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How Protective to the Environment is the Pesticide Risk Assessment and Registration Process in the United States?

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Abstract

The media, public, and other stakeholders are generally unaware of the degree of protection provided to the environment by the current pesticide registration process in the United States. Each pesticide product must meet extensive fate and toxicological data requirements (typically 100+ studies) to be considered by the U.S. Environmental Protection Agency (EPA). The EPA uses that information to conduct ecological, human health, and benefits assessments and make decisions on whether to register pesticides and, if so, under what conditions. The assessments rely on conservative assumptions, models, and inputs to consistently err on the side of caution throughout the pesticide registration process. The rigorous compliance requirements specified in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Endangered Species Act (ESA) are designed to preclude unacceptable adverse effects. However, this reality seldom, if ever, makes headlines. Pesticides are not causing the dire widespread apocalyptic effects often portrayed by some media outlets. Rather, pesticides have been doing what they were intentionally designed to do, controlling pests and increasing yields, within the stringent limitations of registered labels. The continually evolving pesticide registration process was originally predicated on the unintended adverse effects neither anticipated nor considered over 50 years ago, due to insufficient regulation and oversight at the time. However, the contemporary regulatory paradigm in the U.S. is data rich and analysis intensive by design, and perhaps understandably, biased towards ensuring environmental protection when registering pesticides.

Keywords:
pesticide risk assessment, pesticide registration, conservatism, environmental protection

1. Introduction

For decades, agricultural production in the United States (U.S.) has met the demands of a rapidly expanding population without increasing the amount of land under cultivation (Figs. 1 and 2) [27]. Increased agricultural efficiency has resulted from improvements in pesticide technology, application methods, soil conservation measures, and the advent of genetically-modified crops [7].

Pesticides provide many benefits to society and the environment, including improved yields for farmers, reduced prices for consumers, control of unwanted weeds in lawns, golf courses, transit corridors and beneath power lines, control of invasive weeds in forests, wetlands, and other natural areas, supporting conservation tillage (e.g., reduced till and no till practices) to promote soil health, protection of human health, livestock, and pets from disease-carrying organisms, and many others [17, 19].

Despite their many benefits, pesticides have the potential to adversely impact the environment because they are biologically active and widely used. Consequently, risks to the environment and human health must be assessed to evaluate whether a pesticide should be authorized for use and if any use restrictions are required. Required restrictions should not exceed what is necessary to protect the environment and human health. Thus, balancing risks and benefits of pesticide use is reflected in the statute that governs pesticide registration and licensing in the United States, the Federal Insecticide and Rodenticide Act (FIFRA). Under the FIFRA, a pesticide product must not cause "unreasonable adverse effects on the environment", which is defined as:

- "Any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide.

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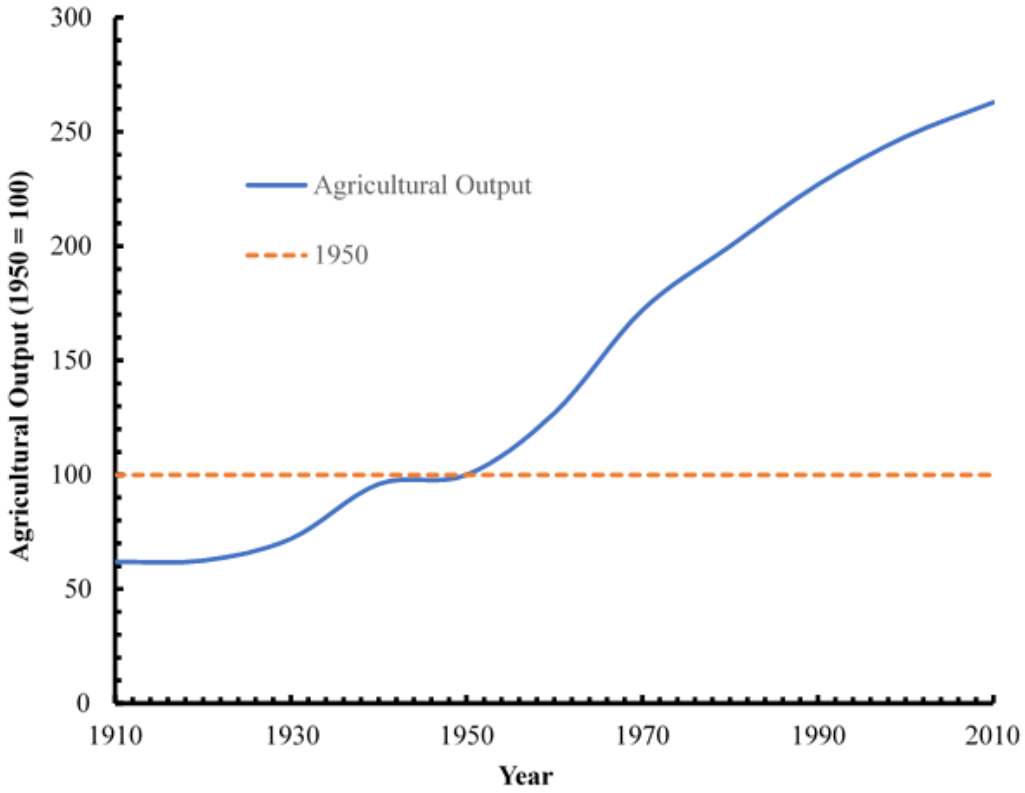

Figure 1: U.S. agricultural output since 1910. All values are scaled as a percentage to the output from 1950 (approximately when use of man-made chemicals on farms began to steeply increase) as a baseline. Adapted from Gianessi [28]. For additional detail, see USDA [52].

- Any human dietary risk from residues that result from use of a pesticide in or on any food inconsistent with the standard under section 408 of the Federal Food, Drug, and Cosmetic Act." [66].

The FIFRA is administered by the U.S. Environmental Protection Agency (EPA), which was established in 1972 in response to inadequate regulation of chemical pollutants, including the organochlorine class of insecticides, a class that includes dichlorodiphenyltrichloroethane (DDT) [16, 22]. In addition to their FIFRA responsibilities, the EPA must also ensure the pesticide registration (or "action") is also in compliance with the Endangered Species Act (ESA). The Fish and Wildlife Service and National Marine Fisheries Service, collectively the "Services", were formed in 1940 [24] and 1970 [2], respectively, and are responsible for administering the ESA of 1973 [73]. The ESA was created in response to the growing number of critically imperiled species in the U.S. resulting from numerous anthropogenic activities. Under the ESA, the Services are mandated to ensure that actions carried out by other agencies, including the EPA registration of new pesticides or re-registration of existing pesticides, are not likely to jeopardize the continued existence of any threatened or endangered species or result in the destruction or adverse modification of a critical habitat of such species [73]. Clearly, the intent of the pesticide laws and regulations in the U.S. is to ensure that the environment and human health are protected. Similar statutes for pesticide regulation exist in Europe, Canada, China, Australia, and many other jurisdictions worldwide, but the role of the ESA in pesticide regulation is somewhat unique to the U.S.

Although broadly recognized among the regulated community (e.g., pesticide registrants), the public and other stakeholders are generally not aware of the rigorous regulatory evaluation process and layers of safety factors that are included in the current pesticide registration paradigm in the U.S. The purpose of this paper is to describe the registration process, data requirements, and the methods for assessing pesticide risks in the U.S., primarily focusing on the ecological component (e.g., plants, fish, invertebrates, wildlife, etc.). In so doing, we hope to illustrate the high degree of protection provided by the pesticide registration process in the U.S.

2. Overview of the Pesticide Reigistration Process in the United States

Although the primary federal law governing oversight of pesticide use and registration in the United States is the FIFRA, the registration process involves several other laws, including the Food Quality Protection Act (FQPA), the Federal Food, Drug, and Cosmetic Act (FFDCA), Pesticide Registration Im-

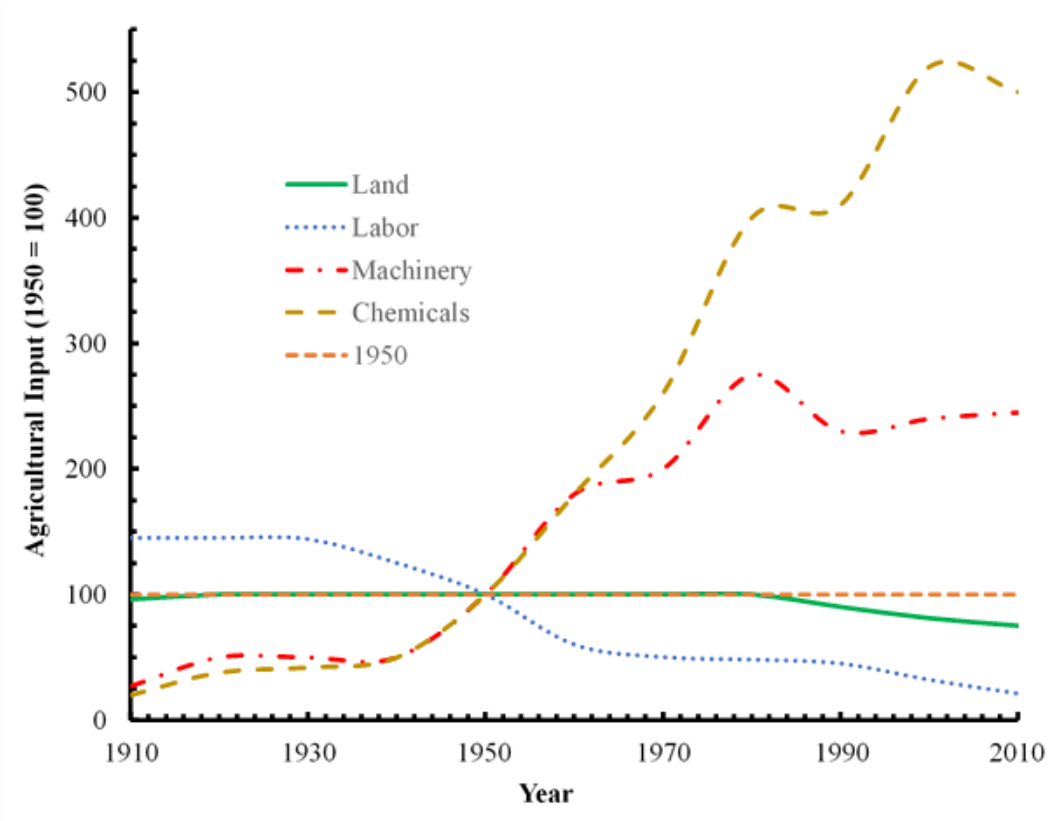

Figure 2: Aggregate inputs to U.S. farms since 1910. All values are scaled as a percentage to the output from 1950 as a baseline. Increased mechanization and chemical inputs to farms have dramatically increased yield while decreasing the amount of land and labor required to produce that yield. Adapted from Gianessi [28]. For additional detail, see USDA [52].

provement Act of 2003 (PRIA), the Clean Water Act (CWA), and the ESA [66].

Any substance intended for preventing, destroying, repelling, or mitigating any pest, for use as a plant regulator, defoliant, or desiccant, or any nitrogen stabilizer must be registered as a pesticide under the FIFRA [63]. When a product enters the registration process (Figure 3), the FIFRA and the FFDCA require a careful, intensive review. If a pesticide use could lead to residues on food or feed items, it may not be registered unless the residues are deemed "safe" under the FFDCA, defined as there being a "reasonable certainty of no harm" [26]. If safety can be established, tolerances (i.e., maximum permissible pesticide residues on food or feed commodities) may be promulgated.

There are several assessments that a pesticide must undergo prior to registration to determine potential impacts on humans, the environment, and the economy (Figure 3). The human health risk assessment (HHRA) is designed to identify and mitigate the potential for adverse effects to human health for applicators, farmers, and consumers. Only pesticides that do not pose an unreasonable risk of harm to humans may be registered [65].

In addition to the HHRA, all pesticide products must undergo an ecological risk assessment (ERA). The first step of an ERA is to prepare a problem formulation to determine which plants and animals may be at risk and by which routes of exposure, and to formulate an analysis plan for how to assess the potential risks. Following problem formulation, exposure and toxicity to different receptors are characterized. The final phase of an ERA is risk characterization, wherein risk is estimated by combining exposure estimates and toxicity endpoints. If a pesticide has the potential to adversely affect plants, animals or water sources, restrictions may be promulgated on use patterns and where and how the chemical may be applied [65].

The EPA also conducts a benefits assessment to determine the potential economic impacts of allowing or restricting the use of a pesticide. The EPA assesses benefits by identifying the crops on which the product will be used, determining expected crop yields when treated with the product versus the yields achieved with alternative products or methods, evaluating alternative pest control practices, and quantifying potential economic consequences on users and on the public of having or not having the product available (e.g., effects on food prices) [76]. Because pest resistance can develop when the same pesticide or similar ones with the same mode of action are used repeatedly, it is important to have multiple modes of action that can be rotated over time to deal with pests. Thus, pesticides that contribute to pest resistance management are providing key benefits.

The EPA is also responsible for registration review and re-

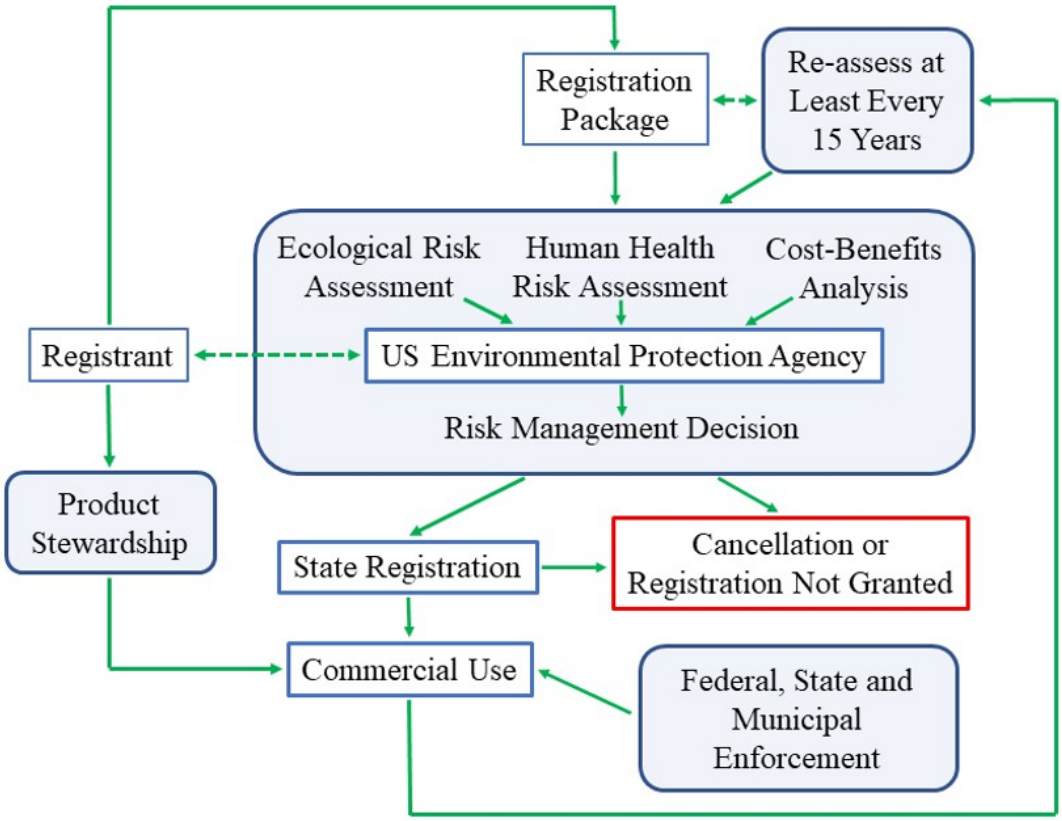

Figure 3: Pesticide registration and re-registration process in the United States

registration activities that occur approximately every 15 years for existing pesticides, including post-registration review activities, product re-registration, and implementing certain tolerance reassessment decisions. The re-registration process ensures that new scientific studies and data on pesticide use are incorporated on a regular basis in the EPA's assessments and that the assessments reflect the current state of the science. Potential adverse effects that occur during registration to non-target plants, wildlife, pollinators, fish, and other organisms are reported to the EPA by manufacturers, other government agencies, non-government organizations, and the public. The EPA considers this "incident" information when evaluating the risks from exposure to a pesticide. Incident reports help the EPA determine whether the application directions need to be clarified, certain uses of the pesticide need to be restricted, or additional safety measures are required. If risks associated with exposure to a pesticide cannot be reduced, the EPA has the authority to remove it from the marketplace.

In addition to the EPA, pesticides may be further regulated by a variety of other agencies in the United States. Federal agencies, including the U.S. Department of Agriculture (USDA), U.S. Department of Defense (DoD), and U.S. Forest Service (USFS) have detailed policies governing pesticide usage on their lands. Once registered at the federal level, pesticides must also be registered by the states. The states are the key enforcers responsible for ensuring that pesticide labels are followed. Often, counties and municipalities have their own pesticide policies. The states and other agencies can choose not to use or restrict the use of pesticide products further than required by the EPA. Under an agreement with the EPA, State Pesticide Safety Education Programs (PSEPs) provide training for applicators of restricted-use pesticides, that is, those pesticides designated as potentially hazardous to human or environmental health unless applied with additional restrictions by certified applicators. The goal of the PSEPs is to promote responsible pesticide use and handling to protect users, public health, crops, livestock, and the environment. All regulations and policies must, at a minimum, adhere to FIFRA and other relevant federal laws [60].

There are systems in place to ensure compliance with federal and state requirements regarding the registration, distribution, sale, and use of pesticides. Generally, states and tribes monitor and enforce pesticide use requirements, certify and license commercial pesticide applicators, certify private pesticide applicators who apply restricted use pesticides, and conduct inspections of manufacturing facilities and marketplaces on behalf of the EPA to ensure that labels are being followed. The EPA's Office of Enforcement and Compliance Assurance also inspects pesticide-producing facilities, oversees imports and exports, inspects laboratories under the Good Laboratory Practices compliance monitoring program, gathers data on product use and any incidents that occur during registration, and conducts inspections to ensure workplace safety. More information concerning compliance with FIFRA can be found in the 2015

Compliance Monitoring Strategy [60].

Due to the requirements of FIFRA and other regulatory statutes and agencies, development and registration of a novel pesticide product can often take up to 11 years and typically costs $286 million [33]. Much of that timeframe is required to meet the rigorous data and safety requirements of the FIFRA and other statutes. In addition, the registration process has several steps, each of which is open to public review. The process begins with opening a docket for public input. The docket includes a preliminary workplan, anticipated data and risk assessment needs, and an estimated timeline. Following a public comment period of at least 60 days, a final workplan is issued. The EPA then proceeds to meeting with interested stakeholders as needed, reviewing submitted data, and conducting the necessary assessments. The EPA posts draft risk assessments to the docket for public review. The Agency also announces the availability of a revised risk assessment. If risks of concern are identified, the EPA may invite the public to submit suggestions for mitigating risks. Following consideration of public comments and consultations with other federal agencies, the EPA publishes a Federal Register notice announcing the availability of an interim decision. That notice provides the public with a comment period of at least 60 days. After considering comments regarding the proposed decision, the EPA may then issue a Final Registration decision, including an explanation of changes to the interim decision and responses to significant comments. In some cases, decisions remain interim or conditional pending completion of studies requested to address data gaps or reduce sources of uncertainty, as well as completion of an endangered species assessment. The availability of the decision is published in a Federal Register notice. Thus, the registration and re-registration processes are rigorous, detailed, and transparent.

3. Data Requirements

The large number of studies and data required to register a pesticide ensures that the EPA has the information required to assess the potential for unintended consequences when the product is used. Such consequences may arise because of direct exposure during application or following application due to runoff, spray drift or other routes of exposure. The studies provided by a registrant are far-reaching and must comply with detailed guidelines and protocols regarding their conduct (Table 1) [23]. The EPA has test guidelines for each of the listed tests and conducts a rigorous problem formulation to ensure that the correct data are available for the risk assessments. Some tests may not be applicable to certain pesticides and thus would not be required. For other tests, multiple studies are required, e.g., different soil types for soil biodegradation and multiple test species for fish and birds. As shown in Table 1, each registration package for a pesticide must include the results of at least 100 studies to characterize physical-chemical properties, environmental fate and transport, analytical methods for determining residues in different media and on various foodstuffs, and other specialized studies to determine occupational and residential exposure. At least 80 toxicity studies are required for aquatic and terrestrial organisms, including surrogates for human health. Numerous other fate and effects studies may be required, particularly for widely used pesticides, to address areas of uncertainty or concern.

Generic data are required for every use pattern of a product, with additional specific requirements as needed depending on whether the application is industrial or residential, the crop is for food or animal feed, and the pesticide is applied to terrestrial or aquatic (including marine) receiving environments [23]. In most cases, Good Laboratory Practice (GLP) studies must be conducted for each category of data provided by the registrant to the EPA. GLP studies must follow rigorous protocols to ensure consistency, reliability, reproducibility, high quality, and integrity of results. The EPA also considers other available non-registrant submitted studies such as publications from academics in peer-reviewed journals, although many such studies do not follow GLP, which in some cases leads to lower quality results. For open literature studies, the EPA considers whether generally-accepted methods were used, sufficient measurements were made to achieve statistical reliability, and sufficient controls (where applicable) were included in the study. Details on how the EPA evaluates the quality of ecological toxicity studies published in the open literature are available [58].

Environmental fate studies are required to understand how a pesticide may move through the environment following application and lead to exposure of aquatic and terrestrial organisms. Fate studies are conducted to determine persistence in soil and water under high and low oxygen conditions, potential to move to surface and ground waters, susceptibility to breakdown by photolysis and photooxidation, rate of dissipation in aquatic and terrestrial environments, and volatility. An array of crop residue studies and foliar dissipation studies are required to characterize dietary exposure for wildlife, consumers, and workers. When the pesticide product is in a liquid form, information on formulation composition, application methods, and other properties are required to enable the EPA to determine how far spray could drift from the applied area and in what quantities. The EPA has recently released a directive to prioritize eliminating the use of animals in chemical safety testing by 2035 [64], and efforts are underway to develop new methods to replace animal testing [67].

For the ERA, a wide variety of acute and chronic ecotoxicology studies is required. In general, the required tests are conducted on species that are representative of important receptor groups like aquatic plants and invertebrates, fish, birds, mammals, pollinators, and terrestrial plants, amenable to testing in the laboratory, and typically sensitive to many pesticides and contaminants. For some products, additional studies on sensitive species that are not routinely tested are requested by the EPA under FIFRA to address potential concerns or sources of uncertainty.

4. Ecological Risk Assessment

As will become apparent, the EPA's assessment methods

Table 1: Required and conditionally required data for registration of a pesticide in the United States [23].

Type of Study	Group	Required Information and Tests	
Product Chemistry	A – Product Identity, Composition, and Analysis	Background for product properties	Discussion of formation of impurities
		Product identity and composition	Preliminary analysis
		Description of materials used to produce the product	Certified limits
		Description of production process	Enforcement analytical method
		Description of formulation process	Submittal of samples
	B – Physical and Chemical Properties	Color	Vapor pressure
		Physical state	Dielectric breakdown voltage
		Odor	pH
		Stability to normal and elevated temperatures, metals, and metal ions	UV/visible absorption
		Flammability, explodability	Viscosity
		Storage stability	Melting/boiling point and melting/boiling range
		Miscibility	Density/relative density/bulk density
		Corrosion characteristics	Dissociation constants in water
		Particle size, fiber length, and diameter distribution	Water solubility, estimation by the column elusion method and/or the generator column method
		Partition coefficient (n-octanol/water), estimation by liquid chromatography, shake flask method, and/or liquid chromatography	
Product Performance	A – General	Overview, definitions, and general considerations	
	B – Antimicrobial Efficacy	General considerations for testing public health antimicrobial pesticides	Sanitizers for use on hard surfaces/fabrics and textiles
		Sterilants, sporicides, and decontaminants	Air sanitizers
		Disinfectants for use on environmental surfaces	Disinfectants and sanitizers for use in water
		Antimicrobial efficacy	Disinfectants with prion-related claims
	C – Invertebrate Control Agent	General considerations	Premise treatments
		Soil treatments for imported fire ants	Structural treatments
		Livestock, poultry, fur- and wool-bearing animal treatment	Insect repellents to be applied to human skin
		Treatment to control pests of humans and pets	Efficacy of testing termite baits
		Mosquito, black fly, and biting midge (sand fly) treatments	Laboratory product performance for bed bug pesticide products
Fate, Transport, and Transformation	A – Laboratory Transport	Biodegradation testing	Activated sludge sorption isotherm
		Leaching studies	Soil thin layer chromatography
		Adsorption/desorption (batch equilibrium)	Laboratory volatility

Type of Study	Group	Required Information and Tests	
		Sediment and soil adsorption/desorption isotherm	
	B – Laboratory Abiotic Transformation	Direct phytolysis in water by sunlight	Hydrolysis as a function of pH and temperature
		Photodegradation in water	Hydrolysis
		Photodegradation in air	Photodegradation in soil
		Maximum direct photolysis rate in air from UV/visible spectroscopy	
	C – Laboratory Biological Transformation	Aerobic aquatic degradation	Ready biodegradability
		Sediment/water microcosm biodegradation	Ready biodegradability – CO_2-sealed vessels
		Anaerobic mineralization in surface water	Anaerobic biodegradability, and in digested sludge
		Zahn-Wellens/EMPA test	Shake flask die-away
		Modified SCAS test	Inherent biodegradability
		Porous pot test	Biodegradability in sea water
		Simulation of primary and ultimate biodegradability in wastewater	Soil biodegradation
		Simulations of anaerobic sewage treatment A (sludge) and B (biofilms)	
	D – Transformation in Water and Soil	Anaerobic/aerobic soil metabolism	Anaerobic/aerobic aquatic metabolism
	E – Transformation Chemical-Specific	Modified SCAS test for insoluble and volatile chemicals	Anaerobic biodegradation in the subsurface
		Indirect photolysis screening: sunlight photolysis in waters containing dissolved humic substances	
	F - Field Dissipation	Terrestrial field dissipation	Forestry dissipation
		Aquatic (sediment) field dissipation	Combination and tank mixes field dissipation
	G – Ground Water Monitoring	Ground water monitoring studies	
	H – Volatility from Soil	Field volatility	
Spray Drift		Spray droplet size spectrum	Spray drift field deposition
Ecological Effects	A – Aquatic and Sediment-Dwelling Fauna and Aquatic Microcosms	Aquatic invertebrate acute toxicity	Daphnid chronic toxicity
		Gammarid amphipod acute toxicity	Fish early life stage toxicity
		Oyster acute toxicity	Oyster bioconcentration factor
		Mysid acute toxicity	Fish bioconcentration factor
		Penaeid acute toxicity	Bivalve acute toxicity
		Freshwater and saltwater fish acute toxicity	Spiked whole sediment 10-day and long-term toxicity for fresh- and saltwater invertebrates
	B – Terrestrial Wildlife	Avian acute oral toxicity	Avian dietary toxicity
		Avian reproduction	Wild mammal toxicity
		Field testing for terrestrial wildlife	
	C – Terrestrial Beneficial Insects, Invertebrates, and Soil and Wastewater Organisms	Honey bee acute and chronic toxicity for larvae and adults	Toxicity of residues on foliage to honey bees
		Field testing for pollinators	Earthworm subchronic toxicity
		Soil microbial community toxicity	Modified activated sludge, respiration inhibition test

Type of Study	Group	Required Information and Tests	
	D – Terrestrial and Aquatic Plants, Cyanobacteria, and Terrestrial Soil Core Microcosm	Seedling emergence and growth	Vegetative vigor
		Early seedling growth toxicity	Terrestrial plants field study
		Aquatic plant toxicity	Aquatic plants field study
		Algal toxicity	Cyanobacteria toxicity
		Rhizobium-legume toxicity	Plant uptake and translocation
		Terrestrial soil-core microcosm test	
	F – Field Test Reporting	Environmental chemistry methods and associated independent laboratory validation	
Residue Chemistry		Chemical identity	Food handling
		Direction for use	Meat/milk/poultry/eggs
		Residue analytical method	Nature of residue: plants, livestock
		Multiresidue method	Proposed tolerances
		Storage stability data	Processed food/feed
		Water, fish, irrigated crops	Crop field trials
		Field accumulation in rotational crops	Confined accumulation in rotational crops
Health Effects	A – Acute Toxicity	Acute oral toxicity	Acute eye irritation
		Acute dermal toxicity	Acute dermal irritation
		Acute inhalation toxicity	Skin sensitization
	B – Sub-chronic Toxicity	Repeated dose 28-day oral toxicity in rodents	90-day oral toxicity in rodents and nonrodents
		21/28-day dermal toxicity	90-day dermal/inhalation toxicity
		Prenatal development toxicity	Reproduction and fertility effects
		Reproduction/developmental toxicity (and repeated dose)	
	C – Chronic Toxicity	Chronic toxicity	Carcinogenicity
	D – Genetic Toxicity	Bacterial reverse mutation	Bacterial DNA damage or repair
		Miotic gene conversion in *S. cerevisiae*	Unscheduled DNA synthesis in mammalian cells in culture
		Mouse biochemical specific locus	Gene mutation in *A. nidulans*
		Mouse visible specific locus	In vitro sister chromatid exchange
		Gene mutation in *N. crassa*	In vivo sister chromatid exchange
		Sex-linked recessive lethality in *D. melanogaster*	Mammalian erythrocyte micronucleus
		In vitro mammalian cell gene mutation and chromosome aberration	Mammalian spermatogonial and bone marrow chromosomal aberration
		Rodent dominant lethal assay	Rodent heritable translocation
	E - Neurotoxicity	Acute and 28-day neurotoxicity	Neurotoxicity screening battery
		Developmental neurotoxicity	Peripheral nerve function
		Schedule-controlled operant behavior	Neurophysiology sensory evoked potentials
	F – Special Studies	Companion animal safety	Metabolism and pharmacokinetics
		Dermal penetration	Immunotoxicity
	G – Chemical-specific Health Effect	Combined chronic toxicity/carcinogenicity testing of respirable fibrous particles	

Type of Study	Group	Required Information and Tests	
Occupational and Residential Exposure	A – Applicator Exposure Monitoring	Dermal exposure-outdoor	Dermal exposure-indoor
		Inhalation exposure-outdoor	Inhalation exposure-indoor
		Biological monitoring	Application exposure monitoring
	B – Post-application Exposure Monitoring	Foliar dislodgeable residue dissipation	Descriptions of human activity
		Soil residue dissipation	Dermal/inhalation exposure
		Biological monitoring	Data reporting and calculations

Depending on the results of initial screening analyses, additional tests may be required to identify and quantify adverse endocrine-related effects.

consistently err on the side of conservatism. The goal is to ensure that risks to aquatic and terrestrial biota are not underestimated [11].

The EPA uses a tiered approach to estimate potential risks of pesticides to aquatic and terrestrial biota [56]. Each tier contains the traditional four components of an assessment: Problem Formulation, Exposure Assessment, Effects Assessment, and Risk Characterization. A tiered approach is designed to identify "safe" pesticides early in the process and only requires higher, more complex levels of investigation for those that have not passed the previous (i.e., lower) tier. Each tier screens out a percentage of pesticides or use patterns from having to undergo a more rigorous pre-registration review without the need to consider more detailed information [56]. Failing at a screening-level tier does not indicate that there is an unacceptable risk, only that the potential for risk cannot be eliminated at that specific tier.

For each type of organism (e.g., fish, birds, mammals, and pollinators) and use pattern, a risk quotient (RQ) is calculated by dividing a conservative estimate of exposure by the corresponding conservative toxicity endpoint. The resulting RQ is compared to a corresponding level of concern (LOC) to determine whether there is the potential for an unacceptable level of risk, i.e., RQ exceeds the LOC (Table 2) [56]. If the RQ is less than the LOC, negligible risk is concluded. Separate analyses are done for a range of use patterns (e.g., different crops, home uses, etc.) and application methods (e.g., aerial application, ground application, seed treatment, etc.) because pesticide labels specify different application rates and because application method can affect the quantity that could move off treated areas [56]. Thus, likely exposure to organisms varies by use pattern and application method. Levels of concern, and or corresponding toxicity endpoints, are more stringent and therefore protective for threatened and endangered (i.e., listed) species, e.g., by 5-10 times over non-listed species for acute risk.

4.1. Aquatic Exposure Assessment and Risk Characterization

The EPA has several tiers of models of increasing complexity that may be used to estimate pesticide concentrations in receiving water environments. In the past, the Generic Estimated Environmental Concentration (GENEEC) model was commonly used as the Tier I surface water model [53]. GENEEC was designed to simulate a worse-case runoff scenario independent of geographical location, weather, crop, or application timing. Currently, the common practice is for the EPA to begin the aquatic exposure modeling with the more refined Tier II Pesticide in Water Calculator or PWC. The Tier II standard scenarios generate regional and crop-specific estimated exposure concentrations (i.e., EECs). The Tier I and II models conservatively assume that the receiving environment is a generic farm pond with no in- or out-flows located immediately adjacent to a treated field. As a result, the pesticide occurs at higher concentrations than in flowing waters of streams and rivers because the pesticide cannot leave the pond or be diluted by incoming water. The farm pond is also used as a surrogate for estuarine systems, a conservative assumption given that tidal flows dilute pesticide concentrations in estuaries as well as remove it to deeper waters.

Standard Pond. The standard farm pond scenario assumes that pesticide from an application to a 10-hectare field drains via runoff and erosion into a 1-hectare, 2-m deep farm pond, with spray drift from 1 hectare of the field also falling into the pond. Despite not matching receiving environments inhabited by many aquatic organisms (e.g., salmon in fast-flowing rivers), there are reasons why the farm pond scenario is conservative and thus appropriate as a generic receiving environment in a screening-level assessment.

- The edge of the farm pond is assumed to immediately abut the edge of the field where the pesticide is applied. For most fields, there is a buffer or natural area between the field and nearby water bodies that would reduce or eliminate pesticide transport via runoff or spray drift. The USDA provides a thorough summary of the impact of buffer strips on reducing runoff levels [51, 36, 44, 46].
- With the standard pond scenario, the EPA assumes that the runoff water or sediment carrying the pesticide does not have an associated volume which would be an addition to the receiving pond. As a result, pesticide concentration in the pond is overestimated because the dilution associated with addition of runoff water is not accounted for in the exposure model.
- Wind is assumed to always be blowing in the direction of the farm pond, again an unrealistic assumption given that wind direction is variable and that, at any given time, it is

Table 2: Levels of concern in EPA screening-level ecological risk assessment for pesticides.

Receptor	Exposure Duration	Risk Quotient[a]	Level of Concern
Birds, Mammals, Herptiles	Acute, non-listed	EEC/(LC50 or LD50)	0.5
	Acute, listed[b]	EEC/(LC50 or LD50)	0.1
	Chronic (listed and non-listed)	EEC/NOEL	1
Insect Pollinators	Acute (listed and non-listed)	EEC/LD50	0.4
	Chronic (listed and non-listed)	EEC/NOEL	1
Soil Invertebrates	Acute, non-listed	EEC/LC50	0.5
	Acute, listed	EEC/LC50	0.05
	Chronic (listed and non-listed)	EEC/NOEC	1
Other Non-Target Terrestrial Invertebrates	Acute, non-listed	EEC/LR50	0.5
	Acute, listed	EEC/LR50	0.05
	Chronic (listed and non-listed)	EEC/NOER	1
Terrestrial Plants	Acute, non-listed	EEC/ER25	1
	Acute, listed	EEC/ER05 or NOER	1
Fish and Aquatic-Phase Amphibians	Acute, non-listed	EEC/(LC50 or EC50)	0.5
	Acute, listed	EEC/(LC50 or EC50)	0.05
	Chronic (listed and non-listed)	EEC/NOEC	1
Aquatic Invertebrates	Acute, non-listed	EEC/(LC50 or EC50)	0.5
	Acute, listed	EEC/(LC50 or EC50)	0.05
	Chronic (listed and non-listed)	EEC/NOEC	1
Aquatic Plants and Algae	Acute, non-listed	EEC/EC50	1
	Acute, listed	EEC/(EC05 or NOEC)	1

[a] EEC=Estimated Environmental Concentration, LC50/LD50=Lethal Concentration or Dose for 50% of exposed organisms, NOEL/NOEC/NOER=No Observed Effect Level, Concentration or Rate, ER25=Effective Rate affecting 25% of test plants, EC05/50=Effective Concentration affecting of 5/50% of test organisms.
[b] Listed species are threatened and endangered species in the United States as defined under the Endangered Species Act.

less likely for a water body to be downwind of a treated field than it is to be parallel to or upwind of the treated field. Many pesticide labels specify that applications should not be made if the wind is blowing towards a sensitive area such as a wetland or salmon-bearing stream. Wind breaks are also often present, which mitigate the amount of spray drift reaching water bodies.

- Spray drift and runoff are assumed to arrive at the pond at the same time. This scenario is improbable given that farmers are unlikely to apply pesticides during or shortly before significant rainfall events. Thus, runoff typically reaches the pond well after spray drift.

Water Quality Models. Currently, the EPA uses the Pesticide in Water Calculator for Tier II estimations of pesticide concentrations in surface waters. The PWC expands upon the Tier I GENEEC by including other receiving environments such as a reservoir or custom-designed water body that may be more or less vulnerable than the standard pond scenario. The PWC allows for refined habitat characteristics, as well as habitat-specific weather and soil data for locations considered vulnerable to runoff and erosion.

For the receiving water body, the user may select the standard pond, reservoir, or enter data for a custom water body. The latter is not typically done in a screening-level FIFRA assessment but may be done for more refined, habitat- or species-specific assessments. For a custom water body, the user can select a pond with constant volume with or without flow through or a pond of varying volume and varying flow through. The user can also define the fraction of the watershed that potentially receives the pesticide (i.e., percent cropped area). Outputs from the PWC are upper bound concentrations in surface water ranging in duration from daily to yearly. Simulations are generally based on 30 or more years of climatic data. The PWC also calculates the total fraction of pesticide moving from the field, with detailed calculations of runoff, erosion, and drift fractions.

For pesticides that have been previously registered, surface water monitoring data may be available. Typically, the EPA screens monitoring data to determine if modeled predictions are sufficiently conservative, for example, if monitoring concentrations are below modeled predictions. No comprehensive evaluation of monitoring data is done except in higher-tier assessments. Even in higher-tier assessments, depending on the nature of the monitoring program, the EPA generally relies on modeling rather than monitoring data because the latter may or may not capture peak exposure concentrations due to insufficient sampling of high-use areas at times when pesticides are being applied. Statistical methods are being developed to address the uncertainty in estimating pesticide concentrations from monitoring data [74]. Intensive targeted monitoring studies are also being conducted for some pesticides, such as atrazine, that provide adequate statistical power and sampling frequency to address the aforementioned issues [62]. These methods and studies are expected to reduce the uncertainty in estimating upper bound pesticide concentrations from monitoring data.

The Tier II aquatic exposure modeling upon which the EPA typically bases its risk decisions for potential impacts of a pesticide to aquatic receptors is deliberately biased conservative and thus overestimates exposure and risk. In addition to the conservative assumptions noted above for the standard pond scenario, the Tier II exposure models also have the following conservative assumptions:

- The EPA assumes the maximum application rate and number of applications, and minimum re-treatment interval for each use pattern modelled. However, typical use may involve lower application rates and fewer applications [54]. Maximum application rates are often only required for severe pest infestations, whereas lower rates may be sufficient for moderate infestations.

- The standard receiving environment scenarios represent a small fraction of the total area in which any given crop is grown. For a large portion of the crop area, the vulnerability to off-site movement is greatly overstated by the scenario used for evaluation.

- Many parameters in the Tier II standard scenarios are selected to be deliberately conservative, e.g., soils that are vulnerable to erosion, steep slopes. Each parameter is selected to individually represent a 90th percentile vulnerability for that parameter. Collectively, however, combining these parameter values creates a vulnerability scenario much higher than the 90th percentile. PWC scenarios contain numerous conservatively estimated input parameters.

- The current standard scenarios for crops do not include plant uptake as a potential source of pesticide removal from the treated field [55]. For many pesticides, this conservative assumption results in more pesticide being available as runoff from a field than would be expected under real world conditions.

- For foliar applications, foliar wash off from plant leaves is set to 50 percent, which for many products is quite high [54].

- Model inputs derived from laboratory studies are conservative estimates of actual pesticide behavior. For example, the soil adsorption/desorption study is typically run with four soils. For modeling, the lowest or lower end of the measured adsorption coefficient (Kd or Koc) values is used. The intent is to generate a realistic, yet conservative, water column exposure value. The aerobic aquatic half-life is generated from a laboratory environment and is typically shorter in natural pond water. If multiple half-life values are available for aerobic soil or aerobic aquatic metabolism, the EPA assumes the 90th percentile confidence bound on the mean half-life value [54]. If only a single metabolism half-life value is available, the EPA uses three times the half-life value [54].

- Before estimating a "90th percentile" peak daily

> concentration, the EPA determines the highest daily pesticide concentration (or longer-term concentrations for non-acute exposures) for each year in a 30-year period. The EPA then calculates the 90th percentile from the 30 annual peak values (i.e., the 3rd highest value). Therefore, for a 30-year period, the EPA's "90th percentile" is a concentration that would only be exceeded on three days in 30 years that is, a 1-in-10-year event). On a daily basis, this estimate would actually be a 99.97th percentile. In other words, the concentration estimated by the EPA would be lower for 99.97 percent of days, assuming the other components of the modeling were not conservatively biased (which they were not).

The EPA has acknowledged that its modeling procedures are highly conservative and produce overestimates of actual environmental concentrations. For example, the EPA has stated that their models predict environmental concentrations that "are higher than most, if not all, analogous concentrations in the environment resulting from labeled uses" [5]. This is an appropriate approach because pesticides found to be "safe" using a deliberately conservative modeling approach are even more likely to be "safe" in real world environments. As an illustrative example, we compared available monitoring data and the results of aquatic exposure modeling conducted by the EPA for atrazine. Since 2004, the EPA has required the conduct of an extensive monitoring program known as the Atrazine Ecological Effects Monitoring Program (AEEMP) in corn- and sorghum-growing areas and, for a time, in sugarcane-growing areas [62]. The program targeted the most vulnerable watersheds in areas of high atrazine use. The study has monitored more than 70 watersheds since 2004 and currently monitors nine watersheds representing the upper 97th percentile of vulnerability to runoff (the original watershed selection was based on the upper 80th percentile of vulnerability) as predicted by the EPA's watershed regressions model for pesticides (WARP). The AEEMP database contains samples from daily or near-daily sampling efforts between 2004 and 2019. In their assessment, the EPA used their Surface Water Concentration Calculator (SWCC) model to predict atrazine concentrations for a variety of regions and use patterns [62]. According to the EPA, the SWCC model scenarios were intended to be conservative and represent the 90th percentile most vulnerable sites for first-order streams and static water bodies adjacent to atrazine-use areas [62]. However, the SWCC over-predicted the 1-in-10-year peak daily and 60-day average concentrations from all available monitoring data at the time of the assessment (2005-2015) by as much as 260-fold. In considering the most vulnerable watershed sampled in the AEEMP, the SWCC over-predicted 1-in-10-year peak daily and 60-day average concentrations by 12-fold.

4.2. Terrestrial Exposure and Risk Characterization

Wildlife. The Terrestrial Residue Exposure model (T-REX) was developed by the EPA and is their standard model for estimating acute and chronic dietary risks of pesticides to birds and mammals [56]. T-REX estimates risk to granivores, herbivores, and invertivores for flowable, granular, and seed treatment pesticides. The model does not estimate risks to top predators because modern pesticides are not bioaccumulative nor can the model be used for rodenticides. T-REX has a daily time step and can calculate dissipation of a pesticide applied to foliar surfaces for single or multiple applications. For multiple applications during the year, a peak cumulative maximum application rate can be determined. Initial residue levels on wildlife dietary items are estimated using an approach described in Hoerger and Kenaga [29] as modified by Fletcher et al. [25] multiplied by the peak application rate. Both upper and mean residue values are calculated by T-REX for each dietary item.

The T-REX model estimates risk for various size classes and diets of hypothetical birds and mammals [56]. Exposure is estimated for small, medium, and large organisms (20-, 100- or 1000-g birds; 15-, 35- or 1000-g mammals) and compared to sensitive acute and chronic toxicity endpoints.

The T-REX has many conservative assumptions including:

- The model assumes that the diet consumed by wildlife species is exclusively from the treated field. This can result in a significant overestimate of exposure as wildlife species are more likely to move on and off a field to forage [35].
- T-REX assumes that exposed animals consume only one dietary item. This may result in over-estimated risk if the dietary item has high pesticide residue values (e.g., short grass) relative to dietary items that mammals and birds are more likely to consume (e.g., seeds, insects).
- Upper bound residues are assumed for treated dietary items such as broadleaf forage, short and long grass, seeds, fruits, and insects in assessments for aerial and ground spray pesticides. Based on the results of field studies, upper bound residues for different dietary items represent 95th to 99th percentile estimates [56]. As a result, estimates of total daily intake are highly conservative. For pesticide use patterns with potential risks identified using upper bound residues, the EPA will also estimate risk assuming mean residues for dietary items.
- For seed treatment pesticides, the EPA assumes that bird and mammal species forage exclusively in treated fields, the entire diet is comprised of treated crop seeds, and the concentration and availability of the pesticide is constant through time. In the case of granular pesticides, the EPA assumes that every pesticide granule on the soil surface is consumed by birds and mammals, a highly unlikely assumption given that birds are far more likely to consume natural grit to aid digestion and mammals do not consume grit to aid digestion [34]. These assumptions, and others, lead to overestimates of risk for seed treatment and granular pesticides.
- T-REX requires toxicity data for bird and mammal

species such as rat, mouse, bobwhite quail, mallard, canary, and zebra finch to evaluate risk. The toxicity endpoints include mortality in acute studies and various growth and reproduction endpoints in chronic studies. The EPA uses the most sensitive available acute and chronic toxicity endpoints from studies of acceptable quality in their wildlife assessments. T-REX estimates both dose-based and concentration-based acute and chronic risk of pesticides applied as aerial or ground sprays. The toxicity endpoints used to estimate acute, dose-based risk are from oral gavage studies. The uptake and absorption kinetics of a gavage toxicity study differ from the kinetics associated with uptake from a dietary matrix [20]. Absorption kinetics across the gut and enzymatic activation/deactivation of a pesticide may be important and are likely variable across chemicals and species. For many pesticides, a gavage dose represents a very short-term, high-intensity exposure, whereas dietary exposure is generally of a more prolonged nature. With short-term, high-intensity exposure, there is no opportunity for the organism to metabolize the pesticide. Lower-intensity consumption throughout the day is more representative of how birds and mammals forage in agroecosystems [35]. As a result of relying on oral gavage studies in their assessments, the EPA overestimates risk to wildlife except for pesticides that may be consumed in large doses over a short period of time, such as rodenticides used as baits, some seed treatments, and granulars.

- To be conservative, the T-REX model does not consider the fact that many bird and mammal species dehusk seeds, that is, remove the outer hulls, prior to consuming the kernel inside. For example, when a finch, cardinal or grosbeak extracts a sunflower seed from a flower, it maneuvers the seed lengthwise into its beak, and cracks the seed open [77]. The bird's tongue then extracts the kernel inside. Chickadees and other species that lack a heavy-duty beak may chip the hull open by hammering seeds on branches or other hard surfaces. They then discard the outer hull and consume the kernel inside. When seeds are treated with a pesticide, most of the product remains on the outer hull, not in the kernel. For birds and mammals that consume seeds that are typically dehusked first (e.g., sunflower, rice, millet, sorghum), exposure is considerably reduced compared to ingesting entire seeds [15, 39] as is conservatively assumed in the T-REX model. However, not all seeds are dehusked prior to consumption (e.g., corn) and some wildlife species do not dehusk [15], hence the decision to be conservative by the EPA. Avery et al. [3, 4] observed reductions in exposure to imidacloprid, a common seed treatment insecticide, of 34-85 percent across a variety of passerine bird species (e.g., house finch, red-winged blackbird, mourning dove) from dehusking of seeds.

For terrestrial-phase amphibians and reptiles (herptiles), the EPA uses an analogous model known as T-HERPS [56]. Like T-REX, T-HERPS conservatively assumes that terrestrial-phase herptiles forage exclusively on treated areas immediately after application. For most pesticides, toxicity data are not available for herptiles and, out of necessity, the EPA relies on bird toxicity endpoints as a surrogate. This is a major source of uncertainty as there is little scientific support for this surrogacy assumption [37].

Invertebrate Pollinators. Bee-REX is a screening-level model used to estimate exposure concentration (EECs) for individual bees from foliar, soil, seed treatment, and tree-trunk injection applications of pesticides for dietary and contact routes of exposure [72]. Bee-REX is a Tier I model that estimates pesticide exposures based on honeybee castes assuming upper bound, conservative consumption rates. For example, larval food consumption rates are based on 5-day old larvae, which have the highest food consumption rates compared to other life stages.

The model uses the upper bound residue for tall grass from T-REX (v.1.5) to estimate dietary concentrations in pollen and nectar following foliar applications, and uses the Briggs' Model to estimate pollen and nectar concentrations following soil treatments and subsequent systemic translocation through plants [12, 13]. If measured data are available for pollen and nectar in bee-attractive crops, they may be used in place of the tall grass residues. Contact exposures due to direct spray are based on upper bound exposure values published by Koch and Weisser in 1997 [30]. Bee-REX allows for dietary and contact exposure values to be adjusted for different consumption rates of honeybee castes as well as pesticide application rates.

Bee-REX requires the input of acute contact, oral and larval LD50s (doses causing 50 percent mortality), as well as chronic adult and larval oral no observed effect levels for calculation of risk. Modeled exposure outputs are divided by toxicity endpoints to calculate risk quotients (RQs). Bee-REX was specifically developed to ensure that use of default values would provide exposure estimates one to two orders of magnitude higher than expected in nature because of the following conservative assumptions:

- Bee-REX assumes the highest food consumption rates for each bee caste, that is, 5-day old larvae and nectar-foraging adults. These conservative assumptions overestimate exposure for bees. In 2020, Rodney and Purdy [41] and Rodney and Kramer [40] demonstrated that the median food consumption rate for nectar-foraging adults is 6-fold lower than the value assumed in BeeREX.

- When no pesticide-specific data are available, Bee-REX assumes that dietary residues in pollen and nectar from foliar applications are equivalent to those found on tall grass. These residues are 45 and 2.2 times higher than the 95th percentile of the maximum residues measured in the field for nectar and pollen, respectively [71].

- Data for contact exposure are from Koch and Weisser [30]. These data represent mean measured residues on

honeybees from one contact study and two crops, apple and Phacelia, a genus of herbaceous plants in the Borage family. Only the maximum measured value is incorporated into Bee-REX.

- Bee-REX assumes that all pesticides applied by soil drench, seed treatment or trunk injection are systemically transported through plants. However, many pesticides are not transported systemically and therefore would have much lower residue concentrations in pollen and nectar compared to systemic pesticides.

Terrestrial Plants. For terrestrial plants, the TerrPlant screening-level model is generally used by the EPA to estimate exposure and risk [56]. The model assumes fixed percentages of drift and pesticide runoff. Runoff estimates are based solely on the maximum single application rate, chemical solubility in water, and conservative assumptions regarding drainage and receiving areas, rather than considering chemical-specific environmental fate characteristics. Therefore, few refinements within the model are possible. With respect to effects, the most sensitive endpoint for the most sensitive plant species is typically used in screening-level assessments, regardless of the actual flora in near-field areas where the product may be used. This assumes, for example, that an entire stream-side riparian zone is comprised solely of plants with sensitivity equivalent to the most sensitive tested species. The approach also assumes that off-field plant exposure is analogous to the exposure test plants receive in greenhouse toxicity studies, drenching directly under a boom, which is not the case (see below). Moreover, unlike acute toxicity endpoints for animals, plant endpoints are typically based on inhibition of growth rather than mortality. Plants can often recover from drift-level exposures to certain herbicides. Other conservative assumptions in TerrPlant include (modified from [49, 50]):

- Runoff occurs at the time of application, an unlikely event given that farmers/applicators generally avoid applying pesticides on rainy days.
- Spray drift is assumed to be in the direction of non-target plants, including wetlands for semi-aquatic areas. The labels for many herbicides include language directing farmers/applicators not to apply the product when wind is blowing in the direction of sensitive aquatic areas.
- Both runoff and spray drift are distributed uniformly throughout the non-target area. However, there is typically a decrease in runoff and spray drift concentrations with increasing distance from the application area.
- Plants exposed to pesticide residues in the non-target area are in the early emergent stages typical of Tier II plant toxicity tests.
- Estimated transport off the field only considers solubility of the pesticide. Other environmental fate parameters, such as the water and soil half-lives and adsorption coefficient (Kd) of the pesticide, which affect the amount of the pesticide that binds to soil and sediment and pesticide movement within these matrices are not considered. These parameters may considerably reduce the amount of pesticide that leaves the field in runoff.

Several of the above conservative assumptions do not apply to aquatic exposure modeling. For example, aquatic exposure models do not assume that runoff and spray drift occur simultaneously but rather use actual climatic data to simulate varied timing of runoff over a period of 30 years. Although not in current use for ecological risk assessments under FIFRA, the EPA has developed the Plant Assessment Tool [68] to better align aquatic and terrestrial plant exposure models as to pesticide fate and transport.

Spray Drift. As noted above, the EPA often assesses the drift contribution in screening-level assessments by assuming default percentages of application. In cases where in-field buffers (i.e., no spray areas) may be required to protect downwind non-target receptors, which is commonly the case with herbicides, the EPA will conduct spray drift modeling [56]. Typically, the most sensitive endpoints from the vegetative vigor studies (OCSPP 850.4150) are combined with predictions from a conservative spray drift model (Tier I AgDRIFT, for example) to estimate a no-spray buffer distance. This approach assumes that non-target off-field plants experience exposure analogous to in-field target weeds, that is, an overhead spray application that provides even saturation coverage of the foliage [9, 10]. However, non-target plants do not receive even herbicide coverage on the foliage because spray drift is more likely to contact the upwind (via lateral interception) and top (via deposition) portions of the foliage. In addition, numerous properties of the downwind plant community such as plant density and height, drag characteristics of the foliage, plant architecture, and collection efficiency influence exposure of non-target plants to herbicide drift [32].

The models typically used by the EPA to estimate exposure of non-target plants to spray drift with distance from treated areas are highly conservative. For ground spray applications, the Tier I AgDRIFT model is used [48]. This model is based on empirical data collected in the early 1990s using application nozzles and equipment now considered outdated. Several field studies have demonstrated that the combination of using conservative spray drift modeling and sensitive toxicity endpoints from Tier II vegetative vigor studies produces buffer distances that far exceed what is required to protect downwind non-target plant communities [9, 10].

A recent assessment by the EPA for atrazine illustrates this point. Because TerrPlant produced exposure estimates that exceeded sensitive toxicity endpoints for terrestrial plants for a variety of atrazine uses, the EPA conducted spray drift modeling with Tier 1 AgDrift, version 2.1.1, to determine the distance at which effects to non-target plants are no longer of concern [62]. The single maximum label rate for atrazine on corn is 2 lbs active ingredient per acre (a.i./A) or 1.78 kg active ingredient per hectare (a.i./ha). According to the model, drift to non-

target plants following ground application at this rate resulted in greater than 50 percent of species being impacted within 100 feet (30.5 m) to 400 feet (122 m) of the treated area, irrespective of droplet size. Even with coarser droplet sizes and a low boom height, risk extended beyond 300 feet (91.4 m) to 600 feet (183 m) for the most sensitive tested monocot and dicot species. These modeling results imply that a buffer of 600 feet (183 m) or more is required to protect downwind non-target plants with low boom ground applications and, at minimum, a coarse droplet size. A field study conducted in 2019 [9] illustrated the conservativeness of the EPA's approach to determining a safe buffer for atrazine, which is also the standard approach used for many herbicides. That study conducted a field-scale, spray drift study with atrazine that simultaneously determined deposition and effects on two sensitive plant species (cucumber and lettuce). Applications of AAtrex 4L (atrazine) were made at the maximum rate for corn of 2 lbs a.i./A (1.78 kg a.i./ha) using an ultra-coarse droplet size under worst-case drift conditions of bare soil and high wind speeds. Prior to application, seedlings of the two sensitive plant species (cucumber and lettuce) were placed at distances of 5, 15, 25, 35, and 45 ft (1.52, 4.57, 7.62, 10.7 and 13.7 m) from the downwind edge of the spray swath; corresponding upwind control plants were included. Following drift exposure in the field, plants were placed in a greenhouse and evaluated commensurate with standard EPA guidance for vegetative vigor studies. The results indicated a lowest observable effect distance (LOED) of 5 ft (1.52 m) and a corresponding no effects distance (NOED) of 15 ft (4.57 m) [9], significantly less than the 600 feet (183 m) predicted by the EPA's modeling approach for low boom applications and a coarse droplet size. Even with the field study being conducted under worst-case drift conditions, the EPA's use of the Tier 1 AgDrift spray drift model and toxicity endpoints derived from unrealistic exposure scenarios produce highly conservative risk estimates for non-target plants.

4.3. Effects Assessment

The EPA reviews toxicity studies from registrants, which generally follow Good Laboratory Practices (GLP), and studies available from the peer-reviewed literature to determine those that are acceptable for use in risk assessment [23]. The EPA has developed detailed guidance for determining the acceptability of open literature studies for use in their ecological [58] and human health risk assessments [59]. The Agency relies on the most sensitive toxicity endpoints available for tested indicator species from each taxonomic group and exposure duration. The use of Levels of Concern (Table 2) incorporates an additional safety factor to the toxicity portion of the risk assessment. The magnitude of conservatism associated with use of most sensitive available toxicity endpoints can be large. Consider the case of methyl parathion, an organophosphorus pesticide. Methyl parathion toxicity to aquatic invertebrates spans more than five orders of magnitude with acute toxicity values ranging from 0.14 µg a.i./L for daphnids (*Daphnia magna*) to 66,500 µg a.i./L for the midge (*Chironomus tentans*) (Figure 4). As discussed below, community-level protection of aquatic invertebrates could likely be achieved with a much less sensitive toxicity endpoint than the *D. magna* acute toxicity value used in the EPA's most recent assessment for methyl parathion [57].

Most toxicity endpoints used in the EPA's pesticide assessments are from laboratory toxicity tests conducted with single species. Such laboratory studies are required to follow strict regulatory guidelines, and are performed under controlled conditions. However, laboratory conditions are not reflective of the real world. Higher tier studies (microcosms, mesocosms, and field studies) are specifically designed to simulate exposure conditions more representative of natural, real-world environments, and consider species interactions, species recovery, and other ecological factors. Although a laboratory-based toxicity endpoint can consider a broad range of organisms (e.g., all tested fish species) with a species sensitivity distribution [62, 75], it does not account for the more realistic environmental conditions that occur outside the laboratory, such as reduced fitness due to stress from laboratory confinement or indirect effects arising from changes in food, habitat availability, and interspecies interactions.

Adverse effects observed in laboratory studies with single species are not necessarily translated to the community level of organization because effects to one or a few sensitive species may be offset by increases in functionally similar but more tolerant species [43]. Thus, overall community structure and function are not necessarily affected by adverse effects to one or a few sensitive species. In short, the effects of a pesticide such as methyl parathion are not necessarily transmitted to higher levels of organization. This statement is one of the foundations of hierarchy theory as proposed by Allen and Starr in 1982 [1]. There are many examples of aquatic invertebrate communities exhibiting functional redundancy or compensation [6, 45]. At some level, all species are unique, but overlap in resource use is common in food webs [21]. There are often multiple species present for each of the major functional roles of aquatic invertebrates in freshwater ecosystems, such as leaf shredders, suspension feeders, scrapers, detritivores, and others, for example, that are critical to overall production, nutrient cycling, decomposition, and energy flow [18]. In highly-stressed aquatic ecosystems like those with low richness and functional redundancy, the loss of a taxon is likely to have a greater impact on community functioning than in less-stressed systems [47]. Thus, there are limits to the role that functional redundancy plays in preserving community structure and function, so that there may not be functional replacement species for keystone or dominant species. Functional redundancy likely partially explains why the overall aquatic invertebrate community is more resilient to imidacloprid exposure in mesocosm studies than predicted by laboratory studies on single species (Figure 5) [42, 75].

5. Decision Making

The risk assessments and the benefits analysis conducted by the EPA are used to evaluate which, if any, proposed use patterns will be registered for new pesticides or re-registered for existing pesticides. The risk assessments are also used to

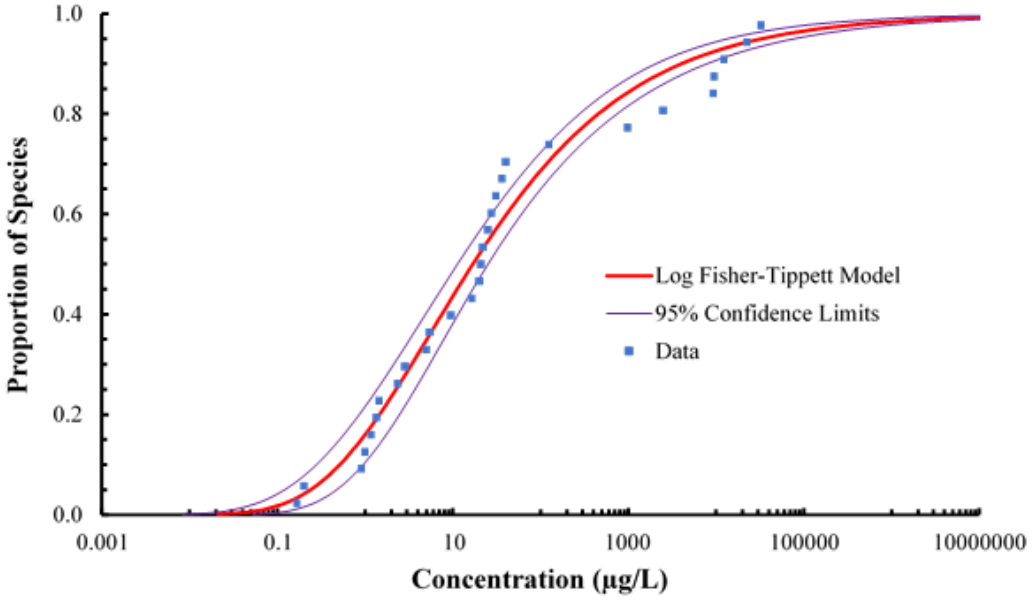

Figure 4: Acute species sensitivity distribution (SSD) for aquatic invertebrate species exposed to methyl parathion. Each datapoint represents an LC50 or EC50.

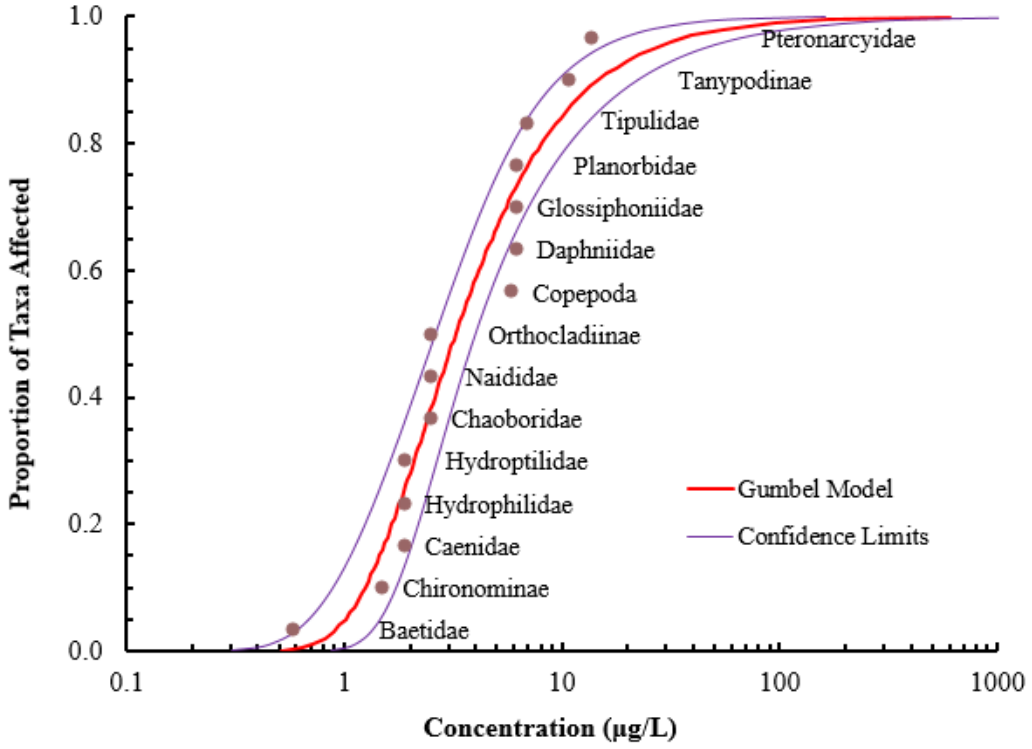

Figure 5: Chronic taxon sensitivity distribution (TSD) for imidacloprid with 95 percent confidence limits for family, subfamily and subclass level data extracted from cosm studies [75]. The most sensitive chronic NOEC from a laboratory study (0.041 μg a.i./L for the mayfly, *Cleon dipterum*; [42]) is an order of magnitude more sensitive than the most sensitive NOEC from the cosm studies.

determine maximum application rates and number of applications, minimum re-treatment interval, tolerances, worker safety standards and many other requirements that will be part of the pesticide label. In addition, the risk assessments are used to develop mitigations and label language to ensure that risk to the environment is acceptable. Common mitigations include use of

mandatory in-field buffers, buffers to protect sensitive areas and wetlands, maximum and minimum wind speeds during which applications may be made, required spray drift reducing measures, and many others.

The EPA follows a Label Review Manual that outlines the policies for approving labels of products containing pesticides [61]. The label specifies where, how, how much, and how often a pesticide can be used, and provides restrictions and precautions to ensure that proper application and disposal techniques are followed. Each label must state that federal law prohibits the use of the product in a manner not specified on the label. Additionally, FIFRA specifies that each product bear Environmental Hazard statements to describe the type of hazard that may be present and inform the user of actions to mitigate possible effects. The presence of a hazard statement does not indicate an unacceptable risk from product use. Rather, the hazard statements are added to labels to ensure applicators follow the label requirements.

6. Discussion

A strong, transparent, and highly conservative, science-based regulatory system currently exists in the United States and many other countries to ensure that pesticides meet rigorous safety standards for protection of the environment. That the pesticide industry is intensively and stringently regulated under FIFRA is widely misunderstood and underappreciated, despite the opportunities available for public participation and scrutiny of the registration process [7, 28].

Pesticides are often thought of as inherently harmful to the environment, in part due to their typically negative coverage in popular and sensationalist media, which typically fails to report on those pesticides that rarely, if ever, cause unintended effects to the environment, nor do they report on the many benefits that pesticides provide for producers, consumers, and, in some ways, the environment [8]. As Cooper and Dobson [17] stated in 2017:

"Part of the explanation for the scarcity of articles highlighting the benefits of pesticides may be that when a product does exactly what the manufacturer says it does, it is not newsworthy."

If pesticides were abolished, the lives lost due to poor diets would outnumber the lives saved by a factor of 1,000 [31]. In addition, far more marginal land that currently supports wildlife communities would be forced into agricultural production to make up for the harvest losses due to increased weed and insect pressures. The co-founder of Greenpeace, Dr. Patrick Moore, believes that if pesticides were eliminated from farming, lost productivity could only be replaced by clear-cutting the world's forests to have sufficient cropland to support the global population [14].

Prior to the development and introduction of modern synthetic pesticides, insects consumed or infested up to one-half of all U.S. crops [38]. A 2008 evaluation of the benefits of insecticides demonstrated that their use on crops allowed U.S. farmers to produce 144 billion additional pounds (65.3 billion additional kilograms) of food, feed, and fiber per year that otherwise would have been lost to insect consumption. As a result, U.S. farmers had an increased net income of almost $23 billion USD in 2008. Growers in California alone added $7.5 billion USD in 2008 to their incomes due to use of insecticides [27]. The benefits of pesticide usage are readily apparent in crop yields before and after the introduction of synthetic pesticides in the 1950s and 1960s (Figs. 1 and 2). Pesticides are mostly used to control disease vectors and agricultural pests, but there are many more benefits of using pesticides, such as reduced prices for consumers, control of invasive species, and reduced spoilage during storage [17]. Typically, a four-fold return is observed for every dollar invested in pest control in the United States [27, 38].

7. Conclusions

Balancing protection of the environment and human health while providing farmers with the tools they need to produce food and fiber is a difficult and complex task. Further, societal goals evolve over time and our scientific knowledge continues to improve. Consequently, the regulatory process for registering pesticides in the United States and elsewhere, including the assessment methods and decision-making processes are continuously evolving and improving. In recent years, for example, much progress has been made in developing approaches and methods for assessing risks of pesticides to bee pollinators as scientists tried to understand the causes of colony collapse disorder [72]. Similarly, tools are continuously being developed and improved to enable assessments of pesticide risks to threatened and endangered species in the United States [69]. Although the approaches and tools used by the EPA for assessing and managing risks of pesticides are imperfect and evolving, the EPA has and continues to consistently err on the side of protecting the environment in its pesticide registration process. This message may not sell newspapers, encourage "likes" on social media, or increase TV ratings, but headlines aside, pesticides are not causing the dire effects portrayed in the media. Rather, they are doing the job for which they were intended, including feeding a world with nearly eight billion people.

8. Declaration of Conflicting Interest

Four of the authors of this paper, Raghavendhran Avanasi, Wenlin Chen, Mark White and Richard A Brain, are employees of Syngenta Crop Protection LLC. No Syngenta pesticide products are promoted in this paper. Rather, the focus is on the pesticide registration process in the United States. No other conflicts of interest exist for the authors of this paper.

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12. References

[1] Allen, T. F. H., & Starr, T. B. (1982). *Hierarchy: Perspectives for Ecological Complexity*. The University of Chicago Press.

[2] AllGov. (2020). *National Marine Fisheries Service*. Retrieved June 25, 2020 from http://www.allgov.com/departments/department-of-commerce/national-marine-fisheries-service?agencyid=7135

[3] Avery, M. L., Decker, D. G., & Fischer, D. L. (1994). Cage and flight pen evaluation of avian repellency and hazard associated with imidacloprid-treated rice seed. *Crop Protection, 13*(7), 535-540. https://doi.org/10.1016/0261-2194(94)90107-4

[4] Avery, M. L., Fischer, D. L., & Primus, T. M. (1997). Assessing the hazard to granivorous birds feeding on chemically treated seeds. *Pesticide Science, 49*(4), 362-366. https://doi.org/10.1002/(SICI)1096-9063(199704)49:4%3C362::AID-PS540%3E3.0.CO;2-W

[5] Birchfield, N., *Washington Toxics Coalition, Northwest Coalition for Alternatives to Pesticides, Pacific Coast Federation of Fisherman's Associations, & Institute for Fisheries Resources (Plaintiffs) vs. Environmental Protection Agency & Christine T. Whitman (Defendants) vs. American Crop Protection Association et al. (Intervenor-Defendants)*. (2003). Case No. C01-0123C in the United States District Court for the Western District of Washington.

[6] Boersma, K. S., Bogan, M. T., Henrichs, B. A., & Lytle, D. A. (2014). Invertebrate assemblages of pools in arid-land streams have high functional redundancy and are resistant to severe drying. *Freshwater Biology, 59*(3), 491-501. https://doi.org/10.1111/fwb.12280

[7] Brain, R. A., & Anderson, J. C. (2019). The agro-enabled urban revolution, pesticides, politics, and popular culture: A case study of land use, birds, and insecticides in the USA. *Environmental Science and Pollution Research, 26*(21), 21717-21735. https://doi.org/10.1007/s11356-019-05305-9

[8] Brain, R. A., & Hanson, M. L. (2021). The press sells newspapers, we should not sell ecotoxicology. *Environmental Toxicology and Chemistry, 40*(5), 1239-1240. https://doi.org/10.1002/etc.5003

[9] Brain, R. A., Goodwin, G., Abi-Akar, F., Lee, B., Rodgers, C., Flatt, B., Lynn, A., Kruger, G., & Perkins, D. (2019). Winds of change, developing a non-target plant bioassay employing field-based pesticide drift exposure: A case study with atrazine. *Science of the Total Environment, 678*, 239-252. https://doi.org/10.1016/j.scitotenv.2019.04.411

[10] Brain, R. A., Perine, J., Cooke, C., Ellis, C. B., Harrington, P., Lane, A., Sullivan, C., & Ledson, M. (2017). Evaluating the effects of herbicide drift on non-target terrestrial plants: A case study with mesotrione. *Environmental Toxicology and Chemistry, 36*(9), 2465-2475. https://doi.org/10.1002/etc.3786

[11] Brain, R. A., Teed, R. S., Bang, J., Thorbek, P., Perine, J., Perangin-angin, N., Kim, M., Valenti, T., Chen, W., Breton, R. L., Rodney, S. I., & Moore, D. R. J. (2015). Risk assessment considerations with regard to the potential impacts of pesticides on endangered species. *Integrated Environment Assessment and Management, 11*(1), 102-117. https://doi.org/10.1002/ieam.1572

[12] Briggs, G. G., Bromilow, A. A., & Evans, R. H. (1982). Relationships between lipophilicity and root uptake and translocation of non-ionised chemicals by barley. *Pesticide Science, 13*(5), 495-504. https://doi.org/10.1002/ps.2780130506

[13] Briggs, G. G., Bromilow, A. A., Evans, R. H., & Williams, M. (1983). Relationships between lipophilicity and the distribution of non-ionised chemicals in barley shoots following uptake by the roots. *Pesticide Science, 14*(5), 492-500. https://doi.org/10.1002/ps.2780140506

[14] Browne, A. (2000). *'Judas' of the eco-warriors spreads his gospel of doubt*. Retrieved July 14, 2020 from https://www.theguardian.com/environment/2000/may/21/activists.uknews

[15] Brühl, C. A., Guckenmus, B., Ebeling, M., & Barfknecht, R. (2011). Exposure reduction of seed treatments through dehusking behaviour of the wood mouse (*Apodemus sylvaticus*). *Environmental Science and Pollution Research, 18*(1), 31-37. http://doi.org/10.1007/s11356-010-0351-x

[16] Carson, R. (1962). *Silent Spring*. Houghton Mifflin Company.

[17] Cooper J, & Dobson, H. (2007). The benefits of pesticides to mankind and the environment. *Crop Protection, 26*(9), 1337-1348. https://doi.org/10.1016/j.cropro.2007.03.022

[18] Covich, A. P., Palmer, M. A., & Crowl, T. A. (1999). The role of benthic invertebrate species in freshwater ecosystems. *BioScience, 49*(2), 119-127. http://doi.org/10.2307/1313537

[19] Damalas, C. A. (2009). Understanding benefits and risks of pesticide use. *Scientific Research and Essays, 4*(10), 945-949. https://doi.org/10.5897/SRE.9000968

[20] Ebert, E. (2004). *Glufosinate Ammonium - Active Substance. Consideration on Appropriate Acute and Chronic Endpoints for Assessment of Risk to Wild Mammals*. Bayer CropScience Inc., Research Triangle Park, NC. Bayer Report Code C045829.

[21] Ehrlich, P. R., & Walker, B. (1998). Rivets and redundancy. *BioScience, 48*(5), 387. http://doi.org/10.2307/1313377

[22] Federal Register. (1972). Environmental Protection Agency; Consolidated DDT Hearings; Opinion and Order of the Administrator. *Federal Register, 37*, 13369-13376.

[23] Federal Register. (2007). Pesticides; Data Requirements for Conventional Pesticides, Technical Amendments, and Data Requirements for Biochemical and Microbial Pesticides; Final Rules. *Federal Register, 72*, 60934-60988.

[24] Federal Register. (2020). *Agencies; Fish and Wildlife Service*. Retrieved June 25, 2020 from http://federalregister.gov/agencies/fish-and-wildlife-service.

[25] Fletcher, J. S., Nellessen, J. E., & Pfleeger, T. G. (1994). Literature review and evaluation of the EPA food-chain (Kenaga) nomogram, an instrument for estimating pesticide residues on plants. *Environmental Toxicology and Chemistry, 13*(9), 1383-1391. https://doi.org/10.1002/etc.5620130902

[26] Food Quality Protection Act. (1996). *Food Quality Protection Act of 1996*, Public Law 104-170.

[27] Gianessi, L. P. (2009). *Executive Summary of the Value of Insecticides in U.S. Crop Production*. CropLife Foundation, Washington, D.C.

[28] Gianessi, L. P. (2012). *The Worldwide Importance of Pesticides for Crop Production*. Presentation for CropLife Foundation, Washington, D.C.

[29] Hoerger, F., & Kenaga, E. E. (1972). Pesticide Residues on Plants: Correlation of Representative Data as a Basis for Estimation of Their Magnitude in the Environment. In F. Coulston, & F. Korte (Eds.), *Environmental Quality and Safety: Chemistry, Toxicology and Technology* (pp. 9-28). George Thieme Publishers.

[30] Koch, H., & Weisser, P. (1997). Exposure of honey bees during pesticide application under field conditions. *Apidologie, 28*(6), 439-447. https://doi.org/10.1051/apido:19970610

[31] Lomborg, B. (2001). *The Skeptical Environmentalist*. Cambridge University Press.

[32] Marrs, R. H., & Frost, A. J. (1997). A microcosm approach to the detection of the effects of herbicide spray drift in plant communities. *Journal of Environmental Management, 50*(4), 369-388. https://doi.org/10.1006/jema.1996.9984

[33] McDougall, P. (2016). *The Cost of New Agrochemical Product Discovery, Development, and Registration in 1995, 2000, 2005-8 and 2010-2014. R&D Expenditure in 2014 and Expectations for 2019*. Retrieved July 7, 2020 from https://croplife.org/wp-content/uploads/2016/04/Cost-of-CP-report-FINAL.pdf

[34] Moore, D. R. J., Fischer, D. L., Teed, R. S., & Rodney, S. I. (2010). A probabilistic risk assessment model for birds exposed to granular pesticides. *Integrated Environmental Assessment and Management, 6*(2), 260-272. https://doi.org/10.1897/IEAM_2009-021.1

[35] Moore, D. R. J., Teed, R. S., Greer, C. D., Solomon, K. R., & Giesy, J. P. (2014). Refined avian risk assessment for chlorpyrifos. *Reviews of Environmental Contamination and Toxicology, 231*, 163-217. http://doi.org/10.1007/978-3-319-03865-0_6

[36] Muñoz-Carpena, R., Ritter, A., & Fox, G. (2019). Comparison of empir-

ical and mechanistic equations for vegetative filter strip pesticide mitigation in long-term environmental exposure assessments. *Water Research, 165*(8). http://doi.org/10.1016/j.watres.2019.114983

[37] Ortiz-Santaliestra, M. E., Maia, J. P., Egea-Serrano, A., & Lopes, I. (2018). Validity of fish, birds and mammals as surrogates for amphibians and reptiles in pesticide toxicity assessment. *Ecotoxicology, 27*(7), 819-833. https://doi.org/10.1007/s10646-018-1911-y

[38] Pimentel, D. (1997). *Techniques for Reducing Pesticide Use: Economic and Environmental Benefits*. John Wiley and Sons.

[39] Prosser, P., & Hart, A. D. M. 2005. Assessing potential exposure of birds to pesticide-treated seeds. *Ecotoxicology, 14*(7), 679-691. https://doi.org/10.1007/s10646-005-0018-4

[40] Rodney, S., & Kramer, V. (2020) Probabilistic assessment of nectar requirements for nectar-foraging honey bees. *Apidologie, 51*(2), 180-200. http://doi.org/10.1007/s13592-019-00693-w

[41] Rodney, S., & Purdy, J. (2020). Dietary requirements of individual nectar foragers, and colony-level pollen and nectar consumption: A review to support pesticide exposure assessment for honey bees. *Apidologie, 51*(1), 163-179. http://doi.org/10.1007/s13592-019-00694-9

[42] Roessink, I., Merga, L. B., Zweer, H. J., & Van den Brink, P. J. (2013). The neonicotinoid imidacloprid shows high chronic toxicity to mayfly nymphs. *Environmental Toxicology and Chemistry*, 32(5), 1096-1100. https://doi.org/10.1002/etc.2201

[43] Rosenfeld, J. S. (2002). Functional redundancy in ecology and conservation. *Oikos, 98*(1), 156-162. https://doi.org/10.1034/j.1600-0706.2002.980116.x

[44] Sabbagh, G. J., Fox, G. A., Kamanzi, A., Roepke, B., & Tang, J. -Z. (2009). Effectiveness of vegetative filter strips in reducing pesticide loading: Quantifying pesticide trapping efficiency. *Journal of Environmental Quality, 38*(2), 762-771. https://doi.org/10.2134/jeq2008.0266

[45] Schriever, T. A., & Lytle, D. A. (2016). Convergent diversity and trait composition in temporary streams and ponds. *Ecosphere, 7*(5), 1-12. http://doi.org/10.1002/ecs2.1350

[46] Schulz, R. (2004). Field studies on exposure, effects, and risk mitigation of aquatic nonpoint-source insecticide pollution: A review. *Journal of Environmental Quality, 33*(2), 419-448. https://doi.org/10.2134/jeq2004.4190

[47] Suarez, M. L., Sanchez-Montoya, M. M., Gomez, R., Arce, M. I., del Campo, R., & Vidal-Abarca, M. R. (2016). Functional response of aquatic invertebrate communities along two natural stress gradients (water salinity and flow intermittence) in Mediterranean streams. *Aquatic Science, 79*(1). http://doi.org/10.1007/s00027-016-0475-2

[48] Teske, M. E., Bird, S. L., Esterly, D. M., Ray, S. L., & Perry, S.G. (2002). *A User's Guide for Agdrift® 2.0.05: A Tiered Approach for the Assessment of Spray Drift of Pesticides*. Regulatory Version. C.D.I. Report No. 01-02. Prepared for Spray Drift Task Force c/o Stewart Agricultural Services, Inc. Macon, MO.

[49] Trask, J. R., Williams, W. M., & Ritter, A. M. (2010). *Overview of USEPA-OPP's Terrestrial Risk Assessment Models*. Prepared by Waterborne Environmental, Inc., Leesburg, VA for CropLife America, Washington, D.C.

[50] Trask, J. R., Williams W. M., & Ritter, A. M. (2010). *Options for Refining the Exposure Component of USEPA-OPP's Terrestrial Risk Assessment Models*. Prepared by Waterborne Environmental, Inc., Leesburg, VA for Croplife America, Washington, D.C.

[51] United States Department of Agriculture. (2000). *Conservation Buffers to Reduce Pesticide Losses*. Natural Resources Conservation Service, U.S. Department of Agriculture, Washington, D.C.

[52] United States Department of Agriculture. (2020). *Agricultural Productivity in the U.S. Economic Research Service*. U.S. Department of Agriculture, Washington D.C. Retrieved from https://www.ers.usda.gov/data-products/agricultural-productivity-in-the-us/

[53] United States Environmental Protection Agency. (2000). *Generic Estimated Environmental Concentration Model – Tier I Screening Model for Pesticide Aquatic Ecological Exposure Assessment, Version 2.0*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 13, 2020 from http://www.epa.gov/oppefed1/models/water/index.htm

[54] United States Environmental Protection Agency. (2002). *Guidance for Selecting Input Parameters in Modeling the Environmental Fate and Transport of Pesticides*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved June 25, 2020 from http://www.epa.gov/oppefed1/models/water/input_guidance2_28_02.htm

[55] United States Environmental Protection Agency. (2003). *Pesticide Root Zone Model Field and Orchard Crop Scenario Metadata*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved June 25, 2020 from http://www.epa.gov/oppefed1/models/water/index.htm

[56] United States Environmental Protection Agency. (2004). *Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency: Endangered and Threatened Species Effects Determinations*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 13, 2020 from http://www.epa.gov/espp/consultation/ecorisk-overview.pdf

[57] United States Environmental Protection Agency. (2006). *Interim Reregistration Eligibility Decision for Methyl Parathion*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved June 15, 2020 from https://archive.epa.gov/pesticides/reregistration/web/pdf/methyl_parathion_red.pdf

[58] United States Environmental Protection Agency. (2011). *Evaluation Guidelines for Ecological Toxicity Data in the Open Literature*. U.S. Environmental Protection Agency, Washington, D.C. Retrieved June 15, 2020 from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/evaluation-guidelines-ecological-toxicity-data-open#guidance

[59] United States Environmental Protection Agency. (2012). *Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved June 15, 2020 from https://www.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf

[60] United States Environmental Protection Agency. (2015). *Compliance Monitoring Strategy for Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)*. Office of Enforcement and Compliance Assurance, U.S. Environmental Protection Agency, Washington D.C. Retrieved July 7, 2020 from https://www.epa.gov/sites/production/files/2015-09/documents/fifra-cms.pdf

[61] United States Environmental Protection Agency. (2016). *Label Review Manual*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 14, 2020 from https://www.epa.gov/pesticide-registration/label-review-manual

[62] United States Environmental Protection Agency. (2016). *Refined Ecological Risk Assessment for Atrazine*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington D.C.

[63] United States Environmental Protection Agency. (2017). *Pesticide Registration Manual*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 7, 2020 from https://www.epa.gov/pesticide-registration/pesticide-registration-manual

[64] United States Environmental Protection Agency. (2019). *Directive to Prioritize Effects to Reduce Animal Testing*. U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 7, 2020 from https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-231249.pdf

[65] United States Environmental Protection Agency. (2019). *Overview of Risk Assessment in the Pesticide Program*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 7, 2020 from https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/overview-risk-assessment-pesticide-program

[66] United States Environmental Protection Agency. (2020). *About Pesticide Registration*. U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 7, 2020 from https://www.epa.govpesticide-registration/about-pesticide-registration#:~:text=Federal%20Pesticide%20Laws,-We%20regulate%20pesticides&text=These%20laws%20have%20been%20amended,to%20be%20registered%20by%20EPA

[67] United States Environmental Protection Agency. (2020). *New Approach Methods Work Plan: Reducing Use of Animals in Chemical Testing*. U.S. Environmental Protection Agency, Washington, D.C. Retrieved July 7, 2020 from https://www.epa.gov/sites/production/files/2020-06/documents/epa_nam_work_plan.pdf

[68] United States Environmental Protection Agency. (2020). *Plant Assess-*

ment Tool (PAT) Version 1.0. User's Guide and Technical Manual for Estimating Pesticide Exposure to Terrestrial, Wetland, and Aquatic Plants in EPA's Listed Species Biological Evaluations. Office of Pesticide Products, U.S. Environmental Protection Agency, Washington, D.C.

[69] United States Environmental Protection Agency. (2020). *Revised Method for National Level Listed Species Biological Evaluations of Conventional Pesticides*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C.

[70] United States Environmental Protection Agency. (2020). *Summary of the Federal Insecticide, Fungicide, and Rodenticide Act*. U.S Environmental Protection Agency, Washington, D.C. Retrieved July 7, 2020 from https://www.epa.gov/laws-regulations/summary-federal-insecticide-fungicide-and-rodenticide-act#:~:text=FIFRA%20defines%20the%20term%20",from%20a%20use%20of%20a

[71] United States Environmental Protection Agency, PMRA, Cal DPR. (2012). *White Paper in Support of the Proposed Risk Assessment Process for Bees*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C.; Environmental Assessment Directorate, Pest Management Regulatory Agency, Health Canada, Ottawa, Canada; California Department of Pesticide Regulations, Sacramento, CA.

[72] United States Environmental Protection Agency, PMRA, CDPR. (2014). *Guidance for Assessing Pesticide Risks to Bees*. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C; Environmental Assessment Directorate, Pest Management Regulatory Agency, Health Canada, Ottawa, Canada; California Department of Pesticide Regulations, Sacramento, CA. Retrieved June 27, 2020 from https://www.epa.gov/pollinator-protection/pollinator-risk-assessment-guidance

[73] United States Fish and Wildlife Service. (1973). *Endangered Species Act of 1973; As Amended through the 108th Congress*. United States Fish and Wildlife Service, Washington, D.C.

[74] Vecchia, A. V. (2018). *Model Methodology for Estimating Pesticide Concentration Extremes Based on Sparse Monitoring Data*. National Water Quality Program, U.S. Geological Survey, Bismarck, ND. Scientific Investigations Report 2017–5159. https://doi.org/10.3133/sir20175159

[75] Whitfield-Aslund, M., Winchell, M., Bowers, L., McGee, S., Tang, J., Padilla, L., Greer, C., Knopper, L., & Moore, D. R. J. (2017). Ecological risk assessment for aquatic invertebrate communities exposed to imidacloprid as a result of labeled agricultural and non-agricultural uses in the United States. *Environmental Toxicology and Chemistry, 36*(5). 1375-1388. http://doi.org/10.1002/etc.3655

[76] Whitford, F., Pike, D., Johnson, B., & Blessing, A. (2008). *Pesticide Benefits Assessment: EPA Balances Risks and Benefits*. Purdue University, West Lafayette, IN. Retrieved July 7, 2020 from https://ppp.purdue.edu/wp-content/uploads/2016/08/PPP-78.pdf

[77] Willson, M.F. (1972). Seed size preference in finches. *The Wilson Bulletin, 84*, 449-455.