A Guide to Pesticide Registration

What is a Pesticide?

A pesticide is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. Pests can be insects, mice and other animals, **unwanted plants (weeds),** fungi, or microorganisms like bacteria and viruses. Though often misunderstood to refer only to insecticides, the term pesticide also applies to **herbicides, algaecides,** fungicides, and various other substances used to control pests. Pesticides are found in nearly every home, business, farm, school, hospital and park in the United States (U.S.).

Pesticide Registration and Use

In the U.S., pesticides require review and registration at two levels: federally through the Environmental Protection Agency (EPA) and at the state level (typically through the Department of Agriculture or a similar agency).

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires that the U.S. EPA register a pesticide product and its uses before it can be sold in the U.S. Before registering a new pesticide or new use for a registered pesticide, EPA must first ensure that the pesticide, when used according to label directions, **can be used with a reasonable certainty of no harm to human health and without posing unreasonable risks to the environment.** To make such determinations, EPA requires pesticide registrants to submit more than 100 different scientific studies and tests, which must be conducted according to EPA guidelines.

At a state level, designated state agencies conduct a review of the pesticide label to ensure that it complies with EPA labeling requirements and any additional state restrictions of use prior to registering the pesticide in that state.

Federal Pesticide Laws and Regulations

EPA regulates pesticides under broad authority granted in two major statutes, both of which were amended by the Food Quality Protection Act (FQPA) of 1996.

> **Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)** – requires all pesticides sold or distributed in the U.S. (including imported pesticides) to be registered by EPA. In addition, EPA can authorize limited use of unregistered pesticides or pesticides registered for other uses to address emergencies and special local needs.
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> **Federal Food, Drug and Cosmetic Act (FFDCA)** – requires EPA to set pesticide tolerances for all pesticides used in or on food. A tolerance is the maximum permissible level for pesticide residues allowed in or on commodities for human food and animal feed.

Under the Food Quality Protection Act of 1996, both FIFRA and FFDCA were amended to require that EPA must determine if a pesticide poses a ***"reasonable certainty of no harm"*** before that pesticide can be registered (or reregistered). The centerpiece of this requirement was the review and assessment of the tolerances (maximum

permitted residues) for all food-use pesticides. Several factors must be addressed before a tolerance can be established, including:

- **the aggregate, non-occupational exposure from the pesticide (exposure through diet, from using pesticides in and around the home, and from drinking water);**
- **the cumulative effects from exposure to different pesticides that produce similar effects in the human body;**
- **whether there is increased susceptibility to infants and children, or other sensitive subpopulations, from exposure to the pesticide; and**
- **whether the pesticide produces an effect in humans similar to an effect produced by a naturally-occurring estrogen or produces other endocrine-disruption effects.**

What is the Pesticide Registration Process?

U.S. EPA

The process of registering a pesticide is a **scientific, legal, and administrative procedure** through which EPA examines the ingredients of the pesticide; the particular site or crop on which it is to be used; the amount, frequency, and timing of its use; and storage and disposal practices. In evaluating a pesticide registration application, EPA assesses a wide variety of potential human health and environmental effects associated with use of the product. The producer of the pesticide must submit data from formal studies done according to EPA guidelines.

These tests evaluate whether a pesticide has the potential to cause adverse effects on humans, wildlife, fish, and plants, including endangered species and non-target organisms, as well as possible contamination of surface water or ground water from leaching, runoff, and spray drift. Potential human risks range from short-term toxicity to long-term effects, such as cancer and reproductive system disorders.

EPA compiles all the scientific data on the pesticide product into a comprehensive **health and environmental risk assessment** to determine the impact that the product or active ingredient will have on the human population and surrounding environment. The health and environmental risk assessment undergoes a process of peer review by scientific experts.

EPA reviews the risk assessment data and peer comments and makes a decision on pesticide registration. Answers to the key questions below must be **quantitatively and qualitatively confirmed;**

- **Does the proposed pesticide use meet EPA's standards for human health protection?**
- **Does the proposed pesticide use meet EPA's standard for worker protection?**
- **Does the proposed pesticide use meet EPA's standard for protecting the environment?**

EPA also must approve the language that appears on each pesticide label. Label instructions are written in such a way as to ensure the product does not cause adverse effects to humans or the environment if used properly.

If the application fails to meet these standards, EPA will request additional data, labeling modifications to mitigate risk concerns, changes to use restrictions or other information to address any deficiencies. Once approved, EPA establishes a tolerance if the pesticide is intended for use on food and publishes a notice in the Federal Register, the official publication of the Executive Branch.

State

After a pesticide is registered by EPA, registrants must register the federally approved label in those states where they intend to sell the product for use. While most states agree with the label language already approved by EPA, select states elect to conduct their own in depth review of the data, label and risk assessments. Individual states may have more stringent requirements for registering and applying pesticides than federal laws, but states cannot mandate what language appears on the label. If a registrant's data package and/or label do not meet an individual states' requirements for registration, the registrant can choose to conduct additional studies to meet these requirements or amend the product label so as to meet a state's registration requirements.

In 1972, the U.S. Congress authorized the states to register pesticides formulated for intrastate distribution to meet unregistered "special local needs" found in a given state. Applications for special local needs (i.e. 24 (c) registration) are submitted to state agencies by both registrants and users. After consultation with EPA, a state may register a pesticide for new uses or for uses which have been denied, disapproved, suspended, or cancelled by EPA.

EPA's 24(c) regulations define special local needs as: "An existing or imminent pest problem with a State for which the State lead agency, based upon satisfactory supporting information, has determined that an appropriate federally registered pesticide product is not sufficiently available."

Data Required for Registration of a Pesticide

The data requirements for registration are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and environmental fate of each pesticide. These data requirements provide the registrant with a formal list of the specific data required to evaluate a pesticide for a given use pattern (i.e., aquatic, nonfood; terrestrial, food crop). Additionally, the regulations provide the minimum framework of how studies must be conducted to determine these data. Minimum data requirements include:

- **Product Chemistry**
- **Residue Chemistry**
- **Environmental Fate**
- **Toxicology**
- **Reentry Protection and Spray Drift**
- **Wildlife and Aquatic Organisms**
- **Plant Protection**
- **Non-target Insect**

The generation of study data must also be conducted under Good Laboratory Practices (GLP). Under GLP regulations, EPA may refuse to accept (for purposes of supporting a FIFRA application or permit) any study that is not conducted in accordance with these standards. EPA requires any such application to be accompanied by a statement signed by the applicant, the sponsor and the study director indicating that the study was conducted in accordance with GLP or that describes in detail all deviations from the GLP standards. In addition to prescribing procedures for conducting studies, the GLP standards also set forth detailed requirements for storage and retention of records. All raw data, documentation , records, protocols and final reports, as well as all correspondence and other documents relating to the interpretation and evaluations of data, must be retained. EPA also requires the operator of a testing facility to permit audit inspections of the facility, its records, and all laboratory specimens at any reasonable time.

What about the inert ingredients?

Inert ingredients are substances intentionally added to enhance the effectiveness of a pesticide or its delivery to the target pest (e.g. carriers, solvents, surfactants, fillers). They include a wide variety of substances, ranging in complexity from clay and cellulose to highly sophisticated surfactants. During the pesticide registration process, manufacturers are required to disclose the contents of their product, including inert ingredients, to EPA. If the pesticide formulation is changed after the initial product registration, the new formulation (including inerts) must be approved by EPA prior to producing the new formula. Under federal law, as determined by the Food and Drug Administration (FDA), no substance can be included in a food use pesticide (even as an inert ingredient) unless a tolerance is established or an exemption from tolerance is granted. Thus, as part of EPA's review of a pesticide application, the active and inert ingredients are reviewed to determine if established tolerances are met or, in the case of a new chemical, what the tolerance should be.

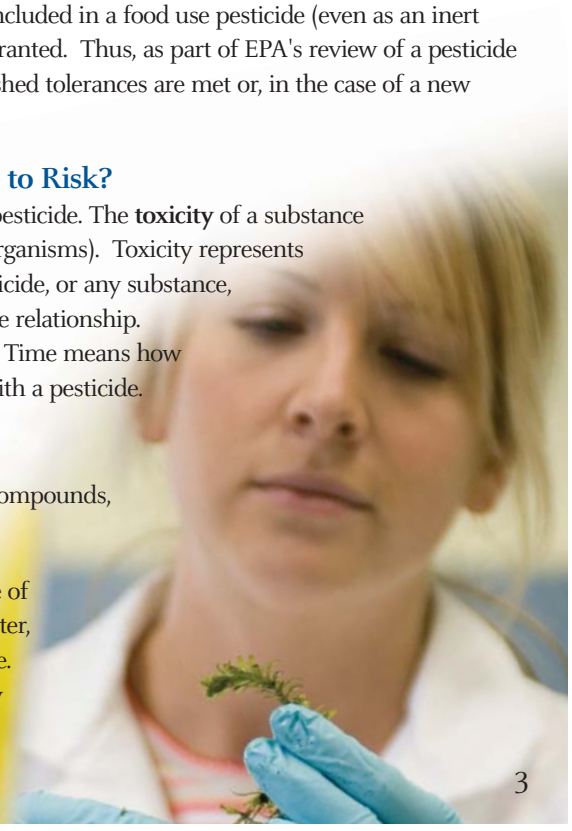
How Does Pesticide Toxicity and Dose-Time Relationship Relate to Risk?

Risk is the likelihood that adverse effect may occur as a result of exposure to a pesticide. The **toxicity** of a substance is its capacity to cause injury to a living system (i.e. human body, pond, forest, organisms). Toxicity represents the kind of damage that can be done by a chemical. The toxicity effect of a pesticide, or any substance, is dependent on a number of factors. The most important factor is the dose-time relationship. Dose is the quantity of a substance that a surface, plant or animal is exposed to. Time means how often the exposure occurs. Pesticide exposure is defined as coming in contact with a pesticide.

RISK = TOXICITY x EXPOSURE

While you cannot change the inherent toxicity of pesticides, or other chemical compounds, you can limit the possibility of harm or damage by limiting dose and exposure.

Hazard is the risk of danger. It is the chance that harm will come from the use of a pesticide to the applicator, bystanders, livestock, wildlife, crops, consumers, water, etc. Hazard is often confused with toxicity, but they are not necessarily the same. The hazard of a toxic chemical is always based on **two characteristics**; its **ability to harm** (i.e. toxicity, corrosiveness) and the **ease with which a person can come in contact with the chemical at a harmful or lethal dose.**



How does EPA Use Information on Toxicity and Health Effects of Pesticides?

EPA assesses risks associated with individual pesticide active ingredients, as well as with groups of pesticides that have a common toxic effect. This latter assessment is called a cumulative risk assessment and is designed to evaluate the risk associated with concurrent exposure to multiple pesticides that share a common mechanism of toxicity (i.e. act the same way in the body). Below are some common types of risk assessments:

Dietary	Occupational Exposure	Aggregate
Acute	Short term	Acute
Chronic	Intermediate	Short term
Carcinogenic	Chronic	Intermediate
	Carcinogenic	Chronic
		Carcinogenic

NOTE: Depending on use pattern and results of these studies, additional studies may be required by EPA.

What is a Human Health Risk Assessment?

A human health risk assessment evaluates the likelihood that adverse human health risk may occur as a result of exposure to a pesticide via direct contact or by ingestion of treated foods. Human risk assessments provide a risk estimate that generally includes a minimum of 100 fold safety factor to a No Observable Adverse Effect Level (NOAEL).

NOAEL refers to the exposure level at which there is no statistically or biologically significant increases in the frequency or severity of adverse effects. Some effects may be produced at this level, but they are not considered as adverse, or as precursors to adverse effects. ***Carcinogenicity assessments include a 1 million fold safety factor to a NOAEL.***

Human health risk assessments are developed by evaluating the following data:

- **Acute toxicity** – used to determine appropriate label precautions from a user standpoint
- **Subchronic toxicity** – used to determine intermediate toxicological exposure endpoints
- **Chronic toxicity** – used to determine long-term exposure endpoints
- **Oncogenicity** – used to determine potential carcinogenicity endpoints
- **Developmental toxicity** – used to determine potential embryo developmental effects
- **Gene mutation** – used to determine the potential for genetic abnormalities
- **Two generation reproduction study** – used to determine potential for reproductive effects

Example

Sonar* exposure via consumption (drinking, swimming)

In a 2004 EPA review of the safety information on Sonar, EPA calculated the Margin of Exposure (MOE) for Sonar for an acute and chronic exposure. MOE is a term used to compare body burden levels to where adverse effects occur. MOE of greater than 100 are not of concern to EPA. MOE's for Sonar were 7,500 to 187,500 including infants which are several magnitudes greater than the target 100 MOE.

Example

Human Risk Assessment for Renovate®

Children's bodies are still developing and they may be more susceptible to the action of a toxicant. Thus, EPA is required to assess each pesticide for its potential to cause toxicity specifically to infants and young children. EPA conducted this assessment for Renovate using animal tests and concluded "Reliable pre-and post-natal data indicate no special sensitivity of young animals to Renovate residues."

What is an Ecological Risk Assessment?

An ecological risk assessment evaluates the likelihood that adverse ecological effects may occur as a result of exposure to a pesticide. Ecological toxicity studies are conducted on avian, mammal and aquatic species.

There are two categories of data required:

- **Environmental Fate and Transport Studies** – used to determine what happens to a pesticides and its degradates once the product has been applied into the environment (i.e. lake, wetland, field, etc).
- **Ecological Toxicity Studies** – used to determine the toxicity of the pesticide and its degradates to the environment (i.e. fish, birds, mammals, non-target plant species)

Data generated must address these questions:

- **Where and how does the pesticide move in the environment?**
- **How long will it persist?**
- **What degradation products are produced and in what quantities?**
- **How much of the pesticide is likely to reach ground water and/or surface water?**

Examples of Environmental Fate Studies

Metabolism studies are used to determine the break down by-products from organisms metabolizing the parent pesticide product. There are four types of fate metabolism studies:

- Aerobic Soil Metabolism
- Anaerobic Soil Metabolism
- Anaerobic Aquatic Metabolism
- Aerobic Aquatic Metabolism

Mobility and Bioaccumulation studies evaluate how the pesticide and its degredates move and accumulate in the environment.

- Volatility – used to determine dissipation of the pesticide thru evaporation
- Dissipation studies – used to determine the extent of dissipation and mobility of pesticide residues under actual use conditions.

Aquatic Field Dissipation, Terrestrial Field Dissipation, Forest Field Dissipation

- Bioaccumulation in Aquatic Non-Target Organisms
- Leaching-Adsorption/Desorption
- Accumulation in Fish
- Dissipation of Active Ingredient and Related Metabolites

Examples

Field Evaluations of Renovate under Experimental Use Permits

After 28-days of exposure, crayfish and freshwater clams displayed no mortality in Lake Minnetonka when it was treated with Renovate to control Eurasian watermilfoil (Petty et al, 1998). It was also noted by Foster et al (1997) that indigenous populations of macro-invertebrates that were found in ponds located in California, Missouri and Texas were largely unaffected by the direct affects of Renovate at 2.5 ppm a.e.

The limited mobility of Renovate in soil, low absorption constant, and high rate of microbial and photolytic degradation in water and sediment would indicate this compound would have little potential for the extensive mobility required to contaminate groundwater supplies.

EPA Summary of Regulatory Position and Rationale: Risk/Benefit Review of Sonar

None of the risk criteria set forth in Title 40 Code of Federal Regulations 162.11 have been exceeded for Sonar. No groundwater contamination issue is associated with direct application to aquatic sites.

The Pesticide Label

Beyond the basic approval process for pesticides, which requires pesticides to meet standards for safety to humans and the environment, the degree of toxicity determines what precautionary language must appear on the pesticide label. Below are some of the many label elements that are determined by product toxicity:

- the use of protective clothing
- the "signal word" (Caution, Warning, Danger)
- the first aid statements
- the use of required personal protective equipment (PPE)
- whether the pesticide may be used only by specially trained and certified applicators
- re-entry and pre-harvest intervals

The pesticide **toxicity categories** are determined by the effects caused if the pesticide is consumed, inhaled, or placed in contact with the skin.

Example

Dermal, ingestion and ocular exposures of Renovate

Only dilute amounts of Renovate (< 2.5 ppm) are needed to kill E. watermilfoil and other target plant species. These dilute concentrations have not been shown to cause skin irritation or other health effects. Renovate is not well absorbed through skin. If ingested (via swimming, drinking water, or domestic use) research has shown that low doses of Renovate are rapidly excreted in humans and are unlikely to accumulate in human tissue or cause adverse effects. In addition, EPA includes precautionary language on the label regarding the required PPE to protect those handling and applying concentrated Renovate.


Specimen Label

Renovate 3

DANGER/PELIGRO

Unique Data Required in Registering an Aquatic Herbicide

- **Amount of Residue in:**
  - Potable Water
  - Fish
  - Irrigated Crops
- **Metabolism studies:**
  - Anaerobic aquatic
  - Aerobic aquatic
- **Dissipation studies in** water and aquatic sediments
- **Accumulation studies in** aquatic non-target organisms
- **Fish and Shellfish tolerances**

A) Tier I Aquatic Tests - Estuarine/Marine species

- **Short-term acute laboratory studies**
  - Estuarine/marine fish testing
  - Estuarine/marine invertebrate testing

B) Tier I Testing-Freshwater Species 6

- **Short-term laboratory studies**
  - Warm water acute toxicity testing
  - Coldwater acute toxicity testing
  - Freshwater invertebrate acute toxicity testing

C) Tier II Studies

- Sub-chronic Testing of Fish
- Full Life Cycle Invertebrate
- Multi-generation Test for Fish

D) Aquatic Plant Studies – algae and macrophytes

E) Terrestrial Plant Studies – seedling emergence and vegetative vigor

Currently, no herbicide product can be labeled for aquatic use if it has more than a one in one million chance of causing significant harmful effects to human health, wildlife, or the environment.

Example

Renovate is used at levels no greater than 2.5 ppm (maximum labeled rate) in lakes, ponds and reservoirs. These levels have been found to pose negligible risk to the environment and non-target species based upon testing conducted under EPA guidelines.

Toxicity to Fish and other Non-Target Organisms

Study	Organism	Results	Comments
	Freshwater Organism Studies[1]		
Fish 96 hour LC_{50}	Bluegill	891 mg/L	Low toxicity
Fish 96 hour LC_{50}	Rainbow Trout	552 mg/L	Low toxicity
Fish 96 hour LC_{50}	Fathead Minnow	44 mg/L	
Non-target Insect	Daphnia Magna	248 mg/L	No effect on number and size
	Avian Studies[2]		
Avian 8 day LC_{50}	Mallard Duck	>10,000 ppm	Practically non-toxic
Avian 8 day LC_{50}	Bobwhite Quail	2,935 ppm	Practically non-toxic
	Marine Organism Studies[1]		
Mullosk 96 hour EC_{50}	Eastern Oyster	58 mg/L	Slightly toxic
Vertebrate 96 hour LC_{50}	Tidewater Silverside	130 mg/L	Practically non-toxic
Invertebrate 96 hour LC_{50}	Grass Shrimp	326 mg/L	Practically non-toxic
Algae 120 hour EC_{50}	Skeletonema Costatum	11 mg/L	Slightly toxic

1 & 2 All studies shown conducted with triclopyr triethylamine salt. LC_{50}: concentration at which 50% of test organisms exhibit a lethal response. EC_{50}: concentration at which 50% of test organisms exhibit a lethal response

Registration Review

The Food Quality Protection Act of 1996 also mandated a new program, **registration review**. This new registration review program requires EPA to periodically reevaluate all registered pesticides. The reevaluation process is done to ensure that as changes in science, public policy, and pesticide use practices will occur over time, older registered pesticides are determined to still pose no reasonable risk to human health, workers or the environment when used according to the label. The registration review program challenges EPA to continuously improve its processes, science, and information management while maintaining a collaborative and open process for decision-making.

Example

In 2004, EPA conducted a Tolerance Reassessment (TRED) of Sonar and concluded that the toxicology studies previously conducted with Sonar meet today's standards and are therefore relevant in quantifying the potential risk to humans. EPA affirmed that the previous Sonar tolerances (including exposure through drinking water) were determined using sound scientific data and the approved Sonar label is relevant and requires no risk mitigation through labeling. In fact, the Agency developed the Sonar TRED through a modified streamlined version of its public process for making tolerance reassessment and reregistration eligibility decisions. " EPA can expeditiously reach decision for pesticides like Sonar, which poses no risk concerns, and require no risk mitigation." (Federal Register, Wednesday, September 29, 2004)

Reducing Pesticide Risk

By their nature as substances that in many cases are designed to kill pests, pesticides can pose risks to humans and to the environment. However, it is possible to reduce those risks in several ways. One way EPA reduces risk is by mitigating the label language by setting dose limits and requiring application techniques that minimize the exposure potential for humans and the environment. Others examples include:

Reduced Risk Pesticides

EPA gives priority to reduced risk-risk pesiticides in its registration program. Reduce risk criteria includes: *low-impact on human health, low toxicity to non-target organisms (birds, fish, and plants), low potential for groundwater contamination, lower use rates, low pest resistance potential, and compatibility with Integrated Pest Management.*

Example

In May 2007, Galleon SC (a.i. penoxsulam) received a reduced risk herbicide classification by U.S. EPA. In July 2007, Galleon SC received a full Section 3 registration for use in managing nuisance and invasive plants in and adjacent to aquatic sites.*

Biopesticides

Some pesticides are by their nature less risky. Many biological pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals pose a lower risk than synthetic pesticides. For example, canola oil and baking soda have pesticidal applications and are considered biopesticides. However, other plant-derived pesticides such as nicotine can be quite toxic.

Example

The fungal pathogen, Mycoleptodiscus terrestis (SP1020), is currently being evaluated in mesocosm and field studies as a potential bioherbicide for the management of hydrilla and other invasive aquatic weed species.

References

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