction. NASS, for example, conducted surveys for fruit and vegetables on alternating years (NASS 1991-2001). However a good indicator of this is the date of registration, as a pesticide cannot be used, other than for experimental or emergency purposes, without being federally registered. The 1947 US Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) required that all pesticides distributed or sold in interstate commerce had to be registered and labeled federally. Responsibility for registration was first under the direction of the United States Department of Agriculture (USDA), but the Environmental Protection Agency (EPA) assumed registration activities after its establishment in 1970. In 1972, FIFRA was expanded, and for the first time required reassessment of pesticide risk, allowing reregistering only if the risk was not unreasonable when compared to the benefits of its use. The Food Quality Protection Act of 1996 (FQPA) not only removed benefits from the risk assessment equations, but also required a cumulative risk assessment of compounds per class. These and other dramatic changes served to further restricted registration. FQPA introduced a strict timetable for re-assessment and 38% of pesticide uses and ingredients were voluntarily or otherwise cancelled in the first five years especially for many belonging to older chemical classes such as organophosphates, carbamates and remaining organochlorines (Mulkey 2002). For any point in time, those pesticides with active registrations served as good proxy for which pesticides were generally put into the market.

Using the year of registration as a proxy for the date of first use, and year of first reported resistance as a proxy for when pesticide resistance first developed, some broad exploration of time to resistance was be made. It was thought that such an analysis would help describe the trend in reduced rate of resistance discovery. To accomplish this, US EPA registration records since 1947 were compared with pesticide resistance reports. This was a step towards meeting the need to anticipate the development of resistance in numerous systems, and or to contribute what measured factors will help such prediction.

Methods

To manage registrations, USEPA stored pesticide data in a computerized database at the NC Computing Center names the Pesticide Product Information System (PPIS) (Office of Pesticide Programs 2000). Periodic snapshots of the data were made available the public as a collect of 24 data sets \as fixed-width ASCII files. Data files dated December 2000 were downloaded from USEPA. The well-documented database included registered product code, percent of each active ingredients, legal uses of the pesticides, or 'sites' (e.g. Apple, foliar), the target pests, original registration date, and cancellation date if any. The date appearing is the first date it was registered in FIFRA section 3 (FIFRA 1996) or 24c. All historical product registrations since 1947 passage of original FIFRA except so-called 'emergency' registrations under FIFRA section 18 section were included in this data. Products were coded by the class of organisms against which there were affected using the standard terminology (insecticide, herbicide, etc). Only products with insecticidal and acaricidal designations were considered.

USEPA pesticide products were formulations of one or more active ingredients (AI). Active ingredients and products are stored in distinct tables in the PPIS database, and share a key table with the product registration number, the active ingredient Shaugnessy code, and the percent concentration of the AI in the product, by weight. First registration date is per product but linkable to AI.

This analysis assumes that, once registered, a pesticide is uniformly adopted wherever pest populations might occur. This is a limitation as sites as added gradually to a pesticide's registration, especially minor uses, Use sites are added over time, however dates are not stored. Therefore this analysis assumes all use sites were available at time of registration.

The MSU database was basis for cases of resistance in the US (see Chapter 2). Pesticide compounds in the MSU Resistance Database were coded with Chemical Abstract Service (CAS) numbers (Ware 1989) and then cross-coded with the USEPA Shaughnessy code using a PPIS data table matching these codes. The relational database structure also linkage of pesticide tables in both database to be linked once common codes are entered.

All data tables were stored and manipulated using relational database system software MySQL version 4.1 (Axmark et al. 2003). Aggregated results were created using standard SQL code (ISO 1992). Statistical summaries and graphics were produced with R-language and computing environment for statistics (Ihaka and Gentleman 1996), version 1.7.0.

Results

Of 98,000 registered products with insecticidal and acaricidal uses registered between 1947 and 2002, approximately 29,000 were identified in the resistance database as compound with a case of resistance in the US. The number of use-sites was tracked for each class of active ingredient (Figure 6). Use sites are associate with pesticide products. However, by associating this with active ingredients it may then be correlated with compounds for which resistance has occurred. While cases of ogranochlorine (OCL) resistance exceed organophosphates (OP) until the 1980s (**Error! Reference source not found.**, Chapter 2, page), registration records show far greater use capacity for the organophophates since the 1950s. This may be due the sheer numbers of OPs registered.

Discussion

The trend for the reduced rate of new species today correlates well with the number of distinct pesticide ingredients input into the environment. Over time pesticides have been developed in new chemical families, increasing the diversity of pesticide chemical classes. These increased in classes we would expect to see an increase in cases, that it, either more insects becoming multiply resistant, adding the novel compounds to the list. The diverse toxins have diverse binding sites or modes of action; hence we don't expect to see cross-resistance. Certainly this has been true for *Leptinotara decimlineata* and

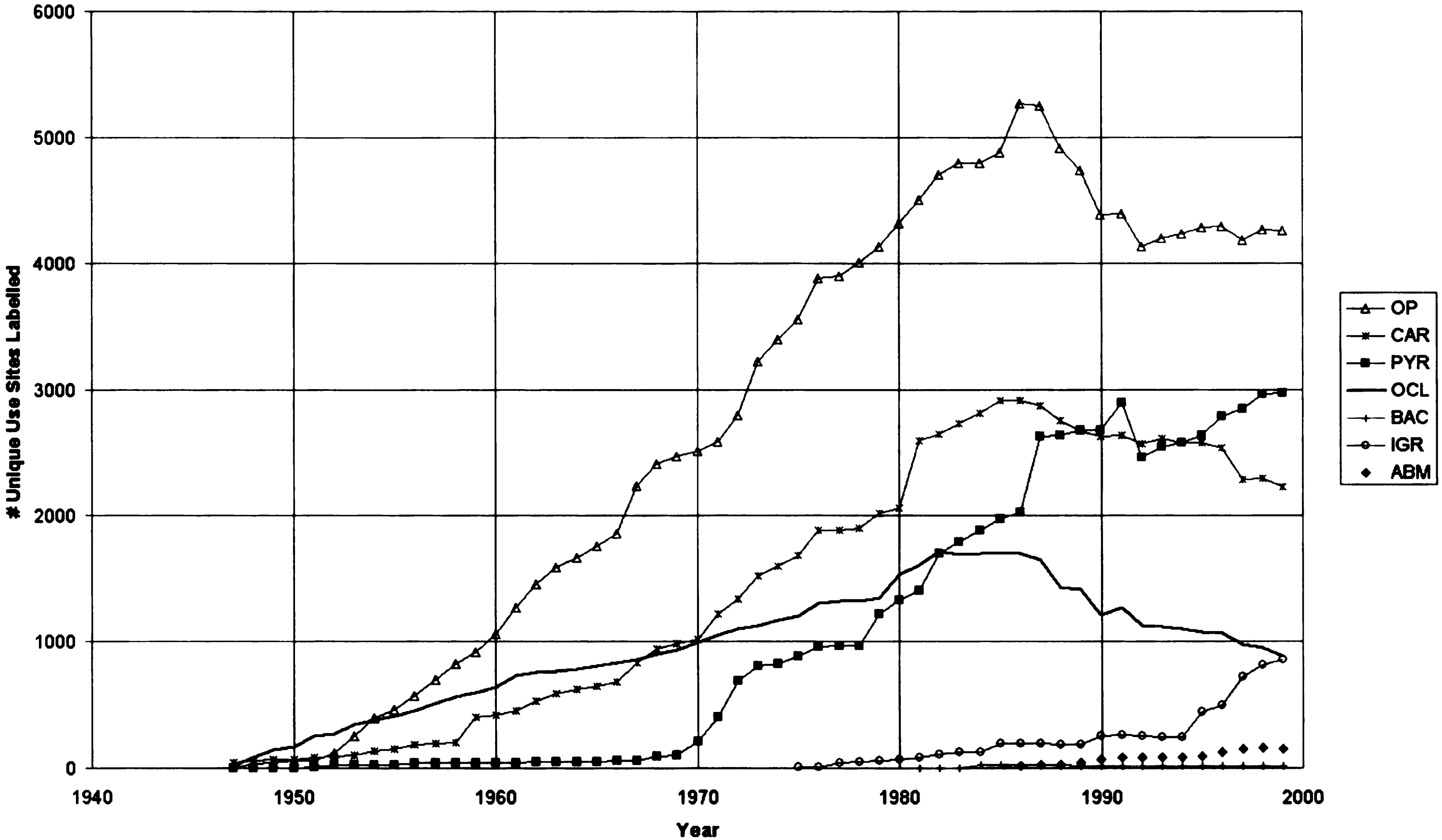

Figure 6. Timeline of US Pesticide Registration: total number of unique 'use sites' for all pesticides in the resistance database, by Chemical Class. OP = Organophosphate, CAR = carbamate, PYR = Pyrethroid, OCL = Organochlorine, BAC = Bacterial, IGR = Insect Growth Regulatro, ABM= Abemectin. Data to 2000.

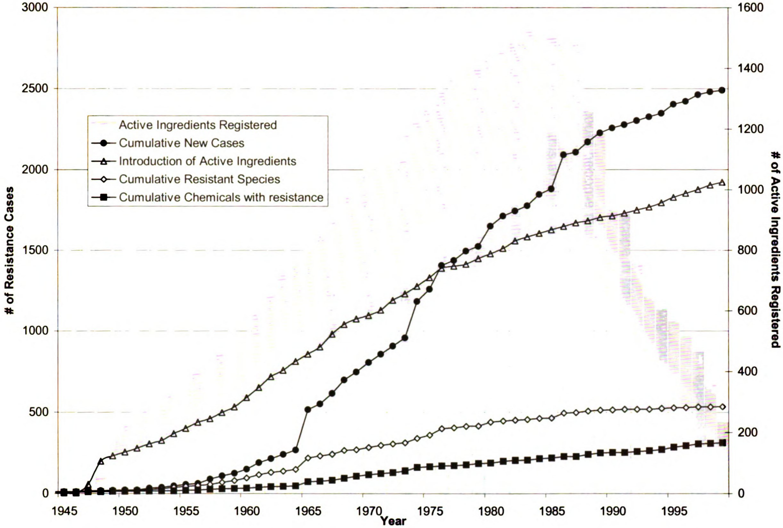

Figure 7. Timeline of Arthropod Pesticide Resistance and Pesticide Registrations in the United States

neriestoxins. But in general could we say that novel compounds are less likely to have resistance? Perhaps the slow appearance of resistant species to classes such as fipronil, tebufenozide, etc is because the areas in which these are used is dramatically less than past compounds.

One argument for the slow down in new resistant species appearance is that we have exhausted the available pests (Georghiou 1990a). As pesticides increase the cover of our landscape in time and space, selection is increased, and those that could become resistant, have been.

Refinements to this analysis would attempt to link where the resistance occurred and a combination of the level of pesticide use, pesticide registration counts, relevant biological factors (weather) may help estimate probability of exposure to pesticide residues and hence selection. Pesticide registration is not a perfect indicator of selection pressure as pesticides are not deployed immediately nationwide but gradually as sites and pests are add to pesticide labels during an on-going registration and re-registration process.

APPENDIX 1

Appendix 1. Structured Query Language data definition code

The following code can be used to recreate the database using MySQL version 4.0 (Axmark, 2002).

```
/*
MysSQL Server version 4.0.12-max
# create database if not exists
*/


/*

Table struture for arthropod_families

*/



drop table if exists `arthropod_families`;
CREATE TABLE `arthropod_families` (
  `taxfamily` varchar(20) NOT NULL default '',
  `taxorder` varchar(20) NOT NULL default '',
  `taxsuborder` varchar(50) default NULL,
  `commonname` varchar(150) default '',
  PRIMARY KEY  (`taxfamily`,`taxorder`),
  KEY `arthropod_familiesorder` (`taxorder`)
) TYPE=MyISAM;



/*

Table struture for arthropod_groups

*/



drop table if exists `arthropod_groups`;

CREATE TABLE `arthropod_groups` (
  `arthropodgroupcode` char(5) NOT NULL default '',
  `arthropodgroup` char(50) default NULL,
  KEY `insectgroupcode` (`arthropodgroupcode`)
) TYPE=MyISAM;
```

```
/*

Table struture for arthropod_orders

*/


drop table if exists `arthropod_orders`;

CREATE TABLE `arthropod_orders` (
  `taxorder` varchar(50) NOT NULL default '',
  `taxclass` varchar(50) default NULL,
  `previousorder` varchar(50) default NULL,
  `commonname` varchar(150) default '',
  PRIMARY KEY  (`taxorder`)
) TYPE=MyISAM COMMENT='from MS Access table arthropod_orders';


/*

Table struture for arthropod_refs

*/


drop table if exists `arthropod_refs`;

CREATE TABLE `arthropod_refs` (
  `arthropodID` int(11) NOT NULL default '0',
  `referenceID` int(11) NOT NULL default '0',
  `topics` varchar(100) default '',
  PRIMARY KEY  (`arthropodID`,`referenceID`)
) TYPE=MyISAM COMMENT='citations to references with general information
about this';


/*

Table struture for arthropod_synonym

*/


drop table if exists `arthropod_synonym`;

CREATE TABLE `arthropod_synonym` (
  `arthropodid` int(11) NOT NULL default '0',
  `speciessynonym` char(50) NOT NULL default '',
  PRIMARY KEY  (`arthropodid`,`speciessynonym`),
  KEY `arthropodid` (`arthropodid`)
) TYPE=MyISAM;
```

```
/*

Table struture for arthropods

*/



drop table if exists `arthropods`;

CREATE TABLE `arthropods` (
  `arthropodid` int(11) NOT NULL default '0',
  `taxfamily` varchar(20) NOT NULL default '',
  `genus` varchar(20) NOT NULL default '',
  `species` varchar(30) NOT NULL default '',
  `pest_of` varchar(100) default NULL,
  `arthropodgroup` varchar(50) default NULL,
  `common_name` varchar(50) default NULL,
  `notes` text,
  `arthropodgroupcode` varchar(50) default NULL,
  `author` varchar(100) default NULL,
  `url` varchar(255) default NULL,
  `taxorder` varchar(50) NOT NULL default '',
  `citation` text,
  PRIMARY KEY  (`arthropodid`),
  UNIQUE KEY `indexspecies` (`genus`,`species`)
) TYPE=MyISAM;



/*

Table struture for compound_group

*/



drop table if exists `compound_group`;

CREATE TABLE `compound_group` (
  `chemgroupid` char(10) NOT NULL default '',
  `chemgroupsubid` char(50) NOT NULL default '',
  `chemicalgroup` char(255) default NULL,
  `group_description` char(50) default NULL,
  `groupedasother` tinyint(4) default NULL,
  `newgen` tinyint(4) default NULL,
  KEY `chemgroupid` (`chemgroupid`),
  KEY `chemgroupsubid` (`chemgroupsubid`)
) TYPE=MyISAM;



/*
```

```
Table struture for compound_synonym

*/



drop table if exists `compound_synonym`;

CREATE TABLE `compound_synonym` (
  `msuchemid` int(11) NOT NULL default '0',
  `chemsynonym` char(50) NOT NULL default '',
  `synonymtype` char(50) default NULL,
  `synonymsource` char(50) default NULL,
  PRIMARY KEY  (`msuchemid`,`chemsynonym`),
  KEY `chem_id` (`msuchemid`)
) TYPE=MyISAM;



/*

Table struture for compounds

*/



drop table if exists `compounds`;

CREATE TABLE `compounds` (
  `compoundid` int(11) NOT NULL default '0',
  `compoundname` char(75) default NULL,
  `cas` int(11) default NULL,
  `shaugnessy` int(11) default NULL,
  `msuchemgroup` char(10) default NULL,
  `entry_notes` char(100) default NULL,
  `mode_of_action` char(255) default NULL,
  `other_properties` char(255) default NULL,
  PRIMARY KEY  (`compoundid`),
  KEY `name` (`compoundname`),
  KEY `shaugnessy` (`shaugnessy`)
) TYPE=MyISAM;



/*

Table struture for compounds_in_formulation

*/



drop table if exists `compounds_in_formulation`;

CREATE TABLE `compounds_in_formulation` (
  `formulationid` int(11) NOT NULL default '0',
```

```
  `compoundid` int(11) NOT NULL default '0',
  PRIMARY KEY  (`formulationid`,`compoundid`)
) TYPE=MyISAM;



/*

Table struture for countries

*/



drop table if exists `countries`;

CREATE TABLE `countries` (
  `countryid` int(10) NOT NULL auto_increment,
  `country` char(50) NOT NULL default '',
  `continent` char(50) default NULL,
  `westerncountry` tinyint(1) default '0',
  PRIMARY KEY  (`countryid`)
) TYPE=MyISAM;



/*

Table struture for documentation

*/



drop table if exists `documentation`;

CREATE TABLE `documentation` (
  `id` int(11) NOT NULL default '0',
  `author` varchar(255) NOT NULL default '',
  `year` double default NULL,
  `journal_title` varchar(255) default NULL,
  `volumepage_num` varchar(255) default NULL,
  `title` varchar(255) NOT NULL default '',
  `key_words` varchar(255) NOT NULL default '',
  `summary` blob,
  `category` varchar(100) default NULL,
  `select_field` tinyint(4) default NULL,
  `checkedoutby` varchar(20) default NULL,
  `checkedoutdate` datetime default NULL,
  `document_type` varchar(100) default NULL,
  `lyear` year(4) default NULL,
  KEY `authorindex` (`author`),
  KEY `key_words` (`key_words`),
  KEY `id` (`id`),
  KEY `titleindex` (`title`)
) TYPE=MyISAM;
```

```
/*

Table struture for formulation_type

*/



drop table if exists `formulation_type`;

CREATE TABLE `formulation_type` (
  `form_id` int(11) NOT NULL default '0',
  `form` char(50) NOT NULL default '',
  `form_description` char(100) default NULL,
  PRIMARY KEY  (`form_id`)
) TYPE=MyISAM;



/*

Table struture for literature

*/



drop table if exists `literature`;

CREATE TABLE `literature` (
  `id` int(11) NOT NULL default '0',
  `author` varchar(255) NOT NULL default '',
  `year` double default NULL,
  `title` varchar(255) NOT NULL default '',
  `journal_title` varchar(255) default NULL,
  `volumepage_num` varchar(255) default NULL,
  `summary` blob,
  `category` varchar(100) default NULL,
  `key_words` varchar(255) NOT NULL default '',
  `lyear` year(4) default NULL,
  PRIMARY KEY  (`id`)
) TYPE=MyISAM;



/*

Table struture for pesticide_formulation

*/



drop table if exists `pesticide_formulation`;
```

```
CREATE TABLE `pesticide_formulation` (
  `formulationid` int(11) NOT NULL default '0',
  `pesticide` char(100) default NULL,
  `form_type` int(11) NOT NULL default '0',
  `with_synergist` tinyint(4) default NULL,
  `fromlabel` tinyint(4) default NULL,
  `epanumber` char(50) default NULL,
  `msuchemgroup` char(10) default NULL,
  `entry_notes` char(255) default NULL,
  `reviewedby` char(3) default NULL,
  PRIMARY KEY  (`formulationid`),
  KEY `formulation_typepesticide_formulation` (`form_type`)
) TYPE=MyISAM;



/*

Table struture for ref_epa_chemname

*/



drop table if exists `ref_epa_chemname`;

CREATE TABLE `ref_epa_chemname` (
  `pc_code` int(11) NOT NULL default '0',
  `cname_type` char(1) NOT NULL default '',
  `seq_nr` char(3) default NULL,
  `pc_prefix` char(15) default NULL,
  `pc_name` char(253) NOT NULL default '',
  KEY `chemnamecname_type` (`cname_type`),
  KEY `chemnamepc_code` (`pc_code`),
  KEY `name` (`pc_prefix`,`pc_name`)
) TYPE=MyISAM;



/*

Table struture for ref_years

*/



drop table if exists `ref_years`;

CREATE TABLE `ref_years` (
  `year` double default NULL,
  `dYear` date default NULL
) TYPE=MyISAM;
```

```
/*

Table struture for res_backup

*/



drop table if exists `res_backup`;

CREATE TABLE `res_backup` (
  `arthropodid` int(11) NOT NULL default '0',
  `formulationid` int(11) NOT NULL default '0',
  `literatureid` int(11) NOT NULL default '0',
  `chemical` char(50) NOT NULL default '',
  `year` int(11) NOT NULL default '0',
  `region` char(50) default '',
  `cross_resistance` tinyint(4) default NULL,
  `error_check` tinyint(4) default NULL,
  `notes` char(50) default NULL,
  `source` char(6) default NULL,
  `subref` char(255) default NULL,
  `resistancedev` char(3) default NULL,
  `faorefok` tinyint(4) default NULL,
  `reviewer` char(50) default NULL,
  `subrefid` int(11) default NULL,
  `rYear` date default NULL,
  `countryid` int(10) default '0'
) TYPE=MyISAM;



/*

Table struture for resistance

*/



drop table if exists `resistance`;

CREATE TABLE `resistance` (
  `arthropodid` int(11) NOT NULL default '0',
  `formulationid` int(11) NOT NULL default '0',
  `literatureid` int(11) NOT NULL default '0',
  `chemical` char(50) NOT NULL default '',
  `year` int(11) NOT NULL default '0',
  `region` char(50) default '',
  `cross_resistance` int(11) default '0',
  `error_check` tinyint(4) default NULL,
  `notes` char(50) default NULL,
  `source` char(6) default NULL,
  `subref` char(255) default NULL,
  `resistancedev` char(3) default NULL,
  `faorefok` tinyint(4) default NULL,
  `reviewer` char(50) default NULL,
```

```
  `subrefid` int(11) default NULL,
  `rYear` date default NULL,
  `countryid` int(10) default '0'
) TYPE=MyISAM;




drop table if exists `subrefs`;

CREATE TABLE `subrefs` (
  `subref` varchar(255) NOT NULL default '',
  `full_citation` text,
  `year` int(11) default NULL,
  `msulitid` int(11) NOT NULL default '0',
  `lib_call_num` varchar(50) default NULL,
  `subrefid` int(11) NOT NULL auto_increment,
  PRIMARY KEY  (`subrefid`),
  KEY `short_ref` (`subref`),
  KEY `msulitid` (`msulitid`)
) TYPE=MyISAM COMMENT='Full citations for embedded references in
GLT91';
```

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