A review of the risk assessment process for evaluating the potential of glyphosate to cause adverse effects on human health.

What is glyphosate?
Glyphosate is a common herbicide ("weed-killer") used in crop and non-crop lands, including residential areas such as home lawns and gardens. Glyphosate was first registered in the United States in 1974 as the active ingredient in Roundup but is now available in many commercial herbicide products. There is currently increased concern about glyphosate impacts on human health, including risks of cancer. This article reviews the risk assessment process for evaluating the potential of glyphosate to cause adverse effects on human health and aims to improve understanding of recent studies on its carcinogenicity.

Hazard vs. risk.
All chemicals, including herbicides, are potentially hazardous to human health. However, a basic principle of toxicology is that “the dose makes the poison”. Therefore, the risk of a hazardous effect to human health is a function of the toxicity of the chemical and the likelihood of exposure to a biologically relevant dose. A chemical can be toxic at very low doses (ex: dioxin) but present a low risk of hazardous effects if there is minimal likelihood of exposure to a biologically relevant dose.

Chemical properties.
The chemical properties of an herbicide are a primary determinant of toxicity and persistence in the environment. The glyphosate molecule (below) is unique among herbicides. Approximately 95% of registered herbicides are molecules made from aromatic ring structures. In comparison, glyphosate is a small molecule made of a linear carbon chain with weaker bonds, which makes glyphosate less persistent in the environment. In commercial products, glyphosate is formulated with salts to improve its water solubility and proprietary surfactants to improve plant uptake.

Glyphosate toxicity.
Acute toxicity describes the hazard associated with a single exposure to a chemical, such as dermal or oral exposure during the herbicide application process. Chronic toxicity describes the hazard associated with long term exposure to a chemical, such as repeated ingestion of low doses in food residues. Glyphosate has lower acute toxicity to humans than 94% of all herbicides and many common household chemicals, including vinegar and table salt. Glyphosate also has lower chronic toxicity to humans than 90% of all herbicides.
**Likelihood of exposure.**
Glyphosate use has increased dramatically in the past 20 years due to its frequent use in Roundup Ready crops (corn, soybean, cotton). Consequently, the likelihood of glyphosate exposure has increased for pesticide applicators. However, the EPA has concluded that there is low potential for the general public or non-applicators to be exposed to a recurring biologically relevant dose of glyphosate based on models of glyphosate persistence in the environment and dietary exposure.

**Glyphosate fate in environment.**
The chemical properties of glyphosate generally minimize off-target movement and promote dissipation in the environment.

Glyphosate is degraded in soil and water by microbes and binds tightly to soil particles, which prevents leaching of glyphosate into ground water. Glyphosate does not degrade quickly in plants. As a result, it is possible that glyphosate residues can occur in food products. However, glyphosate is generally not applied to crops that are produced for direct human consumption. The vast majority of glyphosate is applied to fallow fields or in crops that are used for animal feed (corn, soybean), energy (corn) or fiber (cotton) and is applied early in the growing season to young vegetative crops many weeks before plants produce grain or are harvested.

**Herbicide regulation.**
The herbicide registration process requires EPA review of over 120 studies that focus on herbicide toxicological properties, environmental fate and the potential for non-target effects. These studies are used to conduct formal risk assessments that quantify the likelihood of adverse effects to humans using toxicological data and models of exposure. The Food Quality Protection Act (FQPA, passed in 1996) requires a “reasonable certainty that no harm will result from aggregate exposure” to pesticides and establishes enforceable residue standards based on models of food consumption. The USDA Food and Drug Administration actively monitors the level of glyphosate on foods in the marketplace.
Cancer risks associated with glyphosate.

Several organizations have evaluated cancer risks associated with glyphosate in recent years. These assessments consider epidemiological, toxicology and genotoxicity studies. In 2015, the World Health Organization’s International Agency for Research on Cancer (IARC) concluded that “Glyphosate is probably carcinogenic to humans”. The IARC’s study aimed to identify hazards that can result in cancer outcomes but did not consider the risk of exposure to doses that are likely to occur in the environment. Put another way, the IARC asked “Can glyphosate cause cancer under any circumstance?” Based on this criteria, other probable human carcinogens included red meat, late-night work shifts and indoor emissions from burning wood. In 2016, the EPA evaluated the carcinogenic potential of glyphosate and concluded that glyphosate was “not likely to be carcinogenic to humans at doses relevant to human health risk assessments”. In contrast, the EPA assessment accounted for the likelihood of exposure in order to quantify carcinogenic risks. Based on review of epidemiological studies, the EPA found no evidence of association between glyphosate exposure and numerous cancer outcomes but indicated more data was needed to determine association between glyphosate exposure and Non-Hodgkin Lymphoma.


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Penn State College of Agricultural Sciences research and extension programs are funded in part by Pennsylvania counties, the Commonwealth of Pennsylvania, and the U.S. Department of Agriculture.

Where trade names appear, no discrimination is intended, and no endorsement by Penn State Extension is implied.

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Code: ART-5809