Practical Problems and Solutions concerning the Safety Evaluation of Agrochemicals to Native Plants, Terrestrial Animals and Aquatic Species

Dr. T. Priester
(Compliance Services International, USA)

Practical Problems and Solutions Concerning the Safety Evaluation of Agrochemicals to Native Plants, Terrestrial Animals and Aquatic species

Thomas Martin Priester, Ph.D.
Compliance Services International, USA
Tel: 253 272-6345
FAX: 253-272-6241
E-mail : tpriester@complianceservices.com

Introduction

Ecotoxicology test data submitted to regulatory agencies are generally required to show the potential toxicity and exposure hazards to fish and wildlife. This data is needed to determine both toxicity, probability of exposure, and level of risk (Table 1). The Environmental Protection Agency's (EPA) need for this data can be found in Subdivision E of the Pesticide Assessment Guidelines. These guidelines clearly state that this data is required:

- To establish acute toxicity of active ingredients.
- To compare toxicity information with measured or estimated pesticide residues in the environment in order to assess potential impacts.
- To provide data determining the need for precautionary label statements in order to minimize the potential for adverse effects.
- And to indicate the need for further studies.

For example,

- "To estimate the potential for chronic impacts taking into account the measured or estimated residues in the environment.
- "To determine if additional field or laboratory data are necessary to evaluate hazards.

Simulated field or actual fields tests are required so that data can be developed to examine acute and chronic adverse effects in or near natural environments. These tests need to be conducted when predictions of adverse effects cannot be made or the potential for adverse effects from the use of a pesticide product is very high.

The most extensive data is required for products that will be directly applied to the environment (Table 2). That is:

- When the end-use product will be introduced directly into the outdoors.

- When inert ingredients are expected to enhance the toxicity of the active ingredient.

- When the specific EC50 of the manufacturing (technical) product is approximately equal to the expected residue levels that will be found in the field after application.

However, regulators do not require that all formulated end-use products be tested for acute toxicity. New tests on formulations with similar inert ingredients are not necessary. This can save on cost and prevent unnecessary suffering to test organisms. Only products differing substantially from the original end-use product need to have additional acute toxicity studies conducted on them.

Agricultural products are the most important in this sense (Table 3). Wildlife will certainly be exposed to products used in the agricultural environment to control crop and livestock pests. The required tests are extensive and expensive and should not be conducted unnecessarily. For example, most of the tests on wildlife may be excluded for agricultural products only applied indoors. Pest control products used in greenhouses, residences, food handling establishments, and for structural protection often fall into the indoor use category. Similarly, most veterinary and pharmaceutical products will not have to be tested for toxicity to wildlife unless the manner of application or disposal for these products will expose wildlife to the active ingredient. Bioengineered products used to control agricultural pests may have a reduced set of required tests. Examples of these bioengineered products include corn and cotton containing *Bacillus thurigiensis* Cry genes or NPV viruses containing a gene for the insect specific venom of a scorpion, *Antroctonus austalis*. Reduced risk pesticides may require fewer ecotoxicological and human health tests and may be evaluated on a "fast-track".

Safety Evaluations or Risk Assessments in Ecotoxicology

When are acute tests required?

Detailed acute toxicity tests can be avoided when products are known to have low toxicity to fish and wildlife (Table 3). Registrants primarily interested in registering products that have low toxicity in the environment should conduct screening tests to determine the acute toxicity on terrestrial and aquatic wildlife early in the discovery process.

Single dose or screening tests to determine oral and dietary toxicity in birds and mammals and pesticide toxicity on aquatic organisms can be useful if the intention is to show that end-use products are of no concern when wild-life are exposed to them. Agricultural products are generally not considered to be of concern to wildlife if the specified critical values are not exceeded. Tier 1 tests are almost always required. But other more complicated tests like chronic reproduction and growth tests, semi-field and field tests can be avoided if the product can be shown to be non-toxic.

It is necessary to use statistical tests to determine whether or not the criterion in Tier 1 tests has been exceeded (Table 4).

- Where an LD50/LC50 is the criterion for adequacy of the Tier 1 test, various dosage response tests should be used to determine these values.

- Typically, log-probit, log-logit, binomial approximation or moving average angle dosage response tests is used to determine LD50s or LC50s. The most acceptable test will be the test giving the best fit as indicated by a chi square test, correlation coefficient or goodness of fit (G) test.

- Where an absolute cutoff of 25% mortality is the criterion for the acceptabilty of the Tier I test, a paired t-test or Wilcoxon's Signed Tank test can be used.

The guidelines may also require that a no observable effects concentration (NOEC) be indicated (Table 5A). It is best to use a statistical test to determine the lowest observable effects concentration (LOEC) and subsequently the NOEC and the maximum acceptable toxic concentration (MATC). This may require transformation of the data prior to analysis if Analysis of Variance (ANOVA) based statistical methods are required.

Typically (Table 5B)

- ANOVA based tests are used if data is normal and variances are equal. ANOVA based tests would typically be conducted on continuous data (growth) or data with a large numbers of responses (reproduction).

ANOVA based tests with a wide currency include:

- William' Multiple Comparison test.
- Dunnett's Multiple Comparison test.
- Bonferroni's test.
- And pooled t-test for comparison of two samples or multiple samples.

ANOVA based tests may not be appropriate if the data is not normal or the variances are not equal. Usually, if the variances are equal, the database is large enough to be considered normal. However, if the data is not statistically normal, non-parametric rank sum tests like Wilcoxon, Kruskal-Wallace or Mann-Whitney are more appropriate.

- Statistical tests more suitable to morality versus survival evaluations are distribution-free and less subject to False Positives (Type I or Alpha Errors) typically found in ANOVA based tests or False Negatives (Type II or Beta Errors) typically found in other non-parametric tests.

Examples of distribution-free tests that are widely accepted include:

- the Chi Square.
- the Fisher's Exact test.
- and the Normal Approximation or 2-Proportion Z-test.

The registrant should not allow government agencies to regulate based on an LOEC that is only nominally higher than that occurring in the controls. The LOEC should be determined with a statistical comparison test that indicates the dosage significantly affects the test organism.

How do Results of Acute Toxicity Tests Relate to Risk Assessments or Safety Evaluations? (Table 6)

In general, ecological risk assessments or safety evaluations compare the LC50 or some other indicator of toxicity with the Expected Environmental Concentration (EEC). Ideally, the indicator of toxicity: LC50, LD50, NOEC, or MATC should be compared with the maximum concentration of the pesticide found in the environment. However, since no history of the product use is available during the initial registration process, the maximum concentration or the time-weighted maximum concentration is often estimated by predictive models such as Generic Expected Environmental Concentration (GENEEC 2.0), Pesticide Root Zone Models (PRZM 3.0)/ Exposure Analysis Modeling System (EXAMS II 2.94). (Table 6).

The GENEEC Model is a Tier 1 computer program designed to estimate the concentrations of a pesticide occurring in a 6-foot deep, one-acre farm pond after spraying a 10 acre field with the pesticide at certain specified number of times. This model assumes that a percentage of the pesticide on the sprayed field enters the pond approximately three days after the last application event. GENEEC 2.0 also takes into account the amount of drift into the water body after application. This model accounts for chemical parameters of the pesticide including degradation on the soil and in the water body and amount of binding that occurs to soil and sediment prior to exposure of the resident aquatic organisms. The GENEEC model is designed to mimic the PRZM/EXAMS Tier 2 models. However, EPA's Office of Pesticide Products does not take significant adverse action based on Tier 1 models.

If Tier 1 models indicate that adverse impact is likely from exposure to the pesticide in the field, Tier 2 models (PRZM/EXAMS) may be used to refine the estimated environmental concentration.

Using PRZM and EXAMS may decrease the Estimated Environmental Concentrations (EECs) of pesticides in ecologically sensitive areas. These models take into account all the factors documented under GENEEC 2.0 and can also estimate environmental concentrations based on certain user inputs. For example, the user can specify buffer zones and application methods to reduce drift. The user may also specify the presence of filtration zones and bermed levies to prevent runoff. Dilution and dispersion effects may also be determined by accounting for linear and transverse flow, the effects of tributaries and the effects of pulsed exposures due to rainfall or runoff events.

In the United States, the FIFRA Endangered Species Task Force (FESTF) – Information Management System (IMS) database documents where endangered species may be found. This database should then document species that can be excluded from risk due temporal or geographic absence. For those species that cannot be excluded from exposure, methods can be developed to protect endangered species with habitat in a specific area.

Although models that predict pesticide exposure of aquatic organisms are readily available in models like GENEEC, PRZM/EXAMS, SlutBox, and Simulator for Water Resources in Rural Basins (SWERB), no similar models are available that predict pesticide exposure of terrestrial organisms. To make approximations of the exposure risk to mammals and birds, we currently depend on the general fieldwork done by Hoerger and Kenaga (1972). This data is used to predict the upper limits and typical limits of exposure for various pesticicides immediately after application of 1 lb./acre treatment (Table 7).

Plant Category	Immediately After Application		6 Weeks After Application	
	Upper Limit	Typical Limit	Upper Limit	Typical Limit
Short grasses	240	125	30	5
Long grasses	110	92	20	1-5
Leafy crops	125	35	20	<1
Forage crops (legumes)	58	33	1.0	<1
Pods containing seeds and small insects	12	3	1.5	<1.0
Grain	10	3	1.5	<1.0
Fruit and large insects	7	1.5	1.5	<0.2
Soil (0.1 acre-inch in depth)[2]	22	-	-	-
Water (0.5 acre-foot in depth)	0.734	-	-	-

The Consol Model (Esterly, 2002) can decrease these numbers if the half-life of the pesticide and the exposure period for at risk terrestrial animals is known. However, EPA prefers to use the upper limit immediately after application for assessing short-term risk. However, EPA may agree to a time-weighted average exposure assumption or upper limit exposures at six-weeks after applications to estimate long-term exposure risk.

How Risk Assessment is Conducted and Some Practical Examples of Risk Assessments?

Historically, risk assessment has been quite liberal in the interpretation of what indicates adverse risk (Table 8). For example:

- When the risk quotient (RQ) = <0.1 or TER = >10
  Adverse Effects are not anticipated.

- When RQ = ≥0.1 but ≤10 or TER = ≤10 but ≥0.1
  Adverse Effects are possible.

- When RQ = >10 or TER = <0.1
  Adverse Effects are probable.

Note that the European Union uses the inverse of the Risk Quotient and refers to it as the Toxicity Exposure Ratio.

For practical use, EPA considers a product to be safe for most species if the acute RQ is less than 0.1 to 0.2. Toxic effects may be mitigated if the acute RQ is greater than or equal to 0.1 to 0.2 and less than 0.5 to 1.0. Generally, risk is considered to be unacceptable if the short-term RQ is greater than or equal to 0.5 to 1.0. For chronic or long-term risk, which usually measures growth and reproduction as the most important end-points, when RQ is less than one, the product would be considered safe. If the long-term RQ is greater than one, the risk would be considered unacceptable. In the European Union a safety factor that is five- to ten-fold higher than is typically used in the U.S. is needed to show low risk.

Generally, EPA determines risk by generating a Risk Quotient, which is defined as the Expected Environmental Concentration (EEC) divided by the toxicity (LC50 or LD50 for short-term exposure and NOEC or NOEL for chronic exposure (Table 9).

Practical Example of the Relatively Safe Alachlor Herbicide

There are a few examples of products where Tier 2 testing was not originally required because the products were practically non-toxic. For example, the acute toxicity of Alachlor herbicide in birds and mammals is very low (Table 10). The LD50s and LC50 approaches or exceeds the level at which a product is considered practically non-toxic (LC50 = >5000 ppm and LD50 = ~1500 mg/Kg) body weight. Note that typical LC50s can be estimated from LD50s assuming that small birds and mammals eat approximately 30 to 40% of their body weight each day. For fish and aquatic invertebrates the acute LC50 is approximately 2.0 to 10.0 ppm. In these cases, the expected environmental concentration is much lower than the acute toxicity. So, we would expect short-term exposure of terrestrial and aquatic animals to not have great potential for adverse impact. Chronic exposure of mammals and freshwater invertebrates has greater potential to cause adverse impact than short-term exposure. Therefore, these taxa are likely to be at risk from the long-term exposure to Alachlor. It is not reasonable to expect that aquatic plants or terrestrial plants would be unaffected by a herbicide. In fact, the short-term EEC is much higher than the dosage that has been shown to adversely impact plants.

There is great potential for harm to native plant species from short-term exposure and to terrestrial vertebrates and aquatic invertebrates from long-term exposure. Mitigation measures that may be useful in protection of sensitive species have been developed (Table 11). For example:

- Substantial reduction in risk to birds and aquatic species can only be obtained by a widespread reduction in use. The registrant has voluntarily reduced the maximum single application rate of Alachlor from 6 to 4 lb a.i./acre.

- ... The scope and seasonal pattern of use is a concern because Alachlor may adversely affect avian reproduction. Use of Alachlor should be avoided when birds are nesting or breeding.

- Because the EEC is likely to exceed the acute EC50 in terrestrial and aquatic plants, additional terrestrial and aquatic plant studies (Guideline 122-2) are required with Alachlor and the Alachlor degradate, Alachlor ESA.

- Similarly, avian reproduction studies are now required on mallard duck and quail with Alachlor and its degradate Alachlor ESA. Avian reproduction studies are required because mammal reproduction studies indicate that mammals will probably be affected by long-term exposure to Alachlor. Historical experience with pesticides indicates that birds are more prone to adverse long-term exposure affects than mammals.

- Changes in the label must reflect the change in use pattern, maximum use rate and the understanding of potential adverse affects to aquatic organisms and birds. The new labels were accepted by EPA on June 30, 1998

Practical Example of Diazinon, a High Risk Insecticide

Unlike the Alachlor example, diazinon can be expected to damage honeybee populations and kill beneficial predators and parasitoids if they are exposed to it. For example, the LC50 of diazinon to honeybees is 0.22 μg/bee, which is equivalent to approximately 0.34 lbs/acre. Since this LC50 value is so much below the proposed maximum treatment rate of 1.0 lb/acre, it is probable that honeybees will be adversely impacted by exposure to diazinon (Table 12). Furthermore, on an acute basis, birds as well as aquatic invertebrates will be adversely impacted by exposure to the expected environmental concentrations associated with the use of diazinon. That is, the LC50 is approximately equal to or very much less than the EEC for these species. However, with reasonable precautions, both fish and mammals should not be affected directly by the short-term exposure to diazinon. Nevertheless, the indirect impacts of diazinon on fish due to elimination of invertebrates as food sources may be a serious issue. Based on the mode of action, which is acetylcholinesterase inhibition, it is not surprising that plants are unaffected by exposure to diazinon at rates that would typically be encountered in the field.

There is great potential for harm to aquatic invertebrates and birds due to short-term exposure and to the birds, mammals, fish, and aquatic invertebrates due to long-term exposure. Various mitigation methods have been proposed to protect sensitive fish-food organism, terrestrial vertebrates, and people (Table 13). These are:

- Cancellation of all granular products. These products have a high potential to cause adverse impact on birds and adversely affect worker safety.

- Deletion of aerial applications. Up to 15% of the applied chemical drifts into waterways. Aerial application may also expose agricultural workers to unacceptable levels of diazinon. Worker exposure factors include drift, lack of

enclosed cabs, and large amounts of pesticide that may be applied by air in a short period of time.

- Requires worker protection procedures. To protect mixer and loaders, engineering procedures like soluble bags for wettable powders and lock and load systems for emulsifiable concentrates must be used. Applicators should be required to operate from an approved enclosed cab. These procedures are required to prevent contact with this highly toxic insecticide.

- Delete foliar applications on all vegetable and melon crops. Usually other pesticides are more effective in controlling insects on vegetable and melon foliage than diazinon.

Table 13B

- Reduce maximum application rate from 4 lbs a.i./acre to 1 lb a.i./acre.

- Incorporate all broadcast applications into soil to a depth of 20 centimeters. This procedure should reduce the exposure of birds to diazinon to levels that will eliminate adverse impact.

- Reduce the number of applications per growing season to one on all crops except crops which have a dormant season. Orchard crops, which have a dormant season, may be treated once during the dormant season and once during the active growth season.

- Limit application on orchard crops to every other year unless pest pressure is severe.

- Cancel uses of products on crops with the greatest potential for environmental impact and for crops where use of diazinon has low economic value. These crops currently include Chinese broccoli, Chinese cabbage, Chinese mustard, clover, corn, cowpeas, dandelions, grapes, guar beans, hops, kiwi, lespedeza, mushrooms, olives, peas with pods, radishes, sorghum, sugarbeets, walnuts, and watercress.

- To confirm the safety of this product, additional ecotoxicology studies must be conducted. These studies include a new early life-stage fresh water fish study, fresh water and marine fish life cycle studies, and acute avian toxicity studies. The toxicity of diazinon is certain. Therefore, these new tests must be conducted on the toxic and potentially persistent degradates, diazoxon and oxypyriimidine. Chronic avian tests with the potentially toxic degradates may be necessary if acute studies with these degradates indicate potentially high chronic toxicity.

- Label must be changed to reflect change in use pattern, maximum use rate and the understanding of potential adverse affects to aquatic animals and birds.

Practical Example of Biologicals like *Agrobacterium radiobacter, Bacillus thuringiensis, Bacillus popilliae, Nosema locustae,* and Nuclear Polyhedrosis Virus, which are Very Target Specific

Ideally, from a registrant's perspective, all studies will be waived (Table 14). This does not happen often. But, occasionally with a product like the microbicide *Agrobacterium radiobacter*, all studies except for acute toxicity studies on mammals may be waived. EPA will agree to such a registration standard if the product contains a biocontrol agent that is known to be pathogenic or toxic only to the target organism. *A. radiobacter* is used to control crown gall bacterium, *Agrobacterium tumefaciens,* on non-bearing orchard crops, berries and ornamentals. It is also known from long experience in the natural environment that *A. radiobacter* has no adverse effect on non-target organisms including mammals, birds, insects, fish, aquatic invertebrates, terrestrial plants, aquatic plants, and people. Furthermore, less than 5% of the acreage planted with non-food and non-feed crops are treated with *A. radiobacter.* Therefore, this control agent may be used in the field with only minimal worker protection standards and no required residue tolerance.

However, for most biologicals like *Bacillus thuringiencis, B. popolliae, Nosema locustae* or *Heliothis* Nuclear Polyhedrosis Virus, acute and chronic tests have been required on mammals to address human health issues. Nevertheless, only acute tests were required on fish and wildlife species. This strategy was accepted by the agency since these products are only pathogenic to a narrow spectrum of insects.

These insect control products have little potential to adversely impact the consumer public, agricultural workers or fish and wildlife. However, certain mitigations and label changes were believed to be necessary (Table 15A). These included:

- For *A. radiobacter* and NPV only minimal precautionary statements need be made concerning worker and public safety. For example, keep out of the reach of children and avoid eye contact. No residue data or tolerances are required for *A. radiobacter* or NPV.

- A requirement that each batch of the product not contain toxins or organisms known to be toxic to humans. With *B. thuringiensis,* acute toxicity to *Daphnia magna* must be tested with each manufactured batch to assure that the toxins contained in the product will not adversely impact this important fish-food organism.

- Products applied directly to water like *B. thurinigiensis israeliensis* must be labeled as potentially toxic to aquatic organisms, particularly to aquatic invertebrates. The toxicity picture of this aquatic insecticide is not completely understood but aquatic diptera are known to be adversely impacted by this product.

- Products known to be toxic to honeybees like *B. thuringiensis aizawai* may be labeled as potentially toxic to honeybees. This change in labeling will depend on practical observations from long term use.

Table 15B

- Products that are dusty must be labeled as requiring the wearing of respiratory protection. This is of particular concern in products that contain living organisms or toxin that may serve as human allergens. These include granule and powder formulations of *B. thuringiensis*, *B. popilliae*, and N. *locustae*.

- Products may not be disposed of by discharge into a waterway. Do not contaminate food or water with these products. May be particulary important for *B. thuringiensis aizawa*, which is toxic to *Daphnia magna,* and *B. thuringiensis israeliensis*, which is potentially toxic to aquatic diptera..

- On those products that may be used legally on food- and feed-crops, a residue method must be developed. This requirement is primarily confined to *B. thuringiensis*.

Use of the FESTF IMS

Products like diazinon and porpargite are known to be toxic to aquatic and terrestrial organisms. The FIFRA Endangered Species Task Force - Information Management System is able to locate and suggest possible protections for endangered and threatened species. Recently, the Task Force has determined that under certain circumstances, endangered and threatened salmonid species may be excluded from need for protection. However, when protection is necessary, the FESTF-IMS database can suggest appropriate protections (Table 16).

Clearly, fish populations do not need to be protected if propargite is no longer used in particular counties. Also, the formerly protected species that no longer occupies a particular habitat do not need protections.

Protection is usually not necessary if propargite is used at extremely low rates or on very small acreage. Under these circumstances, a pesticide will be diluted and/or adsorbed by the sediment before it reaches occupied habitat.

However, in areas where propargite may occur in waterways at environmentally relevant concentrations, fish need to be protected. Suggested protections include buffer zones, preventing runoff, not applying pesticide when wind is moving toward habitat, retaining irrigation water in treated fields for as long as possible after treatment, and not applying in or near occupied habitat.

Conclusions

In order to conduct acceptable Ecological Risk Assessments or Safety Evaluations, appropriate tests must be conducted. These tests show the acute toxicity of a pesticidal product on mammals, birds, fish, aquatic invertebrates, honeybees and other insects, terrestrial plants, and aquatic plants (Table 17). The statistics used to aide in the evaluation of the data must be appropriate to the end point. Contingency Table or other distribution-free statistical tests should used to evaluate survival and mortality. ANOVA or non-parametic rank sum tests should used to evaluate growth and reproduction tests with statistically normal data and non-normal data, respectively. Chronic test do not need to be conducted unless the acute toxicity tests and environmental fate tests indicate that the pesticide is toxic and/or persistent.

To conduct the safety evaluation on fish and wildlife, the environmental concentration of a pesticide must be either known or estimated. With products in current use, environmental concentrations may be measured using appropriate analytical techniques. With products that have not yet been registered, estimates of the environmental concentrations should be made using models. It is also appropriate to use historical data for registered compounds with similar product chemistry.

Safety evaluations are usually made with risk quotients or toxicity exposure ratios that determine the relative environmental concentrations of the pesticide with respect to the toxicity of the pesticide. Attempts are being made to develop Tier 3 and 4 environmental risk assessment models that take into account time-weighted exposure effects. Also, these higher tier assessments try to evaluate the whole biota structure and function and base uncertainty on game theory or Monte Carlo simulations. However, currently only the Tier 1 and possibly 2 models are universally accepted. These lower tier models take into account the initial concentration for short-term exposures and possibly time-weighted average concentrations for long-term exposure. Nevertheless, the most skeptical regulators may not be willing to accept the time-weighted average exposures particularly in avian and mammalian risk assessments. The draw back of the lower tier risk assessments is that they are designed to protect the most sensitive individual species rather than an ecosystem. Individual species may be considered important because they are endangered, sensitive, aesthetically pleasing or economically important. But, the elimination of a single species will rarely impact the overall health of an ecosytem.

Many examples of both human risk and ecological risk from the exposure to pesticides can be found in the EPA "Re-registration Decision" Documents (REDs), which can be easily found by conducting a Google search using "RED" as the exact phrase and "EPA" as the search within the exact phrase.

Exclusions and protections for endangered species can be found on the FESTF- IMS website. This database is currently being developed. This is a dues-paying members-only site. The FESTF-IMS database evaluates where habitat for threatened and endangered species may be found relative to use sites for various pesticides. It is designed to assist the registrant and EPA in developing an effective endangered and threatened species

protection plan for both new products and products currently sold within the United States of America.

References

Burns, L.A. 1991. Exposure Analysis Modeling System: Users Guide for EXAMS II version 2.94, Environmental Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Athens, GA.

Burns, L.A. 1997. Exposure Analysis Modeling System (EXAMSII) Users Guide for Version 2.97.5, Environmental Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Athens, GA.

Carsel, R.F; Smith, C.N.; Mulkey, L.A; Dea, J.D.; and Jowise P. 1984. Users manual for pesticide root zone model (PRZM): Release 1, Rep. EPA-600/3-84-109, 219 pp. Environmental Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Athens, GA

Carsel, R.F.; Imhoff, J.C.; Hummel, P.R.; Cheplick, J.M.; and Donigian, J.S. Jr. 1997. PRZM-3, A Model for Predicting Pesticide and Nitrogen Fate in Crop Root and Unsaturated Soil Zones: Users Manual for Release 3.0; Environmental Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Athens, GA.

EPA. Dates Vary. EPA Publication No. 712-C. Series 96. United States Environmental Protection Agency. Office of Pesticide Programs, Washington, D.C.

Esterly, D. 2002. Consolidated Exposure Model for Ecological Risk Assessments. Version 1.08a. Environmental Focus, Inc. Project No CSI-001. Wilmington, Delaware

Hitch, R.K. 1982. Subdivision E. Hazard Evaluation: Wildlife and Aquatic Organisms. Ecological Effects Branch. Hazard Evaluation Division. United States Environmental Protection Agency. Office of Pesticide Programs, Washington, D.C. EPA 540/9-82-024. PB83-153908. 85 pages.

Hitch, R.K. 1982. Subdivision L. Hazard Evaluation: Nontarget Insects. Ecological Effects Branch. Hazard Evaluation Division. United States Environmental Protection Agency. Office of Pesticide Programs, Washington, D.C. EPA 540/9-82-019. PB83-153957. 29 pages

Hoerger, F.D.; and Kenaga, E.E. 1972. Pesticide Residues on Plants Correlation of Representative Data as a Basis for Estimation of Their Magnitude in the Environment. Environmental Quality. Academic Press, New York, Vol 1. pages 9 to 28.

Holst, R.W.; and Ellwanger, T.C. 1982. Subdivison J. Hazard Evaluation: Nontarget Plants. Ecological Effects Branch. Hazard Evaluation Division. United States Environmental Protection Agency. Office of Pesticide Programs, Washington, D.C. EPA 540/9-82-020. PB83-153940. 55 pages.

Miller, R.G. 1997. Beyond ANOVA: Basic and Applied Statistics. CRC -- Chapman & Hall, New York. ISBN 041207011. 336 pages.

OECD. Dates Vary. Series 200 and Series 300 Guidelines. Organization of Economic Cooperation and Development, Brussels, Belgium.

OPPTS. 1996. Series 850. Ecological Effects Test Guidelines. Office of Pesticides and Toxic Substances. United States Environmental Protection Agency, Washington, DC.

OTS. Date Varies. Series 797 Guidelines. Office of Toxic Substances. TOSCA. United States Environmental Protection Agency. Washington, DC.

Parker, R.D.; Jones, R.D.; and Nelson, H.P. 1995. GENEEC: A Screening Model for Pesticide Environmental Exposure Assessment. in Proceedings of the International Exposure Symposium on Water Quality Modeling; American Society of Agricultural Engineers, pp. 485-490; Orlando, Florida.

Parker, R.D. et al. 2001 GENEEC. Users Manual. EFEF/OPPTS/EPA. Version 2.0.

Urban, D.J.; and Cook, N.J. 1986. Ecological Risk Assessment. Standard Evaluation Procedure. Ecological Effects Branch. Hazard Evaluation Division. United States Environmental Protection Agency. Office of Pesticide Programs, Washington, D.C. EPA 540/9-86/167. PB86-247657. 101 pages.