



The Insecticide Chlorpyrifos:

How Standards Are Set For the Protection of Human Health

Over the past half-century, people in developed nations have enjoyed a diverse supply of fresh, healthy, affordable food produced with the help of modern agricultural technology. Pesticides are an essential part of that technology, minimizing crop loss, damage from insects and plant diseases that can impair food quality.



Chlorpyrifos
protects

alfalfa
corn
cotton
peanuts
sorghum
sugarbeets
tobacco
wheat
citrus
pome fruits
stone fruits
tree nuts
onions
broccoli
cauliflower
cabbage
sweet potatoes

Introduction

Because treating crops with pesticides can leave residues on produce, regulators charged with protecting human health must approve them for sale and use. To approve use of a pesticide in the United States, the Environmental Protection Agency (EPA) must conclude that the uses described on the product label pose “a reasonable certainty of no harm.” This determination occurs only after years of testing and regulatory scrutiny. Similarly rigorous regulatory approval processes are followed in countries around the world, as well as global authorities such as the World Health Organization.

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In order to register a new pesticide in the United States, the review process typically requires manufactures to spend \$150 million to nearly \$200 million to gather data and evaluate potential effects on human health and the environment, according to CropLife America, an agricultural trade group. Such studies can take up to a decade to complete. Additionally, regulators in the U.S., Europe and elsewhere are required to publish their rationale for allowing specific



pesticide uses. Such authorizations are given only after opportunities have been provided for public comment and regulatory review.

In the United States, the EPA is charged with setting pesticide limits in order to protect public health. Before a pesticide may be sold or used, federal law requires that it receive an EPA registration defining conditions of its acceptable use. Use of the product in a manner inconsistent with the registration, as defined by the directions on the product label, is a violation of federal law and, in instances of serious misuse, is punishable by fines and imprisonment.

Consumers naturally want to know how their food is protected. This paper looks at the insecticide chlorpyrifos to illustrate how regulators conclude that labeled uses of a given pesticide offer “a reasonable certainty of no harm.”

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– CropLife America

What Is Chlorpyrifos?

The insecticide chlorpyrifos is one of the most widely used crop protection products in the world. It has been on the market for 40 years and is currently registered in more than 100 nations. Chlorpyrifos protects many fruit, nut, vegetable and grain crops from destructive pests.

Chlorpyrifos is registered for use in most developed nations, including Australia, Canada, France, Italy, Japan, New Zealand, Spain, the United Kingdom and the U.S. The product has been extensively researched, and its labeled uses are supported by more than 3,600 studies and reports.



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fruit tree
leafroller

How the EPA Sets Exposure Limits

Since any substance can cause harm given sufficient exposure, nothing can be called “safe” in absolute terms. A couple tablets of aspirin, for example, can relieve a headache. But an overdose of aspirin can be fatal.

In evaluating pesticides for registration the EPA does not ask whether a product is inherently “safe.” Rather, the EPA asks:

- What is the lowest dose that produces an effect of interest?
The lowest dose that produces an effect is called the *lowest observed effect level* (or *LOEL*).
- What is the next-lowest dose where that effect does not occur?
The next-lowest dose where that effect does not occur is called the *no observed effect level* (or *NOEL*).

To ensure that authorized uses are protective of women and children in addition to the population at large, the EPA includes a safety factor in dealing with pesticides which results in acceptable exposure typically being set somewhere between 100 to 1,000 times less than the *no observed effect level* (*NOEL*).

Example: Chlorpyrifos and Exposure Limits

The major health effects of overexposure to compounds such as chlorpyrifos occur because they inhibit enzymes in nerve cells known as cholinesterases, which are needed to properly control nerve impulses.

Cholinesterases may also be found in red blood cells and blood plasma. These cholinesterases are more sensitive to the effects of chlorpyrifos than cholinesterases in nerve cells, but when inhibited cause no adverse effect.

The EPA and other regulators around the world have concluded that these non-adverse effects on cholinesterases in red blood cells and blood plasma are the most sensitive biological indicator of exposure to chlorpyrifos. Therefore, regulators use levels of these enzymes to regulate exposure.

The EPA considers the lowest observed effect level (LOEL) for chlorpyrifos to be 1,000,000 nanograms per kilogram of body weight (1,000,000 ng/kgBW). This is the single dose needed to inhibit certain enzymes in the most sensitive animal tested. One nanogram weighs a billion times less than one gram.



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root aphids

- The EPA sets the *no observed effect level (NOEL)*, or dose at which this effect does not occur, at 500,000 ng/kgBW.
- In order to protect even potentially sensitive consumers such as women and children, the EPA limits single-dose exposure to chlorpyrifos at 500 ng/kgBW.
- For daily exposures, the EPA limits the exposure level still lower at 30 ng/kgBW.

By comparison, through biomonitoring, average daily exposure to chlorpyrifos for U.S. adults and children has been estimated to range from 3 – 24 ng/kgBW. (Barr et al., 2005; Morgan et al., 2005.)

What is a nanogram? A nanogram is equal to one billionth of a gram. While this is hard to imagine, 500 ng would be the equivalent of about one two-hundredth – and 30 ng would be about one three-thousandth – of a single grain of sand. A grain of sand weighs about 100,000 ng.

SAFETY FACTORS IN THE EPA'S EXPOSURE LIMITS TO CHLORPYRIFOS (nanograms per kilogram of body weight)

Non-Adverse Effect 1,000,000

No Effect 500,000

Maximum Exposure that the EPA Allows on a One-Time Basis from Labeled Use 500

Maximum Allowable Daily Exposure from Labeled Use 30

A grain of sand weighs about 100,000 nanograms.

From this it is clear that:

- Exposures to chlorpyrifos are very low.
- Average consumer exposures fall well within acceptable exposure as defined by regulatory limits.
- Regulatory limits restrict consumer exposures to levels 1,000 times less than those resulting in a non-adverse chemical change in a blood enzyme that is measurable in laboratory tests.

How Big Is The Safety Factor Built Into Allowable Pesticide Exposures?

Authorities in the U.S., European Union, Japan and other groups such as the World Health Organization are required to ensure that consumer exposures to pesticides are restricted to offer a reasonable certainty of no harm for women, children and the population at large. While the extent of the protection offered by these restrictions can be demonstrated scientifically and mathematically, for the general reader it may be difficult to visualize.

Here's one way to think about the safety factor built into pesticide restrictions such as those imposed by the EPA.

Imagine a measuring stick the size of the Eiffel Tower to measure exposure, using chlorpyrifos as an example:



cotton

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armyworm

- At the very top of the tower (320 meters high) would be the dose of chlorpyrifos needed to cause a non-adverse effect in an enzyme measurable in laboratory tests.
- Halfway down the tower (160 meters high) would be the level shown to have no effect.
- Only one centimeter from the base of the tower would be the EPA's maximum allowable daily exposure from labeled use.

From this illustration, it is clear that the margin of protection available for the EPA's registered uses of chlorpyrifos is very large.

These margins have been established by the EPA based on extensive research and testing and are intended to provide ample protection not only for the population at large but also for potentially sensitive subgroups such as women and children.



*nanograms per kilogram of body weight



Real-World Exposure vs. Laboratory Tests

One source of confusion for consumers is that news stories about studies on pesticides often suggest that exposures pose newly discovered risks.

However, these stories typically do not tell the reader:

- **The dose at which effects occurred;**
- **How the dose was administered;**
- **How the tested dose and method of exposure compare with real-world consumer exposures.**



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scale

Researchers evaluating chlorpyrifos exposure in laboratory tests sometimes claim that inhibition of nerve cell enzymes – as measured in blood plasma or red blood cells – may not be the appropriate biological effect for which to test.

Some suggest, for example, that chlorpyrifos affects the development of the nervous system or that it causes other biological effects. But research cited to advance this theory, to date, has relied on doses and methods of exposure that raise serious doubts about their applicability to the real world.

In a recent review of chlorpyrifos (Colborn, 2005), of the dozen or so studies cited involving live animals, all except one examined doses at or above those needed to inhibit or depress certain enzymes in blood or blood plasma.

- As previously noted, the dose needed to inhibit certain enzymes is 1,000,000 ng/kgBW. By contrast, the doses used in these studies exceeded the established lowest observed effect level. In some cases, the doses used were five times as high as the LOEL.
- The sole exception involved an experiment in which university researchers, using hyperdermic needles, injected a dose of chlorpyrifos directly into the brain cavities of newborn rats. The means of exposure in that study bears no relation to authorized use of the product.
- Additionally, in dosing the animals researchers often blended chlorpyrifos with another chemical, dimethylsulfoxide (DMSO), to speed up the body's absorption. This exaggerated the results of exposure levels that already were nearly high enough to kill test animals. However, no commercial chlorpyrifos products contain DMSO, so results gained from mixing the two have questionable real-world value. According to the EPA, an experiment using DMSO-laced injections of chlorpyrifos "makes quantitative interpretation and extrapolation of the results problematic." (EPA memorandum, "Toxicology Chapter for Chlorpyrifos," April 18, 2000.)

Not all Studies Are Useful for Setting Health-Protective Standards

It is no surprise that relatively high doses of chlorpyrifos delivered via extreme routes of exposure would result in toxic effects. Many exposures to everyday compounds that our bodies manage routinely would be toxic if administered at high doses or injected into sensitive tissue, bypassing the body's natural defense mechanisms.

But what do doses of this type and magnitude have to do with real-world exposures to labeled uses of pesticide products?

Real-world studies pay close attention to the dose at which effects occurred. They are benchmarked to determine the lowest dose that produces an effect (*the lowest observed effect level, or LOEL*), and the next-lowest dose where that effect does not occur (*the no observed effect level, or NOEL*).

Typically, however, studies suggesting new biological effects other than inhibition of enzymes as the best test for chlorpyrifos do not provide NOEL or LOEL guidelines. These studies typically involve:

Many exposures to everyday compounds that our bodies manage routinely would be toxic if administered at high doses or injected into sensitive tissue.

- **Relatively massive doses, without providing context of the lowest dose that produced an effect or the highest dosage that produced no effect.**
- **Extreme methods of exposure, such as injecting chlorpyrifos directly into the brain cavities of animals, or mixed with DMSO to heighten its absorption by the body.**
- **Little relation to real-world exposures.**



wheat

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grasshopper

Due to the inherent limitations of such studies, regulators charged with setting exposure limits have found research of this sort largely uninterpretable and not useful for determining permissible exposures for regulatory purposes.

Other scientists have expressed reservations about these studies as well. According to guidance offered by the Society of Toxicology, the independent professional association for practicing government, industry and academic toxicologists:

"The relevance of experiments using doses that are many multiples of conceivable human exposures and unrealistic routes of exposure is, at most, quite dubious. Mechanisms of action may be elicited under such conditions that would not occur with relevant routes and exposure levels To the extent that data based upon excessive doses are used for risk assessment, as has clearly happened in many cases, the predicted risks may have little or no relationship to risk in the real world. . . ."

"[U]se of routes of exposure and high-dose levels, set primarily for purposes of experimental convenience, should be avoided. . . ."

"[I]t would be a step forward if more investigators keep in mind that the doses/concentrations of chemicals they are employing in laboratory experiments should bear some relationship to levels expected to be encountered in the environment." (Connolly et al., 1999.)

Research of this sort will surely continue. In interpreting the results of such studies for themselves, consumers need to know the answers to the three questions noted previously:

- What is the dose?
- How was it administered?
- How does the tested dose and method of exposure relate to real-world exposure?

Conclusion

Because the boundaries of scientific knowledge are constantly expanding, the regulation of pesticides for the protection of public health is an ongoing process.

New studies on pesticides are published in scientific journals every month. And when studies appear, it is not uncommon for research proponents to report findings as novel and contrary to the body of scientific research previously conducted.

In order to make informed decisions about any product, conclusions drawn from any particular study must be tested for accuracy and validity.

In fact, however, reaching a scientific consensus about newly reported findings takes time. In order to make informed decisions about any product, conclusions drawn from any particular study must be tested for accuracy and validity, evaluated in terms of what is already known and then integrated into the total body of knowledge about the product.

While new studies can be expected to prompt questions, the following can be counted on to remain true in the midst of continual change:

- The safety margins built into the regulation of pesticides are extensive.
- Current restrictions have been established to provide “a reasonable certainty of no harm,” not only to the general population but also to infants and pregnant women and their fetuses.
- These restrictions are based on a comprehensive, transparent, and objective evaluation of extensive data.
- A well-defined regulatory process is already in place by which new scientific information is continuously taken into account.

It is hoped that this paper has helped shed light on how government regulators in various countries protect public health by establishing wide safety margins in exposure limits and demanding a rigorous, science-based rationale to support the labeled use of registered pesticide products.

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European corn borer

