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Backgrounder
Glyphosate and Standard Toxicology Studies
Updated November 2014

Toxicology is the study of the harmful effects of substances on living organisms: humans, plants and animals. Toxicological testing evaluates the biological response of living organisms to different routes and durations of exposure to a substance. Modern toxicology contributes to clinical, legal, occupational and veterinary medicine and plays a key role in the development of drugs, food additives, home products, cosmetics, industrial chemicals, agrochemicals, pesticides, etc. Paracelsus, a 16th Century Swiss physician recognized as the "father of toxicology," is noted for his principle that all substances are poisons if the dose is sufficiently high – "the dose makes the poison." He understood that the relationship between dose and response are inseparable. At very low doses, even notorious toxins such as arsenic will not cause harm. Conversely, at very high doses, essential substances such as water will harm or kill.

The story is no different for pesticides; at some dose they are harmful and at some dose they are harmless.

Pesticides (herbicides, insecticides, rodenticides, fungicides, etc.) cannot be categorized simply as "dangerous" just because they are classified as substances that kill pests. Likewise, no chemical, either natural (made by plants or other organisms) or synthetic (made by man), can be determined to be completely "safe." The study of toxicology determines what doses are harmful and what doses would not be expected to pose unreasonable risk. Pesticides are strictly regulated by governmental agencies around the world. In the United States, the U.S. Environmental Protection Agency (EPA) has that responsibility and requires a battery of toxicological and environmental studies. On average, a pesticide active ingredient must undergo at least 120 tests before it can be registered for use. During the many years that glyphosate and glyphosate herbicides have been used, hundreds of toxicology studies have been conducted.

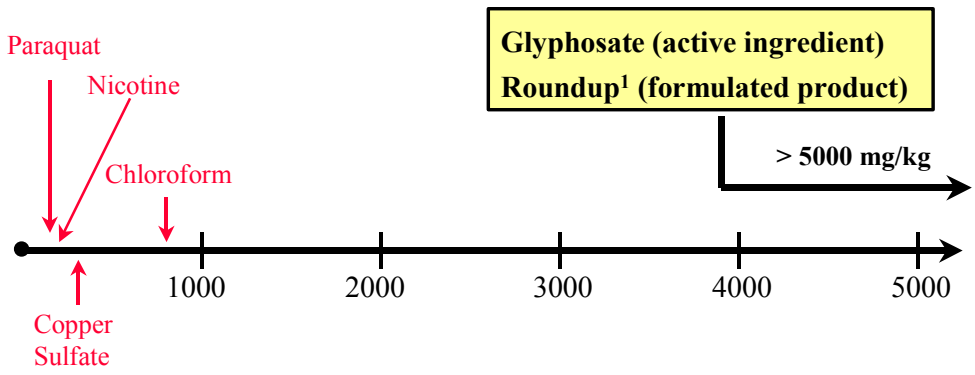
All pesticides are evaluated for acute, sub-chronic and chronic effects. Acute toxicological testing evaluates whether a single high-dose exposure to a substance will produce acute effects. (An acute effect could be anything from a skin rash to death.) Sub-chronic effects are related to several days or weeks of continuous exposure to a substance. Chronic effects occur after a long period (approaching a lifetime) of continuous exposure. Longer-term studies evaluate whether continual exposure to a substance has the potential to cause adverse effects, such as cancer, neurotoxicity, birth defects or reproductive problems.

Acute toxicity studies

Acute toxicity studies evaluate the risk from a single exposure to a substance, typically at a high dose. Acute oral and dermal toxicity studies are frequently designed to express the potency of a substance in terms of a median lethal dose or LD_{50}. The LD_{50} is the dose that is lethal to 50 percent of the laboratory animals in the test. The higher the LD_{50} value, the lower the toxicity.

The dose is calculated as milligrams of the test substance per kilogram of body weight of the tested animals (mg/kg bw).

Figure 1. Acute Toxicology- Comparative



Selected from NIOSH Registry of Toxic Effects of Chemical Substances, 1979
Handbook of Pesticide Toxicology, Second Edition – Agents
[1]"Roundup"refers to the original single active ingredient formulation.

Laboratory studies show that glyphosate has acute rat oral and dermal LD_{50s} of greater than 5,000 mg/kg. The major use of the LD_{50} study is a comparative one, allowing an investigator to assess the relative toxicity of one substance with others tested in the same species (Figure 1). Accepted toxicology standards classify substances with an LD_{50} greater than 5,000 mg/kg as "practically non-toxic." (Remember, nothing can be considered *completely* non-toxic, because as Paracelsus knew, everything is toxic at some dose.)

In addition to acute rat oral and dermal studies, inhalation exposure also is evaluated to determine a spray concentration that is lethal to 50 percent of the test animals (LC_{50}). The dose is measured in milligrams of the test substance per liter of water (mg/L). Acute rat inhalation studies with glyphosate show that a high concentration is required to produce lethality.

The U.S. EPA places pesticides in one of four categories for acute toxicity, based on their LD_{50} and LC_{50} values. Category I is considered the most toxic, and category IV the least toxic. Glyphosate is assigned a Category IV ("practically non-toxic") for all three routes of exposure – oral, dermal and inhalation. Eye and skin irritation studies also are required to assess the potential for a substance to cause irritation. Glyphosate is assigned a Category IV for skin irritation. However because the technical material is an acid it can be moderately to severely irritating to the eyes. Glyphosate formulations are made not with the acid but with a salt of the acid. These salt solutions are considered practically non-irritating to the eyes and are assigned a Category IV. One other acute test is used to evaluate the potential of a pesticide to produce an allergic skin reaction after repeated skin contact. Glyphosate shows no evidence of causing a skin reaction.

Not only do the pesticide active ingredients undergo this battery of testing, but so does each product formulation containing the active ingredient. Most formulated herbicides in which glyphosate is the active ingredient (e.g., Roundup PowerMAX® and Roundup ProMax®) are also in Category IV for acute oral, dermal and inhalation toxicity.

Subchronic and chronic toxicity studies

The acute toxicity studies determine what dose is lethal to 50 percent of the test animals via a specific route of exposure, but they do not determine what dose poses no unreasonable risk. That determination is made by examining effects seen over a range of doses and durations of time. Sub-chronic studies last for a few weeks to months (~10 percent of the normal life span of the test animal), and chronic studies can last for a year or more (the expected lifetime of the test animal). Exposure routes are identical to those of acute testing programs (oral, dermal, inhalation). In sub-chronic and chronic oral toxicity studies, groups of test animals are given various daily doses, from zero to thousands of milligrams per kilogram of their body weight. At the end of a designated exposure period, virtually every organ system and physiological parameter is examined to determine any differences between exposed and non-exposed test animals. High doses must elicit sub-lethal effects, middle doses must evoke only minimal adverse effects and low doses should trigger no toxic effects whatsoever. Generally, three to five dose levels are tested. The highest tested dose level that produces no observed adverse effects is referred to as the NOAEL. Different toxicity studies produce different no-effect levels. The U.S (EPA) bases its risk assessment on the lowest NOAEL recorded in the various studies. See the table below for a summary of NOAELs seen in various glyphosate toxicity studies submitted to the U.S. EPA.

Toxicity Study	**Glyphosate NOAEL (mg/kg/day)[1]**
Rat Subchronic	209
Rat Chronic	409
Rat Reproduction	694
Rabbit Developmental	175
U.S EPA - NOAEL	175

[1] Source: US EPA, 1993

Between the NOAEL and the highest dose tested, there is usually a range of doses that produce a range of effects. Some effects can be quite serious, such as tumors or birth defects; others are minor and would be reversible with cessation of exposure. Through all of these studies, even very high sub-lethal doses of glyphosate have not produced effects such as cancer, birth defects, mutagenicity, neurotoxicity or reproductive abnormalities. Other effects, such as weight loss, elevated enzyme levels, etc. have been detected in those studies, almost always at very high doses. For example, in the rabbit developmental study, designed to determine if glyphosate causes adverse effects in pregnant animals and their developing offspring, no developmental effects were seen even at the highest dose which produced toxicity to the pregnant animal. The NOAEL for this study was considered to be the 175 mg dose. It was the lowest NOAEL from various studies.

Reference dose (RfD) includes uncertainty factors to reduce risk

After a NOAEL is determined the U.S. EPA applies uncertainty factors to account for differences between humans and test animals and individual variability. The agency also considers the types of effects that were seen at higher doses. Less serious effects normally constitute a lower margin of exposure. The margin for glyphosate has been set at 100-fold, as opposed to some other pesticides which have margins of exposure of 1,000 or more because of less favorable toxicological results. ***A 100-fold uncertainty factor means that acceptable human exposure for glyphosate has been established at a level that is 100 times lower than a tested dose that caused no observable adverse effect in tested animals.*** For glyphosate, the acceptable daily dietary exposure, referred to as reference dose (RfD) has been set at 1.75 mg/kg/day (175 mg/kg/day NOAEL divided by 100 = 1.75 mg/kg/day).

In 1996, Congress unanimously passed landmark pesticide food safety legislation called the Food Quality Protection Act (FQPA). The FQPA mandated that allowable exposure levels more closely consider infants and children. The FQPA required the U.S. EPA to apply an additional 10-fold uncertainty factor to account for exposure to children, who have higher relative exposure because of their lower body weight. However, EPA was given the option of applying a lesser uncertainty factor "only if, on the basis of reliable data, such margin will be safe for infants and children" (FQPA, 1996). The additional uncertainty factor, when applied to the RfD, yields an exposure level called the chronic Population Adjusted Dose (cPAD).

EPA reviewed the toxicological database for glyphosate, determined that it was complete and concluded there was no indication of increased sensitivity to glyphosate among infants and children. Therefore, EPA used an FQPA uncertainty factor of 1, resulting in a cPAD for glyphosate of 1.75 mg/kg/day, the same as the RfD.

Calculating human exposure

In order to calculate human exposure to a pesticide, the U.S. EPA considers all possible routes, including food, water, applicator exposure, or bystander exposure from drift. Conservative assumptions are made throughout the process. Consider exposure through food, for example. EPA requires food residue studies for every crop on which a pesticide is to be used. For the study, the pesticide is applied at the maximum labeled rate. (Most farmers use rates much lower than the maximum allowed.) Crops are harvested and liquefied, and very sensitive equipment is used to seek traces of the pesticide. Multiple samples are taken from several test plots grown in various geographic regions. The sample with the highest amount of residue is recorded for the crop in question, even if some unusual condition may have been at play. If no residue is detected in any of the samples, EPA assumes a presence anyway. Based on these studies, EPA calculates how much residue could be present in crops treated with the pesticide. It is then assumed that every acre of every crop for which the pesticide is labeled receives an application of the pesticide (with no allowance for market share). Furthermore, EPA assumes that people consume every crop every day. (Glyphosate is labeled for use on more than 100 crops, so this is a very conservative assumption.) If adding up the residues from each crop yields a dose greater than the EPA's cPAD, the public is assumed to be at risk and some uses must be discontinued in order to reduce public exposure.

In May 2013, EPA established new tolerances for residues of glyphosate. At that time, the agency concluded that even children 1-2 years old, the population receiving the greatest exposure, were exposed to no more than 13 percent of the allowable intake through food (U.S. EPA 2013).

Wildlife toxicology

In addition to many studies with laboratory animals to assess potential effects from human exposure, glyphosate has also been studied to determine effects on wildlife. The same toxicological principles apply – varying doses are given to representative species of birds, fish, insects and other invertebrates. The lethal dose or concentration is determined, and effects seen at lower doses are examined. A no-effect level is also determined. These studies show that glyphosate has very low toxicity to wildlife and that expected exposure from approved uses of glyphosate products would pose no unreasonable risk to wildlife.

Related Document:

Backgrounder: Glyphosate and Wildlife. November, 2014.

References

FQPA (Food Quality Protection Act). (1996) Title IV, Section 408 (a)(4)(c). http://www.epa.gov/pesticides/regulating/laws/fqpa/fqpa_implementation.htm

U.S. EPA. (1993) Reregistration Eligibility Decision (RED): Glyphosate. EPA-738-F-93-011, September 1993. Environmental Protection Agency. Washington, DC. http://www.epa.gov/oppsrrd1/REDs/old_reds/glyphosate.pdf

U.S. EPA. (2013) Final Rule: Glyphosate; Pesticide Tolerance. Federal Register 78(84): 25396-25401. May 1.

http://www.gpo.gov/fdsys/pkg/FR-2013-05-01/pdf/2013-10316.pdf