NATIONAL PESTICIDE INFORMATION CENTER

1.800.858.7378 npic@ace.orst.edu

We're open from 8:00AM to 12:00PM Pacific Time, Mon-Fri

Glyphosate

Technical Fact Sheet

As of 2011, NPIC stopped creating technical pesticide fact sheets. The old collection of technical fact sheets will remain available in this archive, but they may contain out-of-date material. NPIC no longer has the capacity to consistently update them. To visit our general fact sheets, click here. For up-to-date technical fact sheets, please visit the Environmental Protection Agency's webpage.

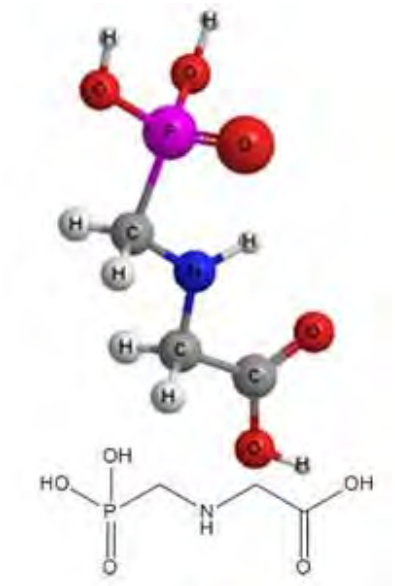
Ecotoxicity Studies
- Regulatory Guidelines

Chemical Class and Type:

Laboratory Testing: Before pesticides are registered by the U.S. EPA, they must undergo laboratory testing for short-term (acute) and long-term (chronic) health effects. Laboratory animals are purposely given high enough doses to cause toxic effects. These tests help scientists judge how these chemicals might affect humans, domestic animals, and wildlife in cases of overexposure.

- Glyphosate is a non-selective systemic herbicide that is applied directly to plant foliage.[1] When used in smaller quantities, glyphosate can act as a plant growth regulator.[2] Glyphosate is a glycine derivative.[1] The International Union of Pure and Applied Chemistry (IUPAC) name for glyphosate is N-(phosphonomethyl) glycine3 and the Chemical Abstracts Service (CAS) registry number is 1071-83-6.[1]
- Glyphosate's potential as an herbicide was reported in 1971.[1,4] Glyphosate was first registered for use by the United States Environmental Protection Agency (U.S. EPA) in 1974[5], and reregistration was completed in 1993.[6] See the text box on **Laboratory Testing**.
- Formulations of glyphosate include an acid, monoammonium salt, diammonium salt, isopropylamine salt, potassium salt, sodium salt, and trimethylsulfonium or trimesium salt.[1,2,4] Unless otherwise stated, all data in this fact sheet refer to the acid form.
- Technical grade glyphosate is used in formulated products, as are the isopropylamine, sodium, and monoammonium salts. Of these, the isopropylamine salt is most commonly used in formulated products.[2,7]

Molecular Structure - Glyphosate



Physical / Chemical Properties:

Glyphosate and associated forms

Active Ingredient	Form[1,4]	Vapor pressure[1,4,8]	Henry's constant[8]	Molecular weight[1,4,8]	Solubility in water (mg/L)[1,4]	Log K_{ow}[1,4,8]	K_{oc}[3]
Glyphosate acid	odorless, white solids	1.31×10^{-2} mPa (25 °C) 1.84×10^{-7} mmHg (45 °C)	4.08×10^{-19} atm·m^3/mol	169.07 g/mol	pH 1.9: 10,500 mg/L pH 7.0: 157,000 mg/L	Less than -3.2	300 - 20,100
Glyphosate isopropylamine salt	odorless, white solids	2.1×10^{-3} mPa (25 °C) 1.58×10^{-8} mmHg (25 °C)	6.27×10^{-27} atm·m^3/mol	228.19 g/mol	pH 4.06: 786,000 mg/L	-3.87 or -5.4	300 - 20,100
Glyphosate ammonium salt	odorless, white solids	9×10^{-3} mPa (25 °C) 6.75×10^{-8} mmHg (25 °C)	1.5×10^{-13} atm·m^3/mol	186.11 g/mol	pH 3.2: 144,000 mg/L	-3.7 or 5.32	300 - 20,100

Uses:

- Glyphosate is one of the most widely used herbicides with applications in agriculture, forestry, industrial weed control, lawn, garden, and aquatic environments.[1,6] Sites with the largest glyphosate use include soybeans, field corn, pasture and hay.[2,6]
- Some plants have been genetically engineered to be resistant to glyphosate. Glyphosate-tolerant soybeans, corn, cotton, and canola are examples of such plants.[4,9] This fact sheet does not address glyphosate-tolerant crops.
- Uses for individual products containing glyphosate vary widely. Always read and follow the label when applying pesticide products.
- Signal words for products containing glyphosate may range from Caution to Danger. The signal word reflects the combined toxicity of the active ingredient and other ingredients in the product. See the pesticide label on the product and refer to the NPIC fact sheets on **Signal Words** and **Inert or "Other" Ingredients**.
- To find a list of products containing glyphosate which are registered in your state, visit the website **http://npic.orst.edu/reg/state_agencies.html** and search by "active ingredient."

Mode of Action:

Target Organisms

- In plants, glyphosate disrupts the shikimic acid pathway through inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase. The resulting deficiency in EPSP production leads to reductions in aromatic amino acids that are vital for protein synthesis and plant growth.[1,4]
- Glyphosate is absorbed across the leaves and stems of plants and is translocated throughout the plant.[1,3] It concentrates in the meristem tissue.[10]
- Plants exposed to glyphosate display stunted growth, loss of green coloration, leaf wrinkling or malformation, and tissue death. Death of the plant may take from 4 to 20 days to occur.[4,10]
- The sodium salt of glyphosate can act as a plant growth regulator and accelerate fruit ripening.[2]

Non-target Organisms

- The shikimic acid pathway is specific to plants and some microorganisms. The absence of this pathway in mammals may explain the low toxicity of glyphosate to non-target organisms.[11,12]
- Studies indicate that the surfactant polyoxyethyleneamine or polyethoxylated tallow amine (both abbreviated POEA), used in some commercial glyphosate-based formulations, may be more toxic by the oral route to animals than glyphosate itself.[13,14]
- The mechanism of toxicity of glyphosate in mammals is unknown, but it may cause uncoupling of oxidative phosphorylation.[15] However, this hypothesis has been disputed.[16]

Acute Toxicity:

Oral

- Glyphosate is low in toxicity to rats when ingested. The acute oral LD_{50} in rats is greater than 4320 mg/kg.[17] See the text boxes on **Toxicity Classification** and **LD_{50}/LC_{50}**.
- The acute oral LD_{50} for rats was also reported to

be greater than 5000 mg/kg. The acute oral LD_{50} was greater than 10,000 mg/kg in mice and 3530 mg/kg in goats.[1]

- The isopropylamine salt is of very low toxicity to rats, with an LD_{50} greater than 5000 mg/kg.[1]
- The acute oral LD_{50} for the ammonium salt is 4613 mg/kg in rats.[1]
- The acute oral LD_{50} in three formulated products ranged from 3860 to greater than 5000 mg/kg in rats.[4]

LD_{50}/LC_{50}: A common measure of acute toxicity is the lethal dose (LD_{50}) or lethal concentration (LC_{50}) that causes death (resulting from a single or limited exposure) in 50 percent of the treated animals. LD_{50} is generally expressed as the dose in milligrams (mg) of chemical per kilogram (kg) of body weight. LC_{50} is often expressed as mg of chemical per volume (e.g., liter (L)) of medium (i.e., air or water) the organism is exposed to. Chemicals are considered highly toxic when the LD_{50}/LC_{50} is small and practically non-toxic when the value is large. However, the LD_{50}/LC_{50} does not reflect any effects from long-term exposure (i.e., cancer, birth defects or reproductive toxicity) that may occur at levels below those that cause death.

Dermal

- Glyphosate is low in toxicity to rabbits when applied to the skin. The acute dermal LD_{50} in rabbits is greater than 2 g/kg.[17]
- Glyphosate is low in toxicity for eye irritation and very low in toxicity for dermal irritation. In studies with glyphosate manufacturing use products, researchers observed mild eye irritation in rabbits that cleared in seven days.[18,19]
- Glyphosate was not found to be a skin sensitizer.[6]
- The isopropylamine and ammonium salts are also low in toxicity via the dermal route. The LD_{50} in rabbits was greater than 5000 mg/kg for both salts, and these salts are considered slight eye irritants but not skin irritants.[1]
- Of three formulated products tested, skin irritation varied from none to moderate, and eye irritation was rated as none, moderate, and severe. Dermal LD_{50} values in rabbits exposed to these products were greater than 5000 mg/kg.[4]
- The formulated product Roundup®, containing 41% glyphosate, was applied to the skin of 204 male and female volunteers in a modified Draize test. No sensitization was observed. The researchers concluded that exposure would not lead to photoirritation or photosensitization.[20]

Inhalation

- Glyphosate is very low in toxicity to rats when inhaled. The acute inhalation LC_{50} in rats is greater than 4.43 mg/L based on a 4-hour, nose-only inhalation study.[21]
- The 4-hour LC_{50} for rats exposed to the isopropylamine form of glyphosate was greater than 1.3 mg/L air.[1]
- The LC_{50} for rats exposed to the ammonium salt form of glyphosate was greater than 1.9 mg/L in a whole body exposure.[1]
- Inhalation LC_{50} values for two formulated products were greater than 1.3 mg/L and 3.2 mg/L in rats.[4]

TOXICITY CLASSIFICATION - GLYPHOSATE

	High Toxicity	Moderate Toxicity	Low Toxicity	Very Low Toxicity
Acute Oral LD_{50}	Up to and including 50 mg/kg (≤ 50 mg/kg)	Greater than 50 through 500 mg/kg (>50-500 mg/kg)	**Greater than 500 through 5000 mg/kg (>500-5000 mg/kg)**	**Greater than 5000 mg/kg (>5000 mg/kg)**
Inhalation LC_{50}	Up to and including 0.05 mg/L (≤0.05 mg/L)	Greater than 0.05 through 0.5 mg/L (>0.05-0.5 mg/L)	**Greater than 0.5 through 2.0 mg/L (>0.5-2.0 mg/L)**	**Greater than 2.0 mg/L (>2.0 mg/L)**

Dermal LD_{50}	Up to and including 200 mg/kg (≤200 mg/kg)	Greater than 200 through 2000 mg/kg (>200-2000 mg/kg)	**Greater than 2000 through 5000 mg/kg (>2000-5000 mg/kg)**	Greater than 5000 mg/kg (>5000 mg/kg)
Primary Eye Irritation	Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days	Corneal involvement or other eye irritation clearing in 8 - 21 days	**Corneal involvement or other eye irritation clearing in 7 days or less**	**Minimal effects clearing in less than 24 hours**
Primary Skin Irritation	Corrosive (tissue destruction into the dermis and/or scarring)	Severe irritation at 72 hours (severe erythema or edema)	Moderate irritation at 72 hours (moderate erythema)	**Mild or slight irritation at 72 hours (no irritation or erythema)**

The highlighted boxes reflect the values in the "Acute Toxicity" section of this fact sheet. Modeled after the U.S. Environmental Protection Agency, Office of Pesticide Programs, Label Review Manual, Chapter 7: Precautionary Labeling. http://www.epa.gov/oppfead1/labeling/lrm/chap-07.pdf

Signs of Toxicity - Animals

- Animals exposed to formulated glyphosate herbicides have displayed anorexia, lethargy, hypersalivation, vomiting, and diarrhea. Symptoms persisted for 2 to 24 hours following exposure. The surfactants in formulated products are thought to be responsible for the clinical signs.[22]
- Clinical signs typically appear within 30 minutes to 2 hours following ingestion. Animals may exhibit excitability and tachycardia at first, followed by ataxia, depression, and bradycardia. Severe cases may progress to collapse and convulsions.[15]
- The Veterinary Poisons Information Service in London, England recorded 150 cases over an 8-year period of dogs exposed to glyphosate primarily from eating grass recently treated with formulated products. Of these, roughly 40% of the dogs exhibited no clinical signs, 45% exhibited mild to moderate clinical signs, and roughly 15% were classified as serious.[15]
- The Centre National d'Informations Toxicologiques Veterinaires of France reported 31 certain cases of intoxication of domestic animals by glyposate-containing products in a 3-year period. Most exposures resulted from animals ingesting the product prior to application. Of these cases, 25 were dogs and 4 were cats. Vomiting occurred within 1-2 hours of ingestion in 61% of the cases. Hypersalivation occurred in 26% of cases, and mild diarrhea was reported in 16% of cases. Centre records did not report long-lasting effects or any fatalities.[23]

Signs of Toxicity - Humans

- In a review of 80 intentional ingestion cases, 79 of which were suicide attempts, researchers identified typical symptoms of erosion of the gastrointestinal tract, dysphagia or difficulty swallowing, and gastrointestinal hemorrhage. Seven cases resulted in death.[24] Accidental ingestions are associated with mild gastrointestinal effects.[14]
- Eye and skin irritation have occasionally been reported from dermal exposure to glyphosate formulations.[13,14] However, adverse health effects are typically associated with exposure that occurs while mixing a concentrated product, not the use of dilute spray solutions.[13] Permanent ocular or dermal damage is very rare.[13,14,25]
- Inhalation of spray mist may cause oral or nasal discomfort, as well as tingling and throat irritation.[14]
- Always **follow label instructions** and take steps to **minimize exposure**. If any exposure occurs, be sure to follow the First Aid instructions on the product label carefully. For additional treatment advice, contact the Poison Control Center at 1-800- 222-1222. If you wish to **discuss an incident** with the National Pesticide Information Center, please call 1-800-858-7378.

Chronic Toxicity:

Animals

- Researchers gave beagle dogs capsules containing 0, 20,100, or 500 mg/kg/day of glyphosate for one year. No effects were observed; the NOEL for systemic toxicity is greater than or equal to 500 mg/kg/day.[26] See the text box on **NOAEL, NOEL, LOAEL, and LOEL**.
- Male rats were fed a diet containing glyphosate at 89, 362, or 940 mg/kg/day and females were similarly fed at concentrations of 113, 457, or 1183 mg/kg/day for 2 years. In the high-dose female group, researchers observed decreased body weight gain. In the high-dose male group, researchers observed decreased urinary pH, increased evidence of cataracts and lens abnormalities, and increased liver weight. No effects were observed in the low-dose and mid-dose groups. The LOEL for systemic toxicity was 940 and 1183 mg/kg/day for males and females, respectively. The NOEL for systemic toxicity is 362 mg/kg/day for males and 457 mg/kg/day for females.[27]

NOAEL: No Observable Adverse Effect Level

NOEL: No Observed Effect Level

LOAEL: Lowest Observable Adverse Effect Level

LOEL: Lowest Observed Effect Level

- Laboratory rats were fed diets containing glyphosate at doses of 0, 100, 300, or 1000 mg/kg/day for two years. After 52 weeks, some rats in the two highest dose groups had enlarged salivary glands with cellular changes. The NOEL was determined to be 100 mg/kg/day.[28]
- The Acceptable Daily Intake (ADI) of a combination of glyphosate and certain metabolites (AMPA, N-acetyl glyphosate, and N-acetyl AMPA) for humans is 1.0 mg/kg. In 2011, the International Estimated Daily Intake (IEDI) of glyphosate and major metabolites was estimated to range from 0-2% of the ADI.[29,30]
- The chronic reference dose for glyphosate is 1.75 mg/kg/day.[31] See the text box on **Reference Dose (RfD)**.

Humans

- Researchers collected urine samples over 8 months from workers at two forestry nurseries where glyphosate was used for weed control. No glyphosate was detected in any of the 355 urine samples. The researchers attributed the lack of detected glyphosate in worker urine samples to the poor absorption of glyphosate through the skin.[32] See the text box on **Exposure**.

Exposure: Effects of glyphosate on human health and the environment depend on how much glyphosate is present and the length and frequency of exposure. Effects also depend on the health of a person and/or certain environmental factors.

- Five forestry workers sprayed glyphosate for 6 hours a day over the course of a week. No statistically significant differences were found in medical examinations and laboratory testing performed on the workers following pesticide application.[33]
- Researchers collected urine samples from farm families in South Carolina and Minnesota as part of the Farm Family Exposure Study. On the day of application, 60% of farmers had a detectable level of glyphosate in their urine of at least 1 ppb. The geometric mean of glyphosate detected was 3 ppb, with a maximum value of 233 ppb. Mean urinary concentrations of glyphosate were higher in farmers who did not use rubber gloves during application.[34]

Endocrine Disruption:

Rats and mice were fed a diet containing 0, 3125, 6250, 12,500, 25,000, or 50,000 ppm of 99% pure glyphosate for 13 weeks. The two highest dose groups of male rats had a significant reduction in sperm concentrations, although concentrations were still within the historical range for that rat strain. The highest dose group of female rats had a slightly longer estrus cycle than the control group.[35]

- Researchers reviewed the scientific literature on glyphosate, its major metabolite AMPA, formulated Roundup® products manufactured by Monsanto, and the surfactant POEA. They found no evidence of endocrine effects in humans or other mammals.[13]
- Glyphosate is included in the draft list of initial chemicals for screening under the U.S. EPA Endocrine Disruptor Screening Program (EDSP). The draft list of chemicals was generated based on exposure potential, not based on whether the pesticide is a known or likely potential cause of endocrine effects.[36]

Carcinogenicity:

Animals

- Researchers fed rats a diet containing glyphosate at 0, 89, 362, or 940 mg/kg/day (males) and 0, 113, 457, or 1183 mg/kg/day (females) for two years. The low-dose and high-dose male groups had a slightly increased incidence of pancreatic islet cell adenomas and hepatocellular adenomas. The mid-dose and high-dose male and female groups had a slightly increased incidence of thyroid C-cell adenomas. The U.S. EPA concluded the adenomas were not treatment related.[27]
- In a carcinogenicity study, mice were fed a diet containing glyphosate (0, 150, 750, or 4500 mg/kg/day) for 18 months. Researchers observed no effects in the low-dose and mid-dose groups. In the high-dose groups researchers observed decreased body weight gain in both male and female mice. In high-dose males, slightly increased incidence of renal tubular adenomas, increased incidence of hepatocellular hypertrophy, hepatocellular necrosis and interstitial nephritis were noted in the high-dose group. In females, researchers noted increased incidence of proximal tubule epithelial basophilia and hypertrophy at the highest doses. The U.S. EPA and an independent group of pathologists and biometricians concluded that the occurrence of adenomas was not caused by glyphosate.[37,38]
- Based on this mouse study, the systemic NOEL and LOEL were determined to be 750 and 4500 mg/kg/day, respectively.[6]
- Goldfish (*Carassius auratus*) were exposed to 5, 10, or 15 ppm of the formulated product Roundup® containing the IPA salt of glyphosate and the surfactant POEA for 6 days. Researchers noted increased DNA and micronuclei damage in the peripheral erythrocytes. This may have resulted from decreased DNA repair. Genotoxicity test results are generally mixed, although formulated products appear to be more likely to cause effects than glyphosate alone.[39]
- Glyphosate has been the subject of numerous genotoxicity tests and the results are overwhelmingly negative.[29]

Humans

- The U.S. EPA classified glyphosate as Group E, evidence of non-carcinogenicity in humans. The U.S. EPA does not consider glyphosate to be a human carcinogen based on studies of laboratory animals that did not produce compelling evidence of carcinogenicity.[6] See the text box on **Cancer**.

> **Cancer: Government agencies in the United States and abroad have developed programs to evaluate the potential for a chemical to cause cancer. Testing guidelines and classification systems vary. To learn more about the meaning of various cancer classification descriptors listed in this fact sheet, please visit the appropriate reference, or call NPIC.**

- Researchers reviewed the scientific literature on glyphosate, its major metabolite AMPA, formulated

Roundup® products manufactured by Monsanto, and the surfactant POEA. They found that Roundup® and its components did not cause mutations or tumor formation. The researchers concluded that glyphosate is not carcinogenic.[13]

- Researchers assessed the exposure-response relationship between use of products containing glyphosate and cancer in 57, 311 licensed pesticide applicators participating in the Agricultural Health Study. Exposure to glyphosate was not associated with overall cancer incidence or most cancer subtypes. In a small number of cases, there was a "suggested association" between glyphosate exposure and multiple myeloma incidence.[40]
- The International Agency for Research on Cancer (IARC) classified glyphosate as Group 2A, "probably carcinogenic to humans".[41]

Reproductive or Teratogenic Effects:

Animals

- Researchers dosed pregnant rats with glyphosate by gavage (stomach tube) on gestation days 6-19 at doses of 0, 300, 1000, or 3500 mg/kg/day. At the highest dose, they detected decreased body weight gains in both the dams and fetuses, increased maternal mortality, and an increased number of fetal skeletal abnormalities. The NOEL for maternal and developmental toxicity was 1000 mg/kg/day and the LOEL was 3500 mg/kg/day.[42]
- In a developmental study, scientists exposed pregnant rabbits to glyphosate by gavage on gestation days 6-27 at doses of 0, 75, 175, or 350 mg/kg/day. They detected no developmental effects. At the highest dose tested, the animals exhibited diarrhea, nasal discharge, and increased mortality; too many animals died in this group to assess developmental effects at this dose. The NOEL for maternal effects was 175 mg/kg/day.[43]
- Dietary concentrations of up to 10,000 ppm or 293 mg/kg/day of glyphosate given to rats over two generations had no effect on male or female sexuality and fertility. The NOAEL for parental and offspring toxicity is 3000 ppm, based upon a reduction of body weight at 10,000 ppm.[29,44]
- Researchers reviewed the scientific literature on glyphosate, its major metabolite AMPA, formulated Roundup® products manufactured by Monsanto, and the surfactant POEA. They concluded that neither glyphosate, AMPA, nor POEA caused reproductive effects in various animal studies.[13]

Humans

- Questionnaires filled out by farm operators and eligible couples collected during the Ontario Farm Family Health Study suggested that there was an association between preconception exposure to pesticide products containing glyphosate and elevated risks of late spontaneous abortion.[45]

Fate in the Body:

Absorption

- Animal studies have indicated that 30-36% of glyphosate is absorbed after ingestion.[11,13,46]
- Dermal absorption of glyphosate is poor.[6] An *in vitro* experiment with human skin resulted in a maximum of 2.2% of 2.6 µg/cm^2 glyphosate was absorbed across the skin. Absorption peaked 8 hours after administration.[47]
- Researchers applied glyphosate to abdominal skin of monkeys at doses of 5400 µg or 500 µg over 20 cm^2 of skin. Over a 7 day period, 73.5% and 77.1% of the applied dose remained on the skin.[47]

Glyphosate is non-volatile. Absorption from inhalation exposure is not expected to be significant.

Distribution

- Rats dosed orally with 10 mg/kg glyphosate attained peak concentrations in their tissues 6 hours following dosing. The gastrointestinal tract contents accounted for 50% of the dose, with the tissue of the small intestine accounting for an additional 18%. Approximately 5% of the dose was found in bone and 6% in the carcass, with 1% or less of the dose distributed to abdominal fat, blood, colon, kidney, liver, and stomach.[46]
- Researchers gave rats a single oral dose of 10 mg/kg or 1000 mg/kg of glyphosate. Seven days after administration, the absorbed dose had distributed throughout the body, although it was primarily concentrated in the bone.[48]
- Researchers fed hens and goats glyphosate and found glyphosate and its major metabolite AMPA in eggs, milk, and the animals' body tissues.[13,49,50]

Metabolism

- Glyphosate undergoes little metabolism and is excreted mostly unchanged in the feces and secondarily in the urine.[3,13,51]
- Samples taken from goats and hens fed glyphosate contained the parent compound and AMPA, but there was no evidence of other glyphosate metabolites in body tissues, eggs, or milk.[6]
- High ratios of glyphosate to AMPA were detected in a human patient's blood serum 8 hrs (22.6 µg/mL glyphosate to 0.18 µg/mL AMPA) and 16 hrs (4.4 µg/mL glyphosate to 0.03 µg/mL AMPA) post-ingestion, as well as in the patient's total amount of urine. This indicates that glyphosate metabolism was minimal.[52]

Excretion

- Animal studies indicate that glyphosate is primarily excreted through the urine and feces.[3,13,51]
- A rat given a single oral dose of glyphosate eliminated 0.27% of the administered dose as carbon dioxide, and excreted 97.5% as glyphosate in urine and feces. Researchers detected AMPA in urine (0.2-0.3% of administered dose) and feces (0.2-0.4% of administered dose).[53,54]
- Glyphosate is cleared from the body of rats 168 hours after administration.[11]
- Two human patients who were poisoned with glyphosate had peak plasma glyphosate concentrations within 4 hours of ingestion. After 12 hours, glyphosate was almost undetectable.[55]

Medical Tests and Monitoring:

- Glyphosate exposure can be monitored through measurement of glyphosate and AMPA concentrations in blood or urine.[11,56,57] Detection methods include gas chromatography and high-performance liquid chromatography.[52,57,58] However, the clinical significance of residues in human tissues is unknown.
- Researchers developed a sensitivity enhanced multiplexed fluorescence covalent microbead immunosorbent assay (FCMIA) for the measurement of glyphosate in urine.[59] This method was used to detect glyphosate in a study among farm and non-farm households in Iowa.[60]

Environmental Fate:

Soil

The median half-life of glyphosate in soil has been widely studied; values between 2 and 197 days have been reported in the literature.[7,51] A typical field half-life of 47 days has been suggested.[4] Soil and climate conditions affect glyphosate's persistence in soil.[1] See the text box on **Half-life**.

- Glyphosate is relatively stable to chemical and photo decomposition.[6] The primary pathway of glyphosate degradation is soil microbial action, which yields AMPA and glyoxylic acid. Both products are further degraded to carbon dioxide.[3]
- Glyphosate adsorbs tightly to soil. Glyphosate and its residues are expected to be immobile in soil.[6]

The "half-life" is the time required for half of the compound to break down in the environment.

1 half-life = 50% remaining
2 half-lives = 25% remaining
3 half-lives = 12% remaining
4 half-lives = 6% remaining
5 half-lives = 3% remaining

Half-lives can vary widely based on environmental factors. The amount of chemical remaining after a half-life will always depend on the amount of the chemical originally applied. It should be noted that some chemicals may degrade into compounds of toxicological significance.

Water

- The median half-life of glyphosate in water varies from a few days to 91 days.[1]
- Glyphosate did not undergo hydrolysis in buffered solution with a pH of 3, 6, or 9 at 35 °C. Photodegradation of glyphosate in water was insignificant under natural light in a pH 5, 7, and 9 buffered solution.[61,62]
- Glyphosate in the form of the product Roundup® was applied to aquatic plants in fresh and brackish water. Glyphosate concentrations in both ponds declined rapidly, although the binding of glyphosate to bottom sediments depended heavily on the metals in the sediments. If chelating cations are present, the sediment half-life of glyphosate may be greatly increased.[63]
- Glyphosate has a low potential to contaminate groundwater due to its strong adsorptive properties. However, there is potential for surface water contamination from aquatic uses of glyphosate and soil erosion.[6]
- Volatilization of glyphosate is not expected to be significant due to its low vapor pressure.[6]

Air

- Glyphosate and all its salts are very low in volatility with vapor pressures ranging from 1.84×10^{-7} mmHg to 6.75×10^{-8} mmHg at 25 °C.[1,4,8]
- Glyphosate is stable in air.[1]

Plants

- Glyphosate is absorbed by plant foliage and transported throughout the plant through the phloem.[3] Glyphosate absorption across the cuticle is moderate, and transport across the cell membrane is slower than for most herbicides.[4] Because glyphosate binds to the soil, plant uptake of glyphosate from soil is negligible.[3]
- Glyphosate accumulates in meristems, immature leaves, and underground tissues.[4]
- Very little glyphosate is metabolized in plants, with AMPA as the only significant degradation product.[3]
- Lettuce, carrots, and barley contained glyphosate residues up to one year after the soil was treated with 3.71 pounds of glyphosate per acre.[64,65]
- Glyphosate had a median half-life of 8 to 9 days in leaf litter of red alder and salmonberry sprayed with Roundup®.[51]

Indoor

- All surface wipe and dust samples collected from five farm households in Iowa contained detectable levels of glyphosate ranging from 0.0081-2.7 ng/cm^2. In six non-farm households, 28 out of 33 samples collected contained detectable levels of glyphosate ranging from 0.0012-13 ng/cm^2.[66]

Food Residue

- Glyphosate was not included in compounds tested for by the Food and Drug Adminstration's (FDA) Pesticide Residue Monitoring Program (PRMP), nor in the United States Department of Agriculture's Pesticide Data Program (PDP).

Ecotoxicity Studies:

Birds

- An acute oral toxicity study found that a single dose of technical grade glyphosate is practically non-toxic to bobwhite quail, with an LD_{50} of greater than 2000 mg/kg.[67]
- Studies with technical grade glyphosate found an 8-day dietary LC_{50} greater than 4000 ppm for mallard ducks and bobwhite quail, indicating slight toxicity.[67,68]
- Glyphosate is not expected to cause reproductive impairment in birds at dietary levels of up to 1000 ppm.[6]
- An ecological risk assessment concluded that the greatest risk posed by glyphosate and its formulated products to birds and other wildlife results from alteration of habitat.[7]

Fish and Aquatic Life

- Technical grade glyphosate ranges from slightly toxic to practically non-toxic to freshwater fish, with a 48-hour LC_{50} of greater than 24 mg/L to 140 mg/L.[6]
- Formulated glyphosate products range from moderately toxic to practically non-toxic to freshwater fish, with 96-hour LC_{50} values ranging from 1.3 mg/L to greater than 1000 mg/L.[6]
- The preparation of the surfactant POEA known as MON 0818 is used in some glyphosate formulations.[7] POEA is moderately toxic to very highly toxic to freshwater fish. The 96-hour LC_{50} values ranged from 0.65 mg/L to 13 mg/L. Products containing MON 0818 state on the label "This pesticide is toxic to fish".[6]
- The LC_{50} of glyphosate for rainbow trout (*Onchorynchus mykiss*) was 140 mg/L, for fathead minnows (*Pimephales promelas*) was 97 mg/L, for channel catfish (*Icalurus punctatus*) was 130 mg/L and for bluegill sunfish (*Lepomis macrochirus*) was 150 mg/L. When they were exposed to Roundup®, the LC_{50}s for these same fish were 8.3, 2.4, 13.0, and 6.4 mg/L, respectively.[69]
- Technical grade glyphosate is slightly toxic to practically non-toxic to freshwater invertebrates, with a 48-hour LC_{50} ranging from 55 ppm to 780 ppm.[6] The 48-hour LC_{50} for Daphnids was 3.0 mg/L and the LC_{50} for midge larvae was 16 mg/L when exposed to the formulated product Roundup®.[69]
- Researchers calculated LC_{50} values for four species of amphibians (the northern leopard frog (*Rana pipiens*), the wood frog (*R. sylvatica*), the green frog (*R. clamitans*), and the American toad (*Bufo americanus*)) exposed to the original Roundup® formulation of glyphosate. The 24-hour LC_{50} values for the different species ranged from 6.6 to 18.1 mg/L.[70]
- Green frogs (*R. clamitans*) were exposed to technical glyphosate in the form of the isopropylamine salt, the surfactant POEA, and six formulated products containing glyphosate. The surfactant was most toxic to R. clamitans with a 24 and 96- hour LC_{50} of 1.1 mg/L (95% CI 1.1-1.2) and 1.1 mg/L (95% CI 1.0-1.1),

respectively. Technical glyphosate was least toxic, with 24 and 96-hour LC_{50} of >38.9 g/L. The toxicity of the formulated products fell between these values.[70]

- A chronic toxicity study with technical grade glyphosate reported reduced reproductive capacity in Daphnia magna with a maximum acceptable toxicant concentration of 50 to 96 ppm.[71]
- Technical grade glyphosate is practically non-toxic to slightly toxic to estuarine and marine organisms. The 96-hour LC_{50} is 281 ppm for grass shrimp (*Palaemonetas vulgaris*) and 934 ppm for fiddler crab (*Uca pagilator*).[72] The 48-hour median lethal time (TL_{50}) is greater than 10 mg/L for Atlantic oyster (*Crassostrea virginica*).[73]

Terrestrial Invertebrates

- Studies indicate that both technical and formulated glyphosate are practically non-toxic to honeybees, with acute oral and acute contact LD_{50} values greater than 100 µg/bee.[74]
- An ecological risk assessment of Roundup® concluded that the greatest risks to arthropods were from altered habitat structure and food availability.[7]
- The earthworm LC_{50} in soil is greater than 5000 ppm for Monsanto's formulated product Roundup®.[4]

Regulatory Guidelines:

- The U.S. EPA classified glyphosate as Group E, evidence of non-carcinogenicity in humans.[6]
- The reference dose (RfD) for glyphosate is 1.75 mg/kg/day.[31] See the text box on **Reference Dose (RfD)**.
- The Acceptable Daily Intake (ADI) of a combination of glyphosate and certain metabolites (AMPA, N-acetyl glyphosate, and N-acetyl AMPA) for humans is 1.0 mg/kg.[29,30]
- The U.S. EPA has set a One-Day Health Advisory of 20 mg/L.[75]
- The U.S. EPA has set a Ten-day Health Advisory of 20 mg/L.[75]
- The maximum contaminant level (MCL) is 0.7 mg/L.[75] See the text box on **Maximum Contaminant Level (MCL)**.

Reference Dose (RfD): The RfD is an estimate of the quantity of chemical that a person could be exposed to every day for the rest of their life with no appreciable risk of adverse health effects. The reference dose is typically measured in milligrams (mg) of chemical per kilogram (kg) of body weight per day.

U.S. Environmental Protection Agency, Technology Transfer Network, Air Toxics Health Effects Glossary, 2009. **http://www.epa.gov/ttnatw01/hlthef/hapglossaryrev.html#RfD**

Maximum Contaminant Level (MCL): The MCL is the highest level of contaminant that is legally allowed in drinking water. The MCL is enforceable. The MCL is typically measured in milligrams (mg) of contaminant per liter (L) of water.

U.S. Environmental Protection Agency, Region 5, Water, Underground Injection Control Terms, 2011. **http://epa.gov/r5water/uic/glossary.htm#mcl**

Date Reviewed: September 2010; revised: June 2015

Please cite as: Henderson, A. M.; Gervais, J. A.; Luukinen, B.; Buhl, K.; Stone, D. 2010. *Glyphosate Technical Fact Sheet*; National Pesticide Information Center, Oregon State University Extension Services. **http://npic.orst.edu/factsheets/archive/glyphotech.html**.

References:

1. Tomlin, C. D. S. *The Pesticide Manual: A World Compendium*, 14th ed.; British Crop Protection Council: Hampshire, UK, 2006; pp 545- 548.

2. *RED Facts: Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
3. Roberts, T. R. *Metabolic Pathways of Agrochemicals-Part 1: Herbicides and Plant Growth Regulators*; The Royal Society of Chemistry: Cambridge, UK, 1998; pp 396-399.
4. *Herbicide Handbook*, 8th ed.; Vencill, W. K. Ed.; Weed Science Society of America: Lawrence, KS, 2002; p 231-234.
5. *Roundup herbicide bulletin Number 1*; Monsanto Agricultural Products Company: St. Louis, MO, 1980.
6. *Reregistration Eligibility Decision (RED): Glyphosate*; EPA-738-R-93-014; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
7. Giesey, J. P.; Dobson, S.; Solomon, K. R. Ecotoxicological risk assessment for Roundup herbicide. *Rev. Environ. Contam. Toxicol.* 2000, 167, 35-120.
8. *SRC PhysProp Database: Glyphosate*; Syracuse Research Corporation. **http://www.syrres.com/what-we-do/databaseforms.aspx?id=386** (accessed Dec 2007), updated Jan 2010.
9. Shaner, D. L. The impact of glyphosate-tolerant crops on the use of other herbicides and on resistance management. *Pest Manag. Sci.* 2000, 56, 320-326.
10. Franz, J. E.; Mao, M. K.; Sikorski, J. A. *Glyphosate: A Unique Global Herbicide*; American Chemical Society: Washington, DC, 1997; pp 521-527, 604-605, 615.
11. WHO. *Data Sheets on Pesticides: Glyphosate*; International Programme on Chemical Safety, World Health Organization, Food and Agriculture Organization: Geneva, Switzerland, 1996.
12. Wu, J. Y.; Chang, S. S.; Tseng, C. P.; Deng, J. F.; Lee, C. C. Parenteral glyphosate-surfactant herbicide intoxication. *Am. J. Emerg. Med.* 2006, 24 (4), 504-506.
13. Williams, G. M.; Kroes, R.; Munro, I. C. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regul. Toxicol. Pharmacol.* 2000, 31, 117-165.
14. Bradberry, S. M.; Proudfoot, A. T.; Vale, J. A. Glyphosate poisoning. *Toxicol. Rev.* 2004, 23 (3), 159-167..
15. Bates, N.; Campbell, A. *Handbook of Poisoning in Dogs and Cats - Glyphosate*; Campbell, A.; Chapman, M., Eds.; Blackwell Science Ltd: Oxford, England, 2000; pp 135-138.
16. Monsanto Department of Medical and Health Sciences. Roundup and other gyphosate/tallowamine surfactant-containing herbicides: The clinical effects and their managment. Unpublished report, 1994, cited in Burgat, V.; Keck, G.; Guerre, P.; Bigorre, V.; Pineau, X. Glyphosate toxicosis in domestic animals: A survey from the data of the Centre National d'Informations Toxicologiques Veterinaires (CNITV). *Vet. Hum.Toxicol.* 1998, 40 (6), 363-367.
17. Birch, M. Toxicological investigation of CP 67573-3. Unpublished Report no. 4-70-90, 1970, submitted to U.S. Environmental Protection Agency by Monsanto Corporation, prepared by Younger Laboratories, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
18. Blaszcak, D., Primary dermal irritation study in rabbits for glyphosate technical (wetcake). Unpublished Report no. BD-88- 114, project number 4887, 1988, submitted to U.S. Environmental Protection Agency by Monsanto Corporation, prepared by BioDynamics, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
19. Blaszcak, D. Eye irritation study in rabbits for glyphosate technical (wetcake). Unpublished Report no. BD-88-114, project no. 4888-88, 1988, submitted to U.S. Environmental Protection Agency by Monsanto Corporation, prepared by BioDynamics, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
20. Maibach, H. I. Irritation, sensitization, photoirritation and photosensitization assays with a glyphosate herbicide. *Contact Derm.* 1986, 15, 152-156.
21. Rattray, N. J. Glyphosate acid: 4-hour acute inhalation toxicity study in rats. Unpublished Report no. CTL/P/4882, study no. HR2884, 1996, submitted to WHO by Syngenta Crop Protection AG, Basel, Switzerland, prepared by Zeneca Agrochemicals, Central Toxicology Laboratory, Alderley Park, Maccelsfield, Cheshire, England. *Pesticide Residues in Food - 2004: Toxicological evaluations*; International Programme on Chemical Safety, World Health Organization: Geneva, Switzerland, 1996.
22. Welch, S. Glyphosate. *Clinical Veterinary Toxicology*; Plumlee, K. H., Ed.; Mosby: St. Louis, 2004; pp 162-163.
23. Burgat, V.; Keck, G.; Guerre, P.; Bigorre, V.; Pineau, X. Glyphosate toxicosis in domestic animals: A survey from the data of the Centre National d'Informations Toxicologiques Veterinaires (CNITV). *Vet. Hum. Toxicol.* 1998, 40 (6), 363-367.
24. Talbot, A. R.; Shiaw, M. H.; Huang, J. S.; Yang, S. F.; Goo, T. S.; Wang, S. H.; Chen, C. L.; Sanford, T. R. Acute poisoning with a glyphosatesurfactant herbicide ('Roundup'): A review of 93 cases. *Hum. Exp. Toxicol.* 1991, 10 (1), 1-8.
25. Acquavella, J. F.; Weber, J. A.; Cullen, M. R.; Cruz, O. A.; Martens, M. A.; Holden, L. R.; Riordan, S.; Thompson, M.; Farmer, D. Human ocular effects from self-reported exposures to Roundup herbicides. *Hum. Exp. Toxicol.* 1999, 18 (8), 479-486.
26. Reyna, M. Twelve month study of glyphosate administered by gelatin capsule to beagle dogs. Unpublished Report no. 830116, project no. ML-83-137, 1985, submitted to U.S. Environmental Protection Agency by Monsanto Company Environmental Health. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.

27. Stout, L.; Ruecker, F. Chronic study of glyphosate administered in feed to albino rats. Unpublished Report no. MSL-10495 R.D. 1014, 1990, submitted to U.S. Environmental Protection Agency by Monsanto Agricultural Company. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
28. Atkinson, C.; Strutt, A.V.; Henderson, W.; Finch, J.; Hudson, P. Glyphosate: 104 week combined chronic feeding/oncogenicity study in rats with 52 week interim kill (results after 104 weeks). Unpublished report No. 7867, IRI project no. 438623, 1993, submitted to World Health Organization by Cheminova A/S, Lemvig, Denmark, prepared by Inveresk Research International, Tranent, Scotland. *Pesticide Residues in Food - 2004: Toxicological evaluations*; International Programme on Chemical Safety, World Health Organization: Geneva, Switzerland, 2004.
29. FAO. *Pesticide Residues in Food - 2004: Toxicological evaluations*; International Programme on Chemical Safety, World Health Organization, Food and Agriculture Organization: Rome, Italy, 2004.
30. FAO. *Pesticide Residues in Food - 2011: Toxicological evaluations*; International Programme on Chemical Safety, World Health Organization, Food and Agriculture Organization: Geneva, Switzerland, 2011; pp. 373–385.
31. *Human-Health Assessment Scoping Document in Support of Registration Review: Glyphosate*; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 2009.
32. Lavy, T. L. Conifer seedling nursery worker exposure to glyphosate. *Arch. Environ. Contam. Toxicol.* 1992, 22, 6-13.
33. Jauhiainen, A.; Rasanen, K.; Sarantila, R.; Nuutinen, J.; Kangas, J. Occupational exposure of forest workers to glyphosate during brush saw spraying work. *Am. Ind. Hyg. Assoc. J.* 1991, 52 (2), 61-64.
34. Acquavella, J. F.; Alexander, B. H.; Mandel, J. S.; Gustin, C.; Baker, B.; Chapman, P.; Bleeke, M. Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. *Environ. Health Perspect.* 2004, 112 (3), 321-326.
35. Chan, P. C.; Mahler, J. F. *NTP Technical Report on toxicity studies of glyphosate (CAS No. 1071-83-6) administered in dosed feed to F344/N rats and B6C3F1 mice*. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program: Research Triangle Park, NC, 1992; pp 12-13, 24.
36. Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the Federal Food, Drug, and Cosmetic Act. *Fed. Regist.* June 18, 2007, 72 (116), pp 33486-33503.
37. Knezevich, A.; Hogan, G. A chronic feeding study of glyphosate (Roundup technical) in mice. Unpublished Report no. BDN-77420, project no. 77-2061, 1983, submitted to U.S. Environmental Protection Agency by Monsanto Company, prepared by BioDynamics, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
38. McConnel, R. A chronic feeding study of glyphosate (Roundup technical) in mice: pathology report on additional kidney sections. Unpublished project no. 77-2061A, 1985, submitted to U.S. Environmental Protection Agency prepared by BioDynamics, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
39. Cavas, T.; Konen, S. Detection of cytogenic and DNA damage in peripheral erythrocytes of goldfish (Carassius auratus) exposed to a glyphosate formulation using the micronucleus test and the comet assay. *Mutagenesis* 2007, 22 (4), 263-268.
40. De Roos, A. J.; Blair, A.; Rusiecki, J. A.; Hoppin, J. A.; Svec, M.; Dosemeci, M.; Sandler, D. P.; Alavanja, M. C. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ. Health Perspect.* 2005, 113 (1), 49-54.
41. Guyton, K. Z.; Loomis, D.; Grosse, Y.; El Ghissassi, F.; Benbrahim-Tallaa, L.; Guha, N.; Scoccianti, C.; Mattock, H.; Straif, K. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. *Lancet Oncol.* 2015, 16, 490–491.
42. Rodwell, D. E.; Tasker, E. J.; Blair, A. M.; et al. Teratology study in rats. Unpublished report no. 401-054, unpublished study no. 999- 021, 1980, submitted to U.S. Environmental Protection Agency by Monsanto Company, prepared by International Research and Development Corporation. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
43. Rodwell, D. E.; Tasker, E. J.; Blair, A. M.; et al. Teratology study in rats. Unpublished report no. 401-056, 1980, submitted to U.S. Environmental Protection Agency by Monsanto Company, prepared by International Research and Development Corporation. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U. S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
44. Moxon, M. E. Glophosate acid: multigeneration reproduction toxicity in rats. Unpublished report no. CTL/P/6332, study no. RR0784, 2000, submitted to WHO by Syngenta Crop Protection AG, Basel, Switzerland, prepared by Zeneca Agrochemicals, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, England. *Pesticide Residues in Food - Evaluations Part 2: Toxicological*; International Programme on Chemical Safety, World Health Organization, Food and Agriculture Organization: Rome, Italy, 2004.
45. Arbuckle, T. E.; Lin, Z.; Mery, L. S. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ. Health Perspect.* 2001, 109 (8), 851-7.
46. Brewster, D. W.; Warren, J.; Hopkins, W. E. I. Metabolism of glyphosate in Sprague-Dawley rats: Tissue distribution, identification, and quantification of glyphosate-derived materials following a single oral dose. *Fund. Appl. Toxicol.* 1991, 17, 43-51.
47. Wester, R. C.; Melendres, J.; Sarason, R.; McMaster, J.; Maibach, H. I. Glyphosate skin binding, absorption, residual tissue

distribution, and skin decontamination. *Fund. Appl. Toxicol.* 1991, 16, 725-732.
48. Monsanto Corporation. The metabolism of glyphosate in Sprague Dawley rats- Part I. Excretion and tissue distribution of glyphosate and its metabolites following intravenous and oral administration. Unpublished report no. MSL-7215, 1988, submitted to WHO by Monsanto Ltd, prepared by Monsanto Environmental Health Laboratory/Monsanto Life Sciences Research Center, St. Louis, Missouri. *Environmental Health Criteria 159, Toxicological Evaluations - Glyphosate*; International Programme on Chemical Safety, World Health Organization: Geneva, Switzerland,1988.
49. Bodden, R. M. Metabolism study of synthetic 13C/14C-labeled glyphosate and aminomethylphoshonic acid in lactating goats. Unpublished report, 1988, cited in Williams, G. M.; Kros, R.; Munro, I. C., prepared by Hazelton Laboratories America, Inc. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate for humans. *Regul. Toxicol. Pharmacol.* 2000, 31, 117-165.
50. Bodden, R. M., Metabolism study of synthetic 13C/14C-labeled glyphosate and aminomethylphosphonic acid in laying hens. Unpublished report, 1988, cited in Williams, G. C.; Kroes, R.; Munro, I. C., prepared by Hazelton Laboratories America, Inc. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate for humans. *Regul. Toxicol. Pharmacol.* 2000, 31, 117-165.
51. WHO. *Environmental Health Criteria 159, Toxicological Evaluations - Glyphosate*; International Programme on Chemical Safety, World Health Organization: Geneva, Switzerland, 1994.
52. Hori, Y.; Fujisawa, M.; Shimada, K.; Hirose, Y. Determination of the herbicide glyphosate and its metabolite in biological specimens by gas chromatography-mass spectrometry. A case of poisoning by roundup herbicide. *J. Anal. Toxicol.* 2003, 27 (3), 162-166.
53. Ridley, W.; Mirly, K. The metabolism of glyphosate in Sprague-Dawley rats. Part I. Excretion and tissue distribution of glyphosate and its metabolites following intravenous and oral administration. Unpublished report no. 86139 (MSL 7215), RD no. 877, 1988, submitted to U.S. Environmental Protection Agency by Monsanto Company. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
54. Howe, R.; Chott, R.; McClanahan, R. Metabolism of glyphosate in Sprague-Dawley rats. Part II: Identification, characterization, and quantitation of glyphosate and its metabolites after intravenous and oral administration. Unpublished report no. MSL-7206, RD No. 877, 1988, submitted to U.S. Environmental Protection Agency by Monsanto Company. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
55. Talbot, A.; Ku, T. S.; Chen, C. L.; Li, G. C.; Li, H. P. Glyphosate levels in acute Roundup herbicide poisoning. 1994 Toxicology World Congress Abstracts. *Ann. Emerg. Med.* 1995, 26, 717.
56. Aprea, C.; Colosio, C.; Mammone, T.; Minoia, C.; Maroni, M. Biological monitoring of pesticide exposure: a review of analytical methods. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 2002, 769 (2), 191-219.
57. Motojyuku, M.; Saito, T.; Akieda, K.; Otsuka, H.; Yamamoto, I.; Inokuchi, S. Determination of glyphosate, glyphosate metabolites, and glufosinate in human serum by gas chromatography-mass spectometry. *J. Chromatogr. B* 2008, 875, 509-514.
58. Sato, K.; Jin, J. Y.; Takeuchi, T.; Miwa, T.; Suenami, K.; Takekoshi, Y.; Kanno, S., Integrated pulsed amperometric detection of glufosinate, bialaphos and glyphosate at gold electrodes in anion-exchange chromatography. *J. Chromatogr. A.* 2001, 919 (2), 313-320.
59. Biagini, R. E.; Smith, J. P.; Sammons, D. L.; MacKenzie, B. A.; Striley, C. A.; Robertson, S. K.; Snawder, J. E. Development of a sensitivity enhanced multiplexed fluorescence covalent microbead immunosorbent assay (FCMIA) for the measurement of glyphosate, atrazine and metolachlor mercapturate in water and urine. *Anal. Bioanal. Chem.* 2004, 379 (3), 368-374.
60. Curwin, B. D.; Hein, M. J.; Sanderson, W. T.; Striley, C.; Heederik, D.; Kromhout, H.; Reynolds, S. J.; Alavanja, M. C. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa. *Ann. Occup. Hyg.* 2007, 51 (1), 53-65.
61. Castle, S.; Ruzo, L.; Katheryn, S. Degradation study: photodegradation of carbon 14 glyphosate in a buffered aqueous solution at pH 5, 7, and 9 by natural sunlight. Unpublished report no. 233W-1, 233W:1020, 1990, submitted to U.S. Environmental Protections Agency, prepared by Pharmacology and Toxicology Research Laboratory, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
62. Brightwell, B.; Malik, J. Solubility, volatility, absorption, and partition coefficients, leaching and aquatic metabolism of MON 0573 and MON 0101. Unpublished report no. MSL-0207, 1978, submitted to U.S. Environmental Protection Agency by Monsanto Company. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
63. Tsui, M. T. 60. K.; Chu, L. M. Environmental fate and non-target impact of glyphosate-based herbicide (Roundup) in a subtropical wetland. *Chemosphere* 2008, 71, 439-446.
64. Nicholls, R. Confined rotational crop study of glyphosate Part I: In-field portion. Unpublished report no. EF-88-22, 1990, submitted to U.S. Environmental Protection Agency by Pan-Agricultural Labs, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
65. McMullan, P.; Honeggar, J.; Logusch, E. Confined rotational crop study of glyphosate Part II. Quantitation, characterization and identification of glyphosate and its metabolites in rotational crops. Unpublished report no. MSL-981, 1990, submitted to U.S.

Environmental Protection Agency by Monsanto Agricultural Labs. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA- 738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.

66. Curwin, B. D.; Hein, M. J.; Sanderson, W. T.; Nishioka, M. G.; Reynolds, S. J.; Ward, E. M.; Alavanja, M. C. Pesticide contamination inside farm and nonfarm homes. *J. Occup. Environ. Hyg.* 2005, 2 (7), 357-67.
67. Fink, R.; Beavers, J. One-generation reproduction study in bobwhite quail: glyphosate technical. Unbpublished report no. 139-141. 1978, submitted to U.S. Environmental Protection Agency by Monsanto Company, prepared by Wildlife International Ltd. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
68. Fink, R.; Beavers, J. Final report: One-generation reproduction study in mallard ducks: glyphosate technical. Unpublished report no. 139-143, 1978, submitted to U.S. Environmental Protection Agency by Monsanto Company, prepared by Wildlife International Ltd. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
69. Folmar, L. C.; Sanders, H. O.; Julin, A. M. Toxicity of the herbicide glyphosate and several of its formulations to fish and aquatic invertebrates. *Arch. Environ. Contam. Toxicol.* 1979, 8, 269-278.
70. Howe, C. M.; Berrill, M.; Pauli, B. D.; Helbing, C. C.; Werry, K.; Veldhoen, N., Toxicity of glyphosate-based pesticides to four North American frog species. *Environ. Toxicol. Chem.* 2004, 23 (8), 1928-1938.
71. McAllister, W.; McKee, M.; Schofield, M.; et al. Chronic toxicity of glyphosate (AB-82-036) to Daphnia magna under flow-through test conditions. Chronic toxicity final report ABC 28742. Unpublished report, 1982, submitted to U.S. Environmental Protection Agency by Monsanto Company , prepared by Analytical Bio-Chemistry Laboratories, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
72. Bentley, R., Acute toxicity of roundup (technical) to grass shrimp (*Palaemonetas vulgaris*) and fiddler crab (*Uca pagilator*). Unpublished report no. SF1536, 1974, submitted to U.S. Environmental Protection Agency by Monsanto Company , prepared by Bionomics, Inc. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
73. Bentley, R. Acute toxicity of roundup (technical) to Atlantic oyster (*Crassostrea virginica*). Unpublished report no. SF1536, 1974, submitted to study U.S. Environmental Protection Agency by Monsanto Company , prepared by Bionomics, Inc., CDL 094171-L. *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
74. Frasier, W. D.; Jenkins, G. The acute contact and oral toxicities of CP67573 and MON2139 to worker honey bees. Unpublished report no. 4G1444, 1972, submitted to U.S. Environmental Protection Agency by Monsanto Company , prepared by Huntingdon Research *Reregistration Eligibility Decision (RED) Glyphosate*; EPA-738-F-93-011; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1993.
75. *2006 Edition of Drinking Water Standards and Health Advisories*; EPA-822-R-06-013; U.S. Environmental Protection Agency, Office of Water, U.S. Government Printing Office: Washington, DC, 2006.

Journal of Environmental Studies and Sciences (2018) 8:416–434
https://doi.org/10.1007/s13412-018-0517-2

Glyphosate: A review of its global use, environmental impact, and potential health effects on humans and other species

Martha E. Richmond[1]

Published online: 28 September 2018

Abstract
Glyphosate, [N-(phosphonomethyl) glycine], was synthesized in 1950 and patented as a chemical chelator, capable of binding metals such as calcium, magnesium, and manganese. Glyphosate's ability to bind to manganese was later found to inhibit an enzyme used by plants and bacteria for biosynthesis of three amino acids found in all proteins, and the commercial value of this property led to the development and marketing of glyphosate as a broad-spectrum herbicide. In 1974, the Monsanto Chemical Company introduced the herbicide as Roundup™, a formulation of glyphosate and adjuvants. Roundup™ was originally used for weed control in specific farming and landscaping operations and around power lines and train tracks. Following introduction of Roundup Ready™ seeds, in the 1990s, glyphosate use increased significantly. Although Monsanto's patent on glyphosate expired in 2002, the widespread and growing use of Roundup Ready™ seed globally and competitive glyphosate marketing by other chemical companies have led to glyphosate's significant increase in the environment. Concerns about potential adverse effects have also grown. While, at present, many regulatory agencies have determined that there is little risk of adverse health effects to the general public or to farmworkers using proper handling techniques, the International Agency for Research on Cancer (IARC) assessing hazard data on glyphosate identified it in 2016 as a category 2A carcinogen (likely to cause human cancer). Response to this classification has been divided: The agribusiness industry has been forceful in its opposition, while other experts support IARC's classification. The following article examines these issues. It also examines the basis for regulatory decisions, controversies involved, and questions of environmental justice that may or may not be addressed as glyphosate continues to be used.

Keywords Glyphosate · Environmental health · Ecosystem · Environmental justice · Agribusiness

Introduction

Glyphosate, or [N-(phosphonomethyl) glycine], is a broad-spectrum herbicide that is absorbed through the leaves and foliage of growing plants, inhibiting an enzyme involved in the synthesis of tryptophan, phenylalanine, and tyrosine, amino acids that are essential building blocks of proteins. Animals lacking the plant biosynthetic pathway must take these amino acids in through their diet. Thus, glyphosate does not have the same toxic effect on animals.

Glyphosate was originally synthesized and patented as a metal binding agent by a Swiss chemist in 1950. Although not initially used as a herbicide, it became recognized that glyphosate binds to manganese, essential to an enzyme necessary to the biosynthetic pathway for tyrosine, phenyl alanine, and tryptophan formation (amino acids found in all proteins). The biosynthetic pathway for the formation of the amino acids and the specific step in the pathway inhibited by glyphosate are shown in Fig. 1.

Once the inhibitory effect of glyphosate was seen, it was quickly recognized that it could have commercial applications because of its potential to kill unwanted plants, and, in theory, not harming animals. Further investigations demonstrated not only broad-spectrum herbicidal activity (Dill et al. 2010), but also a low acute toxicity, far less toxic than that of several other broad-spectrum herbicides. Glyphosate's high LD_{50} (mean lethal acute dose) is comparable to that of table salt (Fishel et al. 2013). It is water soluble, and, presumably therefore, readily excreted by animals following intake.

Monsanto marketed glyphosate under the trade name Roundup™ and held the patent from 1974 until its

✉ Martha E. Richmond
mrichmond@suffolk.edu

[1] Suffolk University, Boston, MA, USA

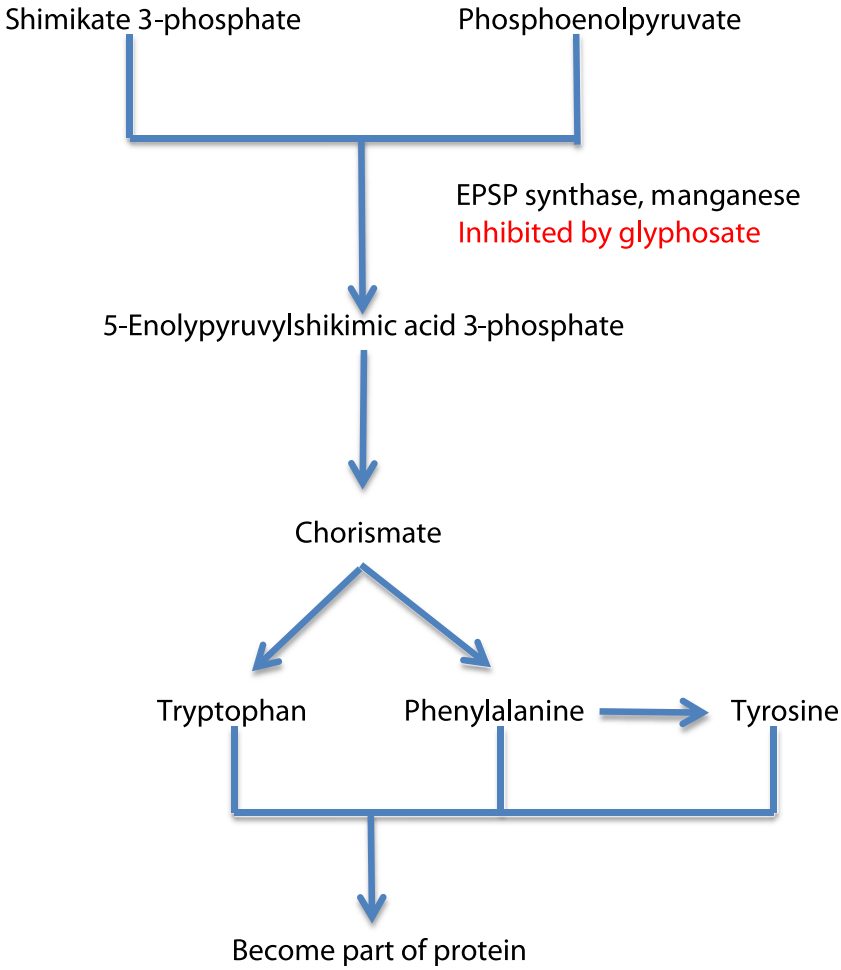


Fig. 1 Biosynthetic pathway for formation of tryptophan, phenylalanine and tyrosine, indicating step inhibited by glyphosate

expiration in 2000. When first marketed, it was heralded as a "breakthrough" in herbicides. Original commercial use was for weed control, including elimination of unwanted plants around power lines and train tracks, in fruit production for elimination of weeds between rows in orchards, and following crop harvest, for removal of unwanted plant growth in fields. However, the volume of glyphosate use increased dramatically with the introduction of Roundup Ready™ genetically engineered commercial crops in the 1990s, making it possible to use glyphosate for weed control before and during crop growth as well as after harvest. It could also be used just prior to harvest in certain applications. The expansion of ways that glyphosate could be used has resulted a dramatic increase in the volume of herbicide used. Today, glyphosate use is global.

Initially, little concern was voiced about its commercial (or other) uses. Nevertheless, as it became consumed more extensively, safety concerns did arise: concerns about safety to the general environment and ecosystem, to the waterways, to animals, and, ultimately, to humans. The following paper discusses each of these issues, examining the growth and global spread of glyphosate use, its short- and long-term effects, its environmental impact, controversies about potential health effects, and other influences that glyphosate use may have on those who are frequently exposed.

Use of glyphosate

Today, a large percentage of glyphosate use is associated with the development and marketing of Roundup Ready™ seed. Initial seed included soybean, corn, and cotton; nevertheless, since the introduction of these original seeds in the mid-1990s, many other glyphosate-resistant seeds have also been developed and marketed. Important commercial crops now include canola, sugar cane, and sugar beets, as well as a number of crops grown on a less wide-scale basis. Glyphosate also continues to be used for weed control in non-farming applications.

Although Monsanto's patent has expired, the development of more glyphosate-resistant seeds; the increased planting of glyphosate-resistant crops; and, because of competition, the decreased cost of the herbicide globally are all major contributors to the larger application of glyphosate/acre and to the increased volume of use worldwide.

Environmental breakdown is primarily through the action of soil microorganisms. The primary breakdown products are aminomethylphosphonic acid (AMPA) and carbon dioxide. Like glyphosate, AMPA binds tightly to soil and is slowly degraded, ultimately breaking down into phosphate, ammonia, and carbon dioxide.

2. Water: Since they are both polar molecules, glyphosate and AMPA readily dissolve in bodies of water. They may enter rivers and streams as run off or may first enter the atmosphere attached to soil dusts, which subsequently dissolve in rivers and streams. In rivers and streams, the half-life of each compound varies, depending on water composition and pH, as well as composition of bottom sediments which can be a major "sink," especially if the sediments contain metal ions. Henderson et al. (2010) report median half-lives ranging from a few to 91 days. A recent report from the US Geological Survey (Battaglin et al. 2014) that examined water and soil samples from 38 states collected from 2001 to 2010 found glyphosate and AMPA to be widespread in the environment, especially in sediments, soils, precipitation, ditches, drains, rivers, and streams.

Since both glyphosate and AMPA bind tightly to soils allowing break down by soil microorganisms, it is often felt that little glyphosate enters groundwater. Nevertheless, a few studies do report small amounts in groundwater samples (Sanchís et al. 2012; Vereecken 2005). The presence of meaningful amounts seems to reflect periods of heavy precipitation. A study reported by Sanchís and coworkers Sanchís et al. (2012) detailed an analysis of 140 groundwater samples taken in Catalonia, Spain. Roughly 40% of samples analyzed contained glyphosate. Although the mean concentration in groundwater was small (mean concentration 200 ng/L), higher concentrations were found where groundwater samples were taken during a period of heavy precipitation that followed earlier periods of drought, suggesting leaching from soil.

3. Soil organisms: Data on the effects of glyphosate on soil organisms are complex, and findings have been contradictory (Soil Association 2016). Perhaps this is not surprising, given the number of factors that come into play: the composition of different soils which not only determines how strongly glyphosate and AMPA bind, but also the make-up of the microorganism community, the water content of the soil, the pattern of glyphosate use (whether soils tested have been exposed once or on multiple occasions), and whether the soils contain breakdown of plant material treated with glyphosate.

Since glyphosate targets a biosynthetic pathway unique to bacteria and plants, it is to be expected that when first applied, the exudate of root tips into soil would inhibit growth of bacteria dependent on this pathway. However, over time, mutational events may select for bacteria resistant to glyphosate's inhibitory effects. It can be theorized that this selection would change the microbial make-up of the area surrounding plant roots (the rhizosphere), an expectation that has been corroborated in a number of studies (Soil Association 2016). It is, however, difficult to determine specific trends in microbiological changes, or to assess the potential significance of changes. In part, this reflects differences in study design. Some investigations have looked at field changes. Some have compared rhizosphere differences between the rhizospheres of resistant and sensitive plants. Some have examined results of multiple applications. Still others have looked at generational differences. Finally, soil compositions and choice of plants for examination differ from study to study. Looking at glyphosate transfer from the rhizosphere of target (weed) to non-target (crop or landscape) plants, Neumann et al. (2006) found that the transfer inhibited root uptake of essential micronutrients by non-target plants, thus posing a threat to non-target plant growth and nutrition. Kremer and Means (2009) found that the rhizosphere of glyphosate-treated plants supported growth of fungal species; roots of treated plants had fewer nodules.

Consistent with the expectation that glyphosate treatment would select for organisms that are resistant to the inhibitory effects on the enzyme involved in biosynthesis of tyrosine, tryptophan, and phenylalanine, Araújo et al. (2003) found an increase in fungi and particular groups of bacteria as well as an increase in markers of bacterial respiration among organisms found in samples of Brazilian soils treated with glyphosate. Newman et al. (2016), in a controlled experiment over several growth seasons, reported differences in the mix of bacteria found in the rhizosphere of corn and soybean cultures and suggest that some of the shifts might lead changes in the nutrient status of the glyphosate-treated plants.

Weed resistance

As noted by a number of investigators (Benbrook 2016; Cerdiera et al. 2011; Duke 2017; Heap and Duke 2018; Mortensen et al. 2012), the large-scale use of glyphosate has led to growth in glyphosate tolerance among target plants, as well as the evolution of glyphosate-resistant weeds. Weed resistance to glyphosate was first reported in 1996 when *Lolium rigidum* was found in an apple orchard in Australia. Resistance has grown considerably since the first report. Heap and Duke (2017) detailed the evolution of 38 resistant weed species in 37 countries. Resistance has been found in 34 different crops, and glyphosate-resistant weeds have been found growing in several non-crop environments. One response to the evolution of glyphosate-resistant weeds has been the development of GM crops resistant to several herbicides. For example, Monsanto has developed a strain of cotton sold as

Use in the USA

The widespread use of glyphosate use in the USA is expected to increase in the foreseeable future. Although exact data for all uses are not available, relatively precise findings and predictions can be made from available information. Benbrook (2016) analyzed information available through the US Department of Agriculture (USDA) National Agricultural Statistics Service and the US Environmental Protection Agency (EPA) to estimate the volume of use. Taking such information, Benbrook noted the following:

- Overall, in the USA, roughly 67% of the total glyphosate use since its introduction in 1974 has taken place in the decade 2004–2014.[1]
- The overall increase of glyphosate use (1974 to 2014) is estimated to be 200-fold, with agricultural use contributing to 90% of this growth.[1] Breaking this down into sector, agricultural use increased 300-fold and non-agricultural use increased approximately 40-fold.[1]
- From 1974 to 1995, glyphosate use grew from 1,400,000 to 40,000,000 lb (roughly 30-fold). Agricultural use grew from 800,000 to 27,500,000 lb (roughly 34-fold) and non-agricultural use grew from 600 to 12,500 lb (approximately 20-fold).[1]
- From 1995 to 2014, while the volume of use was significantly greater than it was before introduction of GM crops, the rate of growth was less: overall use increased approximately 7-fold with agricultural use expanding at a greater rate (9-fold), and non-agricultural use expanding roughly 2-fold.[1]
- By 2010, agricultural applications accounted for 90% of glyphosate use. This pattern has continued.

Global use

The expiration of the Monsanto's glyphosate patent in 2000 and the rise in glyphosate production by other companies (including Bayer, DuPont, Syngenta, BASF, Crop Science, and Dow as well as several Chinese companies) make it increasingly challenging to access data regarding use or volume of sales. At the present time, major sources of specific data are for-purchase trade reports. Descriptive reports indicate that China is today the major producer of glyphosate (Global Information, Inc. 2013).

A recent growth estimate from a trade report (Transparency Market Research 2014) anticipates a global rate of growth from 2012, rated as US$5.46 billion in 2012, to reach US$8.79 billion by 2019. Other points include the following:

- Globally, soybean is the major glyphosate resistant crop (Benbrook 2016).
- The USA, Argentina, and Brazil are the largest users of glyphosate and glyphosate-resistant seeds (Benbrook 2016).
- Patterns of glyphosate use (frequency of application, pattern of application, strength of herbicide) vary according to farming practices as well as time of introduction of glyphosate and glyphosate-resistant crops in different countries.
- Among Asian/Pacific countries, China and India are the primary users of glyphosate, with much of the use tied to GM seed.
- Use of glyphosate in the European Union has fluctuated within recent years as the result of regulatory issues.
- In sub-Saharan Africa, South Africa is a major user of GM seed and glyphosate.

According to the African Centre for Biodiversity, overall use of glyphosate increased from 12 million to 20 million liters from 2008 to 2012. From 2007 to 2011, glyphosate imports increased by 177% (African Centre for Biodiversity 2015). However, sub-Saharan Africa use varies from country to country, in part because of regulatory considerations, but also because of economic forces. Gabowski and Jayne (2016) found that while overall use is increasing, wide variations exist. Large-scale commercial products such as cotton, maize, and soy are more frequently grown using a combination of GM technology and glyphosate weed control, especially true in South Africa where use is extensive. A recent report from South Africa notes that approximately 85% of both maize (corn) and soy seed are genetically modified, often glyphosate tolerant (Albrecht 2017). Initially approved for use in 1975, glyphosate is now used not only for commercial production of maize and corn but for production of many other crops grown in farms, orchards, and vineyards.

Glyphosate in the environment

Soil, water, and soil organisms

1. Soil: Glyphosate readily attaches to soil following spray application and is released relatively slowly. Release rates depend on soil composition, rainfall, water, and the type of tilling (Vereecken 2005). Depending on soil composition, half-lives of attachment can range anywhere from days to several months (Henderson et al. 2010).

[1] Data based on information from US Department of Agriculture, National Agriculture Statistical Service, and the US Environmental Protection Agency (EPA). Data from EPA includes both farming and non-farming uses, and calculations for non-agricultural use represent adjustments, taking the higher EPA estimates into consideration.

Table 1 US agencies: assessment and classification of glyphosate

Agency	Assessment date and ruling	Comments
US Environmental Protection Agency (EPA)	2017 re-evaluation; not likely to be a human carcinogen	Weight-of-evidence assessment of data on glyphosate alone; rat studies est. LOAEL 940 mg/kg/day; chronic dietary intake NOAEL 100 mg/kg/day. "Not likely to be carcinogenic to humans"
Occupational Safety and Health Agency (OSHA)	Advisory information on occupational handling	Primarily address short term occupational exposure effects. TLV (threshold limiting value) not established.
National Institutes of Occupational Safety and Health (NIOSH)	No significant research or assessment	Review on hazardous substances in waste sites
Agency for Toxic Substances and Disease Registry (ATSDR)	Scheduled assessment initiated in 2015	Report release and public comment scheduled for 2018
National Toxicology Program (NTP)	Program to evaluate glyphosate toxicity alone or in formulations and to compare formulation effects scheduled in 2016	No report issued to date. In 1992, NTP determined that glyphosate not a carcinogen risk. Findings in 1992 based on animal and mutagenic studies.
California	In 2017, identified as a hazardous chemical under Proposition 65	Listed under Proposition 65 as causing cancer base; included in hazardous substances list, but based on 2018 court ruling information not listed on glyphosate containing products

were, however, submitted by industry to regulatory agencies as part of approval processes.

In 2015, IARC, using its established risk criteria, classified glyphosate as a category 2A substance (likely to be a human carcinogen). A summary of the IARC assessment can be found in a Lancet Oncology 2015 publication (Guyton et al. 2015). Details of the IARC assessment are published in volume 112 of the IARC Monographs (International Agency for Research on Cancer 2017).

In assessing the carcinogenic potential of glyphosate, the IARC working group considered three areas: epidemiologic studies, animal studies, and in vitro and in vivo studies with various end points of genotoxicity.

1. Epidemiologic studies. Among the evaluated studies were several case control investigations that examined non-Hodgkin's lymphoma (DeRoos, De Roos et al. 2003; McDuffie, McDuffie et al. 2001; and Erikkson, Eriksson et al. 2008) and a prospective cohort investigation which was part of the agricultural health study (DeRoos De Roos et al. 2005). While the IARC working group found the case-control studies, adjusted for confounding effects of other pesticides to show a positive association between glyphosate exposure and the development of non-Hodgkin's lymphoma, this was not found with the agricultural health study (DeRoos, et al., De Roos et al. 2005), a cohort study.
2. Animal studies. IARC found that two animal studies provided strong evidence of carcinogenicity. Included were findings of renal tumors and a rare blood vessel tumor in mice (EPA, 1985; EPA, 1986) as well as benign pancreatic tumors in rats. While several controlled exposure animal studies of the Monsanto-sponsored review articles published prior to deliberations of the IARC working group were cited, it was noted that "The Working Group did not evaluate these studies….because the information

Table 2 International agencies: assessment and classification of glyphosate

Agency	Assessment date and ruling	Comments
International Agency for Research on Cancer (IARC)	Hazard identification of glyphosate as category 2A substance (probable human carcinogen)	Hazard identification not risk assessment; IARC policy to use peer-reviewed published data and other publically available data
European Food Safety Authority (EFSA)	In 2015 determined that glyphosate "unlikely to pose a carcinogenic hazard to humans"	Used peer reviewed literature and analysis of findings and raw data contained in "regulatory guideline studies"
Joint World Health Organization and Food and Agricultural Organization (JMPR)	In 2017 determined dietary intake of glyphosate unlikely to be a carcinogen hazard	Uses published and unpublished data
European Union	In 2017 voted to extend use for five-year period	Extension period "abbreviated." Majority of member nations (18) voted to approve extension. France and Italy opposed. One member-nation abstained.

Bollgard II® XtendFlex™Cotton that is resistant to dicamba, glufosinate, and glyphosate. A strain of soybean, Roundup Ready 2 XtendTM Soybeans, is resistant to dicamba and glyphosate. Other authorities, responding to the emergence of glyphosate resistance, advocate more integrated approaches such as crop rotation and efficient use (time of use, thoroughness of application, and application to weeds at the appropriate growth/developmental stage) as alternative approaches to glyphosate resistance (Young 2018).

Health effects

Overview

Reports of acute toxic effects resulting from accidental or intentional ingestion of glyphosate can be found in the literature. However, the major concerns about health effects consider adverse outcomes that may arise because of the increasingly ubiquitous presence of glyphosate in the environment. This raises issues about the effects it may have on a variety of animals in the larger ecosystem. Finally, while small in amount, glyphosate may also be found in processed foods, especially foods from soy and corn, and may also be found in milk from cows that have ingested small amounts of the herbicide.

Regarded as the so-called active ingredient in commercially available herbicides, many regulatory agencies focus on the health effects of glyphosate alone and have established toxicological parameters for human exposure based on this approach. However, whether or not the adjuvants used in commercial delivery of glyphosate have toxicological properties per se, adjuvants are usually mixtures of more than one chemical, and mixture components may modulate the effects of glyphosate in "real life." Mesnage et al. (2015) summarize the results of 18 in vitro studies comparing various health end points resulting from exposure to glyphosate alone or glyphosate as part of the commercial product Roundup™ or glyphosate in other commercial products. While these investigations examined a variety of cell/organ lines, had different exposure designs, and did not consistently use Roundup™ as the only adjuvant formulation, the vast majority (16/18) reported more toxic effects from glyphosate plus adjuvant than from glyphosate alone.

Ecosystem health effects

Effects of glyphosate and its various formulations have been studied in a number of organisms present in the larger ecosystem. These include invertebrates, specifically, earthworms; insects; and marine crustaceans. They also include a variety of fish as well as non-human mammals.

Findings from more recent studies are summarized below.

1. Earthworms: A frequently cited advantage of using herbicides such as glyphosate in farming is that their use decreases soil tillage and, with less tillage, earthworm populations will increase. A review study reported by Broines and Schmidt (2017) analyzes data gathered over approximately 65 years to support this claim. Implicit in this finding, however, is that herbicides such as glyphosate would not adversely affect the earthworm populations that have a critical role in maintaining soil health. However, a number of reports suggest that glyphosate does affect earthworms. Findings include avoidance (Verrell and Van Buskirk 2004), bioaccumulation (Contardo-Jara et al. 2009), a decrease in interaction between an earthworm species and mycorrhizal fungi (both essential components of healthy soil; Zailer et al. 2014), changes in burrowing/tunneling behavior (Gaupp-Berghausen et al. 2015; Domínguez et al. 2016), and reproductive capacity (Domínguez et al. 2016). With respect to avoidance, a more recent study did not detect avoidance behavior among earthworms exposed to recommended application doses of glyphosate (Santos et al. 2012).
2. Insects and arthropods: The effects of glyphosate on a number of insect species have been reported in the scientific literature. This includes reports of effects on species of mosquitoes (Morris et al. 2016), aphids (Saska et al. 2016), honeybees (Sol Balbuena et al. 2016; Herbert et al. 2014), and varieties of beetles, including a species that was introduced to control plant predators in sub-tropical environments (Mirande et al. 2010). Herbert et al. (2014) report that glyphosate affects the flight pattern and homing time of honey bees, as well as appetite and foraging behavior. In contrast, Thompson and coworkers (Thompson et al. 2014) report no effect of glyphosate on honeybee brood development.

The effects of glyphosate on arthropod predators that are important for biological control of agricultural pests were reported by two groups. Benamú et al. (2010) reported negative outcomes for prey consumption, web building, fertility, and development of progeny among *Alpaida veniliae*, an orb web weaver spider. Evans et al. (2010) reported behavioral changes in the wolf spider, *Pardosa milvina*, changes that could affect the species' predatory behavior and might have an impact on biological control.

3. Marine animals (fish and amphibians): Recognizing that glyphosate can enter waterways through run-off or from soil dusts, and that very small amounts may also enter the water table, a number of investigators have examined the effects of glyphosate on marine animals and amphibians. Many of these studies have looked at effects on marine

organisms or amphibians at doses related to the LC_{50} (mean lethal concentration) and have used glyphosate alone and glyphosate as part of a herbicide preparation. They have also looked at a variety of marine and amphibian species. These studies, while demonstrating toxicity to marine animals, used concentrations that are unlikely to be found in waterways. Hence, findings, while valuable, may not provide comprehensive information about the present long-term effects of glyphosate in the ecosystem and may not reflect anticipated environmental exposure.

4. Potential effects on farm animals: Glyphosate is widely used in commercial corn and soybean production, two important components of livestock feed. A USDA report notes that glyphosate represented 50% of all herbicides used per acre of planted farmland for a group of 21 crops and 85% of all herbicides used in soybean growth in 2008 (Fernandez-Cornejo et al. 2014). In 2011, the USDA reported glyphosate residues of 1.9 ppm in 90.3% of soybean samples analyzed; however, in 2016, the USDA excluded soybean testing (US Right to Know 2016). Glyphosate use in corn production was somewhat less. Given this use, concerns have been expressed that glyphosate may be found in animal feed, which might, in turn, affect farm animals or milk production. Krüger et al. (2014) report that cattle from eight different Danish dairy farms excreted glyphosate. Several biological markers of cell damage were elevated. In contrast, Donkin and coworkers (Donkin et al. 2003) found no differences in fat-corrected milk production or milk composition among cows fed a diet containing Roundup Ready™ corn product or corn product from conventional corn.

Carcinogenicity

The possibility that long-term exposure to glyphosate alone or in formulations might lead to the development of cancer has been investigated for some time. A large number of controlled exposure animal studies, human epidemiology studies, and in vitro investigations have been conducted, from the early 1990s until the present time. Study findings together with information about glyphosate's environmental presence have been used to assess the basis for regulation by a number of local, national, and international agencies. Most regulation is based on risk assessment, although the focus of other organizations has been on hazard identification.

When glyphosate was first introduced as a herbicide, many regulatory agencies assessing health risk to the general population or to farm/orchard and other field workers concluded that, as used, glyphosate was not a carcinogen and posed little other health risk. Its increased use and greater environmental use over time led to a reassessment of hazards, including carcinogenicity. Tables 1 and 2 provide a summary of up-to-date classifications and regulatory actions, locally, nationally, and internationally.

Controversies about carcinogenicity: IARC and the agrichemical community

In 1994, glyphosate was given a low priority for carcinogenic evaluation by IARC (Viano et al. 1994). However, with ensuing developments, this concern was revisited. In 2014, IARC convened a meeting of 21 scientific advisors representing 13 countries, to prioritize chemicals or groups of chemicals identified through a call for nominations. Organophosphate pesticides/herbicides were listed among a group given moderate or high priority for assessment of health hazard (IARC monographs on the evaluation of the carcinogenic risks to humans 2014; Straif et al. 2014). In selecting this group of compounds, IARC considered new findings, especially those of cancer epidemiology and mechanisms that had been published since prior considerations. As noted in the Guyton article, consideration was also given to addressing cancer incidence in low- and medium-income countries.

Prior to IARC's hazard assessment, a series of review articles, in part commissioned by Monsanto, were published in the peer-reviewed literature. As well as Monsanto-associated contributors, representatives from other chemical industries, members of the Glyphosate Task Force (a consortium of some 20 industrial organizations working together to renew the EU glyphosate registration), academicians, and private consultants participated in the series. As a whole, the articles critiqued studies that were expected to be considered by IARC.

Included in the series were the following articles:

- A critical analysis of animal carcinogenicity studies (Griem et al. Greim et al. 2015)
- A critical analysis of data evaluating genotoxicity to humans exposed to glyphosate (Kier 2015).
- An evaluation of several unpublished animal studies looking at the potential of glyphosate exposure to result in developmental cardiovascular toxicity. (Kimmel et al. 2013)
- A critique of studies looking at glyphosate as a genotoxic agent (Kier and Kirkland 2013)

While each article focuses on a different aspect of glyphosate assessment (genotoxicity, animal studies, developmental toxicity), taken together, the overall conclusion of the reviews was that glyphosate does not present significant genotoxic risks to human populations, nor do animal studies support a finding that it has carcinogenic potential in humans. Analyses in the reviews covered not only articles published in the peer-reviewed literature but also other analyses considered proprietary in nature, not available in open literature. These analyses

provided in the review article and its supplement was insufficient"(IARC monographs on the evaluation of the carcinogenic risks to humans 2017).

One controlled exposure animal study (Séralini et al. 2012), published prior to the IARC meeting, warrants attention. The article, which underwent peer review prior to publication, examined and compared the effects over a 24-month period on Sprague Dawley rats fed a diet of GM corn, treated or not treated with Roundup™, rats given water containing Roundup™, and control rats. Reported as a chronic health study, findings were that all treated groups had significantly greater numbers of tumors than control groups. Shortly after it was published, a number of criticisms appeared, coming both from the scientific community and from lay publications. In 2013, Elsevier, the publisher of Food and Chemistry Toxicology, retracted the article (Elsevier 2013) noting that "Ultimately, the results presented (while not incorrect) are inconclusive, and therefore do not reach the threshold of publication for Food and Chemical Toxicology." In its retraction notice, Elsevier provided comments from a large number of authorities, both supporting retraction and supporting the publication. It is noteworthy that while many lay press publications called for retraction, others did not. Ultimately, the Seralini study was re-published in Environmental Sciences Europe (Seralini, et al., Séralini et al. 2014). While cited in the glyphosate monograph, IARC did not consider the later Séralini publication in its consideration of glyphosate, noting that "The Working Group concluded that this study conducted on a glyphosate-based formulation was inadequate for evaluation."

3. Other findings. In addition to epidemiologic and animal studies, the IARC monograph noted studies that described glyphosate metabolites in blood of exposed individuals (Guyton et al. 2015) as well as several findings of genotoxicity, including those seen in residents of areas subject to aerial spraying (Bolognesi et al. 2009)

Response to IARC classification

Response within the scientific and regulatory community Not surprisingly, reaction to the IARC assessment was strong and controversial. The agrichemical industry, facing potential economic challenges as well as litigation, attacked the assessment, and, by extension, US government funding for IARC. IARC and a large number of experts, in turn, responded, pointing out the IARC mission, as well as the strength of the working group observations and its conclusions. Other authorities have responded with an analysis of differences between IARC's approach and analyses by other expert panels, used as risk assessment for regulatory purposes.

1. Industry response in the peer-reviewed literature: Significant response came through Monsanto. Following publication of the IARC monograph, a series of five review articles were published in a supplemental edition of Critical Reviews in Toxicology. The foreword to the review articles notes that [following release of the IARC monograph] "the Monsanto Company engaged Intertek, a scientific and regulatory consulting firm, to convene an independent scientific panel to evaluate and synthesize the scientific evidence of the potential carcinogenic hazard of glyphosate. The activities and conclusions of the independent panel are reported in the five papers in this special issue. Each of the five papers was rigorously reviewed by 5–10 independent reviewers selected by the CRT Editor and anonymous to the authors. A total of 27 different reviewers participated with several of the individuals reviewing all five papers. The authors of each paper were provided the review comments on their paper and asked to make appropriate revisions. The final papers, published here, represented the work product of the authors. Each paper includes an Acknowledgements section and an extensive Declaration of Interest section." (McClellan 2016)

Included in the publication were the following papers:

- "A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment" (Williams et al. 2016a)
- "Glyphosate in the general population and in applicators: a critical review of studies on exposures" (Solomon 2016)
- "Glyphosate epidemiology expert panel review: a weight of evidence systematicreview of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma" (Acquavella et al. 2016)
- "Glyphosate rodent carcinogenicity bioassay expert panel review"(Williams et al. 2016b)
- "Genotoxicity expert panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid" (Brusick et al. 2016)

The first article in the series (Williams et al. 2016a) summarizes the findings of those participating in the commissioned examination of the IARC review as follows:

> The International Agency for Research on Cancer (IARC) published a monograph in 2015 concluding that glyphosate is "probably carcinogenic to humans" (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals. It was also concluded that there was strong evidence of

genotoxicity and oxidative stress. Four expert panels have been convened for the purpose of conducting a detailed critique of the evidence in light of IARC's assessment and to review all relevant information pertaining to glyphosate exposure, animal carcinogenicity, genotoxicity, and epidemiologic studies. Two of the panels (animal bioassay and genetic toxicology) also provided a critique of the IARC position with respect to conclusions made in these areas. The incidences of neoplasms in the animal bioassays were found not to be associated with glyphosate exposure on the basis that they lacked statistical strength, were inconsistent across studies, lacked dose-response relationships, were not associated with preneoplasia, and/or were not plausible from a mechanistic perspective. The overall weight of evidence from the genetic toxicology data supports a conclusion that glyphosate (including glyphosate-based formulations and aminomethylphosphonic acid) does not pose a genotoxic hazard and, therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen. The assessment of the epidemiological data found that the data do not support a causal relationship between glyphosate exposure and non-Hodgkin's lymphoma while the data were judged to be too sparse to assess a potential relationship between glyphosate exposure and multiple myeloma. As a result, following the review of the totality of the evidence, the panels concluded that the data do not support IARC's conclusion that glyphosate is a "probable human carcinogen" and, consistent with previous regulatory assessments, further concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.

2. IARC reply to critique: IARC's initial response to critiques published in the Critical Reviews in Toxicology articles and other comments that questioned the hazard classification, cited its mission, namely that the agency's focus is on assessing cancer hazards, identifying agents capable of causing cancer under some circumstances, rather than risk assessment. It noted that judgments are qualitative, based on an evaluation of available scientific data in "openly available scientific literature," as well as literature accepted for publication, and openly available government documents. IARC further noted that its focus on qualitative evaluation of data rather than assessment of risk to be an important distinction, since something might presently pose a low hazard, but this hazard might change with "new uses or unforeseen exposures" (IARC, 2006). IARC further noted that decisions of policy or regulation, as well as legislation, are the responsibility of individual agencies and governments.

In January, 2018, IARC issued a more detailed response addressing several specific points that developed after publication of its original hazard classification (IARC 2018). In the introduction to this response, IARC noted the following:

> Since the evaluation of glyphosate by the IARC Monographs Program in March 2015, the Agency has been subject to unprecedented, coordinated efforts to undermine the evaluation, the program and the organization. These efforts have deliberately and *repeatedly misrepresented the Agency's work. The attacks have largely originated from* the agro-chemical industry and associated media outlets. They have taken place in the context of major financial interests relating to: a) the relicensing of glyphosate by the European Commission; b) hundreds of litigation cases in the USA brought by cancer patients against Monsanto, claiming that their malignancies were caused by glyphosate use; c) and the decision by the Californian Environmental Protection Agency to label glyphosate as a carcinogen." (California Office of Environmental Health Hazard Assessment 2017)

The response also clarified several points, including the following:

- IARC did not edit parts of the glyphosate monograph to achieve a particular outcome
- Data from the Agricultural Health Study (AHS) [long-term prospective cohort study] were not deliberately excluded from the Monograph
- IARC Monograph evaluations are transparent and open to scrutiny
- IARC has a strong rationale for inclusion of only publicly available studies in Monograph evaluations
- Monograph Working Group members who evaluated glyphosate were free from conflict of interests; this included a discussion regarding the role of an invited specialist who, while invited, was not a member of the IARC working group.
- IARC evaluates only agents that have some evidence of carcinogenicity; however, of those evaluated, roughly half are found not to present evidence of carcinogenicity; 12% have been classified as human carcinogens; and the remaining have been classified as category 2A (probable) or category 2B (possible) carcinogens.
- The monographs program re-evaluates an agent when a substantial additional body of scientific evidence becomes available
- The monograph evaluations place agents in groups according to the strength of evidence of carcinogenicity, not their potency
- IARC monographs identify carcinogenic hazards and do not include a risk assessment

- IARC evaluations make use of the latest scientific data and methodologies
- The monographs do not exclude research conducted by industry per se. Where industry conducted studies are published in scientific journals they are considered, if available in sufficient detail to allow independent scientific review. Under the same conditions, the monographs also take account of industry-conducted research in summary form or if placed in the public domain by national regulatory agencies.

IARC also noted monograph appraisals take account of "real-world" exposures by evaluation of epidemiological studies. These studies are a central part of monograph evaluations and by definition deal with people exposed in daily life, including work. In addition, when considering scientific evidence of carcinogenicity including biological mechanisms, the Working Groups place special emphasis on whether the observations are relevant to humans.

3. Response from other sources: Articles and presentations from other scientists and regulators considering differences in the IARC evaluation and risk assessments from other regulatory agencies have generally taken a more conciliatory approach, either in detailing differences or by raising questions about approach or conclusions. In the National Toxicology Program (NTP) minutes of June 15–16, 2016, as well as a later presentation (National Toxicology Program 2016; Smith-Roe 2016), it was noted that while IARC evaluated glyphosate as a cancer hazard, evaluations of Joint World Health Organization and Food and Agricultural Organization (JMPR), the European Food Safety Authority (EFSA), and the US Environmental Protection Agency (EPA) are comprehensive risk assessments. One member of the JMPR expert panel evaluating glyphosate, comparing the IARC and JMPR assessments, concluded the following: (1) that the carcinogenicity and/or genotoxicity of glyphosate is heavily dependent upon available information, evaluation criteria, and the weighting system used in evaluating the information available; (2) IARC and JMPR had access to different data (publically available vs. published and unpublished studies, respectively), and conclusions reached by both reflect this access and are consistent with criteria used to classify carcinogens; and (3) the JMPR conclusions reflect both data access and the focus on dietary exposures to glyphosate and glyphosate residues (Eastmond 2016).

An evaluation by the EFSA considering a Renewal Assessment Report for glyphosate concluded that "there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma, overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies"(EFSA, 2015). In response to this conclusion, a group of 97 environmental health specialists, toxicologists, epidemiologists, and cancer researchers representing an array of international organizations developed a response commentary (Portier et al. 2017) pointing out not only the differences in the EFSA statement regarding "unequivocal evidence," but also differences, and, as assessed by the authors, weaknesses in the EFSA use of animal and other studies not available to IARC in its deliberations. The authors noted that the EFSA statement was misleading because IARC did not indicate causality between glyphosate and cancer but used the criteria of sufficient evidence, which the IARC working group and others find to be credible. The commentary authors also questioned the way in which the EFSA used data from unpublished studies (hence not available to IARC) to conclude that animal study findings were essentially negative. In 2017, the lead author of the commentary, Christopher Portier, wrote an open letter to Jean Claude Juncker President of European Commission. The letter raised several issues regarding the EFSA and European Chemical Association's evaluation of glyphosate (Portier CJ, Portier 2017).[2] The executive summary of the letter states the following:

> The European Food Safety Agency IEFSA) and the European Chemical Agency IEChA) have completed their assessments of the carcinogenic potential of glyphosate and concluded that the evidence does not support a classification for glyphosate. The raw data for the animal cancer studies for glyphosate have been released, and a reanalysis of these data show eight instances where significant increases in tumor response following glyphosate exposure were not included in the assessment by either EFSA or EChA. This suggests that the evaluations applied to the glyphosate data are scientifically flawed, and any decisions derived from these evaluations will fail to protect public health. I ask that the evaluations by both EFSA and EChA be repeated for all toxicological endpoints and the data underlying these evaluations be publicly released.

[2] Dr. Portier, now a consulting scientist, was formerly director or associate director of several US environmental agencies and, while not participating as a member of the expert panel in the IARC evaluation of glyphosate, did attend the meeting. In his present consulting role, he has been an expert witness for a US law firm involved in glyphosate litigation. Although at the time he attended the IARC meeting, he was not involved in glyphosate litigation, according to a letter from Reps. Lamar Alexander (R-Tex), Andy Biggs (R-AZ), and Frank Lucas (R-OK) (Smith et al. 2017) to Dr. Christopher Wild, IARC Director, Dr. Portier became involved in glyphosate litigation 9 days after the IARC assessment was announced. A publication by Corporate Europe Observatory (Corporate Europe Observatory 2017) defends Dr. Portier's work, noting that he did not sign a contract until 29 days following the IARC meeting, and that more than 90% of his work as an expert witness was "performed and billed" in 2017.

Lay press discussions

At the time it was announced, the IARC designation was given extensive coverage by the lay press and various advocacy organizations. This attention continues.

A number of publications or news services have looked into questions regarding the role that Monsanto may have played in undermining the IARC designation. Others have questioned the integrity of the IARC working group deliberations. The Huffington Post has published a number of articles supporting concerns about glyphosate carcinogenicity and raising questions and issues specifically related to glyphosate and Monsanto. In contrast, the news agency Reuters has published several articles that are in opposition to the IARC finding, and that suggest IARC's evaluations lacked transparency, suggesting that "a draft of a key section of IARC's assessment of glyphosate underwent significant changes before the report was made public" and that "the chairman of the IARC glyphosate panel [not identified] was aware of new data showing no link between the weed-killer and cancer in humans, but the agency did not take it into account because it had not been published." (Kelland 2017).

Both Bloomberg News (Waldman et al. 2017) and the New York Times (Hakim 2017) reported that in 2017, San Francisco federal Judge Vince Chhabria, during litigation proceedings, ordered that internal Monsanto documents be unsealed. Material in the unsealed documents included communications suggesting that Monsanto had ghostwritten research later attributed to academics.

The disclosures highlighted concerns that the academic research Monsanto underwrites and that it frequently cites to back up its safety claims is compromised. As noted earlier, Monsanto, in response to IARC's designation of glyphosate as a category 2A carcinogen, hired a consulting company to identify experts to write articles that were ultimately published in Critical Reviews in Toxicology. When these were published, it was noted that "Neither any Monsanto company employees nor any attorneys reviewed any of the Expert Panel's manuscripts prior to submission to the journal."(McClellan 2016). However, unsealed documents suggest that Monsanto scientists were heavily involved in organizing, reviewing, and editing drafts submitted by the outside experts. A spokeswoman from Taylor & Francis, publisher of Critical Reviews in Toxicology, noted that an investigation is underway. In October 2017, scientists at the Center for Biological Diversity, Center for Food Safety, Pesticide Action Network and Center for Environmental Health, called for retraction of one of the reviews in the series. The group noted that "These are serious offenses and if left unanswered will ultimately undermine the work of many scientists who view scientific ethics to be sacrosanct"(Center for Biological Diversity 2017).

Litigation

IARC's designation of glyphosate as a category 2A carcinogen has been followed by an increase in lawsuits by plaintiffs who have been exposed to glyphosate and who have developed NHL seeking redress. It is difficult, in the US alone, to determine the number of lawsuits. Attorneys for plaintiffs estimate that approximately 4000 lawsuits have been filed (US Right to Know 2017) although verification is challenging.

Interestingly, the conflict between possibility and probability may play a major role in determining the outcome of many lawsuits. Recently, Judge Vince Chhabria, presiding in federal court in San Francisco, assessing whether the plaintiff's arguments demonstrate an exposure-effect relationship was quoted as saying "I do have a difficult time understanding how an epidemiologist in the face of all the evidence that we saw and heard last week" can conclude that glyphosate "is in fact causing" non-Hodgkin lymphoma in human beings. "The evidence that glyphosate is currently causing NHL in human beings" at current exposure levels is "pretty sparse." (Rosenblatt 2018)

While significant litigation involves lawsuits against Monsanto, other litigation does not. In February 2018, a federal judge ruled against cancer warnings on food that may contain trace amounts of glyphosate. The suit against the state of California was brought by major agricultural producers in California (Polansek 2017).

US government response

The IARC assessment of glyphosate as a category 2A carcinogen has been a subject of on-going activity by the congressional House committee on Science, Space, and Technology. In 2017, two senior committee members sent letters to both Christopher Wild, head of IARC and to Acting Secretary of Health and Human Services (HHS) Eric Hargan regarding what the writers regarded as conflicts of interest, the lack of transparency in the IARC deliberations, and statement about funding and the use of US taxpayer funding of IARC work (Committee on Science, Space, and Technology 2017). These same issues were revisited at a February 6, 2018 hearing of the full committee on Science, Space, and Technology. In his opening remarks, the committee chair, citing food security issues as well as "selective use of data and lack of public disclosure" suggested support for withholding US government funding for IARC work in the future (Committee on Science, Space and Technology 2018). A committee member of the minority party, in opening statements, while supporting the importance of innovation by the chemical industry, outlined concerns about industrial pressure on government agencies that may compromise free and open discussion of work evaluating the potential health hazards of glyphosate.

While it can be expected that the debates and controversies regarding glyphosate will continue, to date, no legislation related to US government funding for IARC or WHO has been enacted.

Environmental justice: agricultural workers and glyphosate

It would be difficult to discuss health and safety questions regarding glyphosate without considering environmental justice. No single definition exists for the term environmental justice; however, for purposes of this discussion, environmental justice is characterized by Berkey (2017a) as a productive definition. Specifically, it is defined as "A form of justice based on addressing the political-economic structures that produce environmental problems, aimed at creating a system within which we focus on causes rather than symptoms. Emphasizes participation in the decisions through which environmental burdens are produced. Characterized by a movement from 'not in my backyard' to a 'not in anyone's backyard' political frame". The EPA further characterizes the term in the following legal definition:

> [Environmental Justice is} [T]he fair treatment and meaningful involvement of all people regardless of race, ethnicity, income, national origin, or educational level with respect to the development, implementation and enforcement of environmental laws, regulations and policies. Fair treatment means that no population, due to policy or economic disempowerment, is forced to bear a disproportionate burden of the negative human health or environmental impacts of pollution or other environmental consequences resulting from industrial, municipal, and commercial operations or the execution of federal, state, local, and tribal programs and policies (United States Environmental Protection Agency 2017).

Within this context, it is important to consider whether acute and chronic health effects of glyphosate on farmworkers has been addressed. To date, information has been relatively limited and confined to workers who have steady employment in the farming sector. This includes a study monitoring urinary excretion of glyphosate or AMPA among glyphosate applicators and their family members (Acquavella et al. 2004) that found little glyphosate in urine after a 48-h period, although somewhat more was excreted among workers who wore less protective gear. The Agricultural Health Study considered by IARC as an epidemiologic study of cancer development from glyphosate exposure studied cancers in a cohort of glyphosate application workers, generally long-term farmworkers who, when applying glyphosate, wore protective gear (De Roos, De Roos et al. 2005). This study did not find a statistical association between cancers and glyphosate exposure, although the study was sufficiently short that it might not be adequate to address latency in cancer development. Several case-control studies that did report a stronger association were considered well executed; however, case-control studies may be subject to selection bias.

Missing in almost all investigations is information about acute or chronic toxicity among a very large group of farmworkers, namely, seasonal or migratory farm and agricultural workers. Agricultural workers (including landscape workers) are, most likely, those most exposed on a continual basis, coming into continual contact with glyphosate, often together with a number of other herbicides and pesticides. This contact is frequently without adequate protection. Rao et al. (2004) point out that farmers believe that, since they most often mix and apply pesticides, they, not farmworkers, are most at risk for any negative health outcomes from this exposure [Rao et al. 2004]. Farmers believe that workers, because they do not mix and apply pesticides or herbicides or enter fields immediately after application, are not vulnerable. That is, residues were not seen as a source of exposure. However, despite regulatory requirements, farmworkers were frequently not given adequate information, nor were they fully aware of how they might be better protected (Rao et al. 2004).

However, as noted by Flocks (Flocks 2012)

> Farmworkers are exempt from many regulations that could afford indirect protection under the system of agricultural `exceptionalism,' which emerged during a historical time in the US when institutional discrimination was accepted and prevalent. Even when protective regulation does exist, however, many employers use a variety of practices-such as hiring labor contractors or a temporary workforce-that allow them to circumvent laws and transfer many of the physical and economic risks of agricultural employment to the workers.

While the USA is not representative of farm worker practices on a global basis, policies in the USA are an effective representation of practices in developed nations. Hence, an examination of issues in the USA provides good insight into farm worker issues in developed countries. To date, little definitive information is available about glyphosate's effects on this group. Not only might such information provide greater power to studies looking at chronic effects of glyphosate in real-life exposure scenarios, but if strong links were found between exposure and outcomes, these should strengthen worker protection measures.

Arcury and coworkers (Acury, et al. Arcury et al. 2006) identify several factors that are challenges in collecting consistent information that could be used to ensure environmental

justice for seasonal and migratory farmworkers. Specific challenges include the following:

1. Number of farmworkers at risk. Many workers are seasonal, migratory or both. In the USA, roughly 42 of 50 states employ farmworkers fitting into one or both of these categories. The majority self-identify as Hispanic. The US Department of Labor's National Agricultural Workers Survey provides the following information: (Farmworker Justice 2014)

    - Roughly 48% of farmworkers lack authorization
    - Other sources consider this to be low, estimating that as much or more than 70% of workers may be undocumented
    - Translated to numbers, this means that 1.2 to 1.75 million farmworkers are undocumented
    - Of all farmworkers, roughly 33% are US citizens, 18% are lawful permanent residents, and 1% has work authorization

Given that present immigration policies are unlikely to provide accurate estimations, of undocumented workers, those with seasonal permits, those with residency status, or those who are legal immigrants, and that data cited above have been provided to a US government agency, the actual numbers are unlikely to provide an accurate and current description of farm and agricultural worker composition. Members of many groups may be hesitant to communicate with authorities.

2. Mobility. Documented and undocumented workers move frequently, both within farming season and between seasons.
3. Residence status. Those who are US citizens or permanent residents may, although mobile, be more likely to return to particular work areas and may be more secure to note disparities in health and safety conditions because of work security. Guest workers holding H2 visas are less mobile and, fearing the consequences of reporting, may not report health and safety disparities. Undocumented workers, fearing deportation, are highly unlikely to report adverse health outcomes.
4. Communication obstacles. In the USA, farmworkers speak a variety of languages other than English. Many have not received an education beyond the early secondary level, and some received even fewer years. While Spanish is the most commonly spoken language, many dialects are spoken. In some cases, language is a mixture of indigenous languages and Spanish. Although different in specifics, these same linguistic and obstacles can be found in other developed countries. A study of Kelley (Kelley et al. 2013) examining health care for female farmworkers found that few health clinic workers spoke a language other than English but depended on available translation services for communication.
5. Exposure assessment and bio-monitoring. Typical methods of exposure assessment require that workers donate blood or urine samples or both, that the samples can be properly stored, and that analytic facilities be available for analysis. Equipment limitations, reluctance on the part of workers to donate samples, and, at times, poor cooperation or coordination with local health agencies charged with obtaining samples are often obstacles.
6. Health outcomes: Monitoring short-term acute responses is limited by the availability of health care. Many workers are hesitant to seek health care (Berkey 2017b) because of fears about loss of work or other consequences. Facilities to diagnose and treat long-term chronic conditions are, quite likely, not available, and many health clinicians lack training in occupational health (Kelley et al. 2013). Data about chronic outcomes among workers are also very difficult if not impossible to obtain because of follow-up considerations.

While cancer is often the major focus of long-term effects, it is not the only long-term chronic health outcome. Little or no information is available about such long-term effects as endocrine disruption, pregnancy outcomes, neurotoxicity, or development in children who may be exposed "second hand" from clothing and equipment brought home by parents working in the field. Additionally, agricultural workers are rarely, if ever, exposed only to one herbicide or pesticide. This makes it challenging to attribute any health outcome to glyphosate exposure, and at the same time, it is difficult to predict the synergistic effects of glyphosate in combination with other commonly used pesticides and herbicides.

Addressing many of these issues requires the development of and intervention of advocacy groups. As noted by Reeves and Shafer (Reeves and Schafer 2003) "In many states farmworkers are denied the right to organize, receive no compensation for workplace injuries, and are not paid at a higher rate for overtime work. Farmworkers are specifically excluded from the right to organize under the National Labor Relations Act, which only some states, including California, have redressed by enacting Agricultural Labor Relations acts." Existing advocacy groups include groups such as the California Rural Legal Assistance Foundation, the Pesticide Action Network, and the United Farmworkers, which, although having a voice in California, does not universally have a voice. Despite these limitations, organizations such as the United Farm Workers have worked to address farmworker safety from glyphosate exposure. A letter dated May 08, 2017 from Arturo S. Rodriguez (Rodrigurez, Rodriguez 2017), president of the UFW to Esther Barajas-Ochoa of the

California Office of Environmental Health Hazard Assessment, states:

> On behalf of the United Farm Workers of America, we hereby request that a hearing be held regarding the proposed Safe Harbor for Monsanto's compliance with Proposition 65's required carcinogen warnings for Roundup. We are concerned that the No Significant Risk Level (NSRL) for this Safe Harbor does not take into account the dermal exposure experienced by farm workers. We would like to have a hearing to address appropriate analysis of other studies than the one identified in the Initial Statement of Reasons: Glyphosate Proposition 65 Safe Harbor, and especially to address California Code of Regulations § 25703's requirement that epidemiological data, i.e. human data, be included in the Safe Harbor's NSRL analysis. We believe studies that take into account what our member farm workers endure each day in fields sprayed with Roundup must be part of any Safe Harbor analysis.

The Rodriguez letter is a rare instance in which potential health and safety issues of one agricultural chemical are addressed, an opportunity possible because of California Proposition 65.[3] As noted, however, this is generally not the case. However, key challenges in protecting agricultural workers from potential adverse effects of agricultural chemicals can be identified and addressed. It is also possible to characterize the limitations of immediate health care and follow-up care. Addressing these issues would be a significant step to providing greater protections and addressing injustices.

As IARC notes in its mission statement, in determining the carcinogenic hazard of a substance, its role is to address the issue not only in developed countries but in less developed and developing countries. In such countries, for a variety of reasons, fewer protections may be available (Goldman and Tran 2001). In part, this is because pesticide and herbicide use is not part of traditional agricultural practices, and little training is available about safe use. Farmers are often unaware of the short- and long-term hazards associated with exposure to many pesticide and herbicide products, and they are often used inefficiently and unsafely. This may include excessive use, eating and drinking while working, lack of water and facilities for personal hygiene (often true in developed countries as well), lax storage practices, and careless disposal of empty containers. In addition, poor maintenance facilities for spray equipment can lead to hazardous contamination and use of pesticide mixtures. Occupational health legislation and regulations are often extremely weak in the developing countries. Most developing countries still do not require that imported pesticides be registered.

[3] In November 2017, a lawsuit was filed in California (National Association of Wheat Growers et al. v. Lauren Zeise, director of OEHHA, et al., US District Court, Eastern District of California), by several farm groups and Monsanto against the California Office of Environmental Health Hazard Assessment to halt labeling under Proposition 65. The suit claims that the requirement would mandate that foodstuffs made from crops grown with glyphosate be labeled, and that such a requirement is an undue burden. According to Scott Partridge, Monsanto Vice President of global strategy, "Such warnings would equate to compelled false speech, directly violate the First Amendment, and generate unwarranted public concern and confusion." (Polansek 2017)

Discussion and conclusion

Originally introduced in 1974 as the active ingredient in the herbicide Roundup™, glyphosate was considered to be a breakthrough because of its targeted toxicity to bacteria and plants, as well as its very low acute toxicity in humans and other mammals. It was initially used in farming before crops were sown, and following crop harvest, for weed control among fruit trees in orchards, in landscaping, and to remove weeds surrounding in track and power lines. However, its use grew dramatically following the introduction of genetically engineered Roundup-Ready™ seed by the Monsanto Chemical Company in the mid-1990s. It then became possible to use glyphosate during crop growth to minimize invasion of unwanted plants. Today, a variety of Round-Ready™ crops are grown. The use of both GM seed and glyphosate is global.

Available data suggest that the application of glyphosate has grown 200-fold in farming and 300-fold in non-agricultural practices in the USA over the period 1974 to 2014. Although it is possible to locate information about the number and variety of crops grown using from Round-Ready™ seed in developed countries such as the USA, accurate and up-to-date data are more difficult to obtain when looking at developing and less developed countries. Nevertheless, it is clear that global glyphosate use has also grown and spread significantly over this same time period. Interestingly, while not all growth can be attributed to the introduction of Roundup-Ready™ seed, it is quite likely that most can. Thus, while the Monsanto patent on glyphosate expired in the early 2000s, glyphosate continues to be produced not only by Monsanto, but also by a number of other companies, including several in China. Each may use slightly different formulations of the herbicide, formulations that are generally proprietary in nature.

Because of its low acute toxicity, its rapid breakdown, and the low toxicity of breakdown products, it was initially felt that there was little likelihood that glyphosate would persist in the environment. However, an accumulating body of evidence suggests that it can persist, spreading to the atmosphere attached to soil dusts, as run-off in lakes and streams, and, albeit in small quantities, into the water table. The spread has led to two concerns: the overall impact on ecosystems and potential toxicity to animals from long-term low-level exposures. The

expected continuing growth of glyphosate use can be expected to intensify these concerns.

Glyphosate targets a pathway unique to plants and microorganisms needed for growth. While, as initially used, targeted plants and microorganism "by-standers" cannot grow, both readily undergo mutational changes. The presence of glyphosate in microenvironments thus creates a selective pressure for resistant organisms. In soils, resistant microorganisms have been found to replace other strains. This can change soil composition and may result in less fertile and productive soils. While the precise outcome of these changes is difficult to predict, the increasing number of reports raises concerns. Among plants, the widespread use of glyphosate has also created a selective pressure for resistant weeds. In response to the latter, Monsanto now markets products containing both glyphosate and other herbicides. While each component of these herbicide mixtures may have relatively low toxicity, it is not clear what synergistic effects might result.

An accumulating body of evidence suggests that glyphosate is toxic to a number of animal species found in the environment. Although some studies, focusing on acute toxicity, may not be predictive of long-term outcomes, several studies looking at earthworms found glyphosate in smaller amounts had adverse effects. These may be of concern because of the essential role that earthworms play in maintaining healthy soils.

An equal concern is the potential of adverse human health effects from the continuing and growing use of glyphosate in agriculture. Over time, it is probable that significant and increasing numbers of the general public ingest glyphosate: it is quite likely that commercially processed soy and corn products will contain trace amounts of glyphosate, and it is also likely to be found in a variety of other farm products, especially produce from large-scale industrial farms. It may also, in trace amounts, be found in dairy products. Risk assessment determinations from several regulatory agencies, based on probable dietary intake, find that glyphosate poses no health concerns to the general public. These determinations may not, however, address health concerns for those exposed to larger amounts on a recurrent basis. In the USA and other developed countries, a significant number of those exposed to higher amounts are farm and landscape workers, whose work is seasonal and migratory. Such workers may be undocumented, may face language and literacy challenges, and frequently lack access to consistent health care with any follow-up. Few data are available for these groups.

In 2003, Reeves and Shafer (Reeves and Shaver, Reeves and Schafer 2003) describe an analysis by Pesticide Action Network, United Farmworkers of America, and California Rural Legal Assistance Foundation of government data from California government data on agricultural poisonings and enforcement of worker safety standards that found no evidence of glyphosate carcinogenicity. They note, however, that these data are limited by factors described above and may they not accurately reflect the realities of pesticide exposure, including glyphosate. Another similar study reports an association between cancer and environmental exposure (Avila-Vazquez, Avila-Vazquez et al. 2017). In both cases, the authors point out that more precise information is needed to determine whether or not associations exist.

When initially introduced, both the National Toxicology Program in the USA and IARC as an international agency did not view glyphosate as posing any long-term health threat. This issue has recently been revisited by both agencies. To date, NTP has not issued a final report. The 2016 finding of IARC that glyphosate is a probable carcinogen has been a contentious and polarizing issue. While some of the debates can be found in the peer-reviewed literature and could be regarded as deliberations within the scientific community, others are published in the lay press and have, at times, been accusatory in nature. Scientific integrity has also been questioned in several publications. Recent US congressional hearings, using arguments of food security, suggested that US funding should not be provided to IARC, given their "contested" finding which may "threaten" food security. Within the regulatory community, differences in access to data, and possible differences in use of data, depending on the source can have an impact on risk assessment. Myer and Hilbeck (Meyer and Hilbeck 2013) address this issue with respect to the European Food Safety Agency's risk assessment of glyphosate at that time, noting "critical double standards in acceptance and rigor of the evaluation of feeding studies submitted as proof of safety for regulatory approval to EFSA." The 2013 risk assessment had access both to unpublished data from chronic animal studies as well as articles from peer-reviewed literature; differences in the data may have led to differences in weight given in the final assessment.

Many believe that glyphosate is now ubiquitous in the environment. While it might be argued that given its low acute toxicity and controversies surrounding chronic health and environmental effects, this issue is not of paramount importance. However, the ubiquitous presence makes it challenging to carefully assess negative effects. It is also important to note that the global presence, because it is under corporate control of several agribusiness giants, means that, on a global basis, farmers face higher prices. As noted by Bratspies (2017), farmers now face higher prices (an increase of 143% for GE soy seed between 2000 and 2010). Profits from sales did not keep up with seed cost. As noted earlier, more glyphosate is needed to control weed growth, and, at the same time, more unwanted plants are glyphosate resistant, which has led to industry development of GM seed with resistance to glyphosate and other herbicides. While it may be premature to anticipate global spread of such seed and the use of a mixture of herbicides on the same global basis as glyphosate

use today, the possibility of such a development, the potential for overuse of such mixtures, and the likelihood of global circulation of products could lead to closure of what Faber (1993) describes as "the circle of poison."

It may be worthwhile as the debates about glyphosate continue to consider other so-called breakthroughs. A particularly compelling example is the discovery and development of antibiotics. When they were originally introduced, many believed that infectious disease would be a thing of the past. However, their "over-use" coupled with the ability of bacteria to develop resistance mutations has led, rather than to the eradication of infectious disease, to increasing challenges for infectious disease treatment. Although the pharmaceutical industry is able to develop new antibiotics, no "master strategy" exists. Judiciously used, antibiotics are a powerful tool. Improperly used, they have negative effects, not only on those potentially affected but on the ecosystem as a whole. By comparison, when introduced, few felt that glyphosate created a health hazard. This is now a significant question, and, at the same time, more and more plants are resistant, moving the agri-business community to develop herbicide mixtures that, taken together, may be more toxic.

Acknowledgements The author would like to thank Dr. Rebecca Berkey, Center of Community Service Northeastern University, Dr. Daniel Faber, Professor of Sociology and Director of the Northeastern Environmental Justice Research Collaborative, and Ms. Jennie Economos the Environmental Health Project Coordinator of the Farmworker Association of Florida for their valuable feedback and suggestions for this manuscript.

References

Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, Chapman P, Bleeke M (2004) Glyphosate biomonitoring for farmers and their families: results from the farm family exposure study. Environ Health Perspect 112(3):321–326

Acquavella J, Garabrant D, Marsh G, Sorahan T, Weed DL (2016) Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol 46(sup1):28–43. https://doi.org/10.1080/10408444.2016.1214681

African Centre for Biosafety (2015) Glyphosate in SA: risky pesticide at large and unregulated in our soil. https://acbio.org.za/wp-content/uploads/2015/02/Roundup-Environmental-impacts-SA.pdf

Albrecht L (2017) Debate over glyphosate rages in South Africa. Deutche Welle http://www.dw.com/en/debate-over-glyphosate-rages-in-south-africa/a-36880101

Araújo AS Monteiro RT Abarkeli RB (2003) Effect of glyphosate on the microbial activity of two Brazilian soils. Chemosphere 2003 52(5): 799–804

Arcury TA, Quandt SA, Barr DB, Hoppin JA, McCauley L, Grzywacz JG, Robson MG (2006) Farmworker exposure to pesticides: methodologic issues for the collection of comparable data. Environ Health Perspect 114:923–928. https://doi.org/10.1289/ehp.8531

Avila-Vazquez M, Maturano E, Etchegoyen A, Difilippo FS, Maclean B (2017) Association between cancer and environmental exposure to glyphosate. Int J Clin Med 8:73–85. https://doi.org/10.4236/ijcm.2017.82007

Battaglin WA, Meyer MT, Kuivila KM, Dietze JE (2014) Glyphosate and its degradation product AMPA occur frequently and widely in U.S. soils, surface water, groundwater, and precipitation. J Am Water Res Assn (JAWRA) 50(2):275–290. https://doi.org/10.1111/jawr.12159

Benamú MA, Schneider MI, Sánchez NE (2010) Effects of the herbicide glyphosate on biological attributes of *Alpaida veniliae* (Araneae, Araneidae), in laboratory. Chemosphere 78(7):871–876. https://doi.org/10.1016/j.chemosphere.2009.11.027

Benbrook CM (2016) Trends in glyphosate herbicide use in the United States and globally. Envir Sci Eur 28:3. https://doi.org/10.1186/s12302-016-0070-0

Berkey R (2017a) Environmental justice and farm labor. Taylor and Francis Group, Routledge, p 11

Berkey R (2017b) Environmental justice and farm labor. Taylor and Francis Group, Routledge, p 108

Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJ (2009) Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate. J Toxicol Environ Health A 72:986–997. https://doi.org/10.1080/15287390902929741

Bratspies R (2017) Owning all the seeds: consolidation and control in agbiotech. Environ Law 47:583–608

Broines MJI, Schmidt O (2017) Conventional tillage decreases the abundance and biomass of earthworms and alters their community structure in a global meta-analysis. Glob Chang Biol 23(10):4396–4419. https://doi.org/10.1111/gcb.13744

Brusick D, Aardema M, Kier L, Kirkland D, Williams G (2016) Genotoxicity expert panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. Crit Rev Toxicol 46(sup1):56–74. https://doi.org/10.1080/10408444.2016.1214680

California Office of Environmental Health Hazard Assessment (2017) Glyphosate listed effective July 7, 2017, as Known to the State of California to Cause Cancer https://oehha.ca.gov/proposition-65/crnr/glyphosate-listed-effective-july-7-2017-known-state-california-cause-cancer

Center for Biological Diversity (2017) Scientists to journal: retract pesticide review after revelations of Monsanto funding, influence. https://www.biologicaldiversity.org/news/press_releases/2017/pesticides-10-12-2017.php

Cerdiera AL, Gazziero LP, Matallo M, Duke S (2011) Agricultural impacts of glyphosate-resistant soybean cultivation in South America. J Agric Food Chem 59(11):5799–5807. https://doi.org/10.1021/jf102652y

Committee on Science, Space, and Technology (2017) SST committee investigates potential conflicts of interest at IARC on glyphosate. https://science.house.gov/news/press-releases/sst-committee-investigates-potential-conflicts-interest-iarc-glyphosate

Committee on Science, Space, and Technology (2018) Full committee hearing—in defense of scientific integrity: examining the IARC monograph programme and glyphosate review. https://science.house.gov/legislation/hearings/full-committee-hearing-defense-scientific-integrity-examining-iarc-monograph

Contardo-Jara V, Klingelmann E, Wiegand C (2009) Bioaccumulation of glyphosate and its formulation roundup ultra in Lumbriculus variegatus and its effects on biotransformation and antioxidant enzymes. Environ Pollut 157(1):57–63. https://doi.org/10.1016/j.envpol.2008.07.027

Corporate Europe Observatory (2017) Setting the record straight on false accusations: Dr. C. Portier's work on glyphosate and IARC. https://corporateeurope.org/food-and-agriculture/2017/10/setting-record-straight-false-accusations-dr-c-portier-work-glyphosate

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A (2003) Integrative assessment of multiple

pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 60(9):E11

De Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP, Alavanja MC (2005) Cancer incidence among glyphosate-exposed pesticide applicators in the agricultural health study. Environ Health Perspect 113:49–54. https://doi.org/10.1289/ehp.7340

Dill GM, Sammons RD, Feng PC, Kohn F, Kretzmer K, Mehrsheikh A, Bleeke M, Honegger JL, Farmer D, Wright D, Haupfear EA (2010) Glyphosate: discovery, development, applications, and properties. In: Nandula VK (ed) Glyphosate Resistance in Crops and Weeds: History, Development, and Management. Wiley, Hoboken ISBN 978-0-470-41031-8

Domínguez A, Brown GG, Sautter KD, Ribas de Oliveira CM, Carvalho de Vasconcelos E, Niva CC, MLC B, Bedano JC (2016) Toxicity of AMPA to the earthworm Eisenia andrea Bouché, 1972 in tropical artificial soil. Sci Rep 6:19731 https://www.nature.com/articles/srep19731.pdf. https://doi.org/10.1038/srep19731

Donkin SS, Velez JC, Totten AK, Stanisiewski EP, Hartnell GF (2003) Effects of feeding silage and grain from glyphosate-tolerant or insect-protected corn hybrids on feed intake, ruminal digestion, and milk production in dairy cattle. J Dairy Sci 86(5):1780–1788. https://doi.org/10.3168/jds.S0022-0302(03)73763-1

Duke SO (2017) The history and current status of glyphosate. Publications from USDA-ARS / UNL Faculty. 1766. http://digitalcommons.unl.edu/usdaarsfacpub/1766 https://doi.org/10.1002/ps.4652

Eastmond DA (2016) Glyphosate hazard and risk assessment: a comparison of the approaches of two international agencies. http://cbns.ucr.edu/faculty/EastmondToxForumglyphosatepresentation2.pdf

Elsevier (2013) 'Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize' by Gilles Eric Séralini et al. has been retracted by the Journal Food and Chemical Toxicology. https://www.elsevier.com/about/press-releases/research-and-journals/elsevier-announces-article-retraction-from-journal-food-and-chemical-toxicology

Eriksson M, Hardell L, Carlberg M, Akerman M (2008) Pesticide exposure as risk factor for non-hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer 123(7):1657–1663. https://doi.org/10.1002/ijc.23589

European Food Safety Authority (2015) Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA J 13(11):4302–4409. https://doi.org/10.2903/j.efsa.2015.4302

Evans SC, Shaw EM, Rypstra AL (2010) Exposure to a glyphosate-based herbicide affects agrobiont predatory arthropod behaviour and long-term survival. Ecotoxicology 19(7):1249–1257. https://doi.org/10.1007/s10646-010-0509-9

Faber D (1993) Environment under fire: imperialism and the ecological crisis in Central America. Monthly Review Press, New York, pp 83–116

Farmworker Justice (2014) Selected statistics on farmworkers. https://www.farmworkerjustice.org/sites/default/files/NAWS%20data%20factsht%201-13-15FINAL.pdf

Fernandez-Cornejo J Nehring R Osteen C Wechsler S Martin A Vialou A (2014) Pesticide use in U.S. agriculture: 21 selected crops, 1960-2008. EIB-124, U.S. Department of Agriculture, Economic Research Service, May 2014. https://www.ers.usda.gov/webdocs/publications/43854/46734_eib124.pdf

Fishel F Ferrell J MacDonald G Sellers B (2013) Herbicides: how toxic are they? University of Florida IFAS Extension http://edis.ifas.ufl.edu/pdffiles/PI/PI17000.pdf

Flocks JD (2012) The environmental and social injustice of farmworker pesticide exposure. 19 Geo J on Poverty Law Policy 255 http://scholarship.law.ufl.edu/facultypub/268

Gabowski P, Jayne T (2016) Analyzing trends in herbicide use in sub-saharan Africa. Department of Agricultural, Food, and Resource Economics and the Department of Economics, Michigan State University https://ageconsearch.umn.edu/bitstream/245909/2/IDWP142.pdf

Gaupp-Berghausen M, Hofer M, Rewald B, Zaller JG (2015) Glyphosate-based herbicides reduce the activity and reproduction of earthworms and lead to increased soil nutrient concentrations. Sci Rep 5:12886 https://www.nature.com/articles/srep12886.pdf. https://doi.org/10.1038/srep12886

Global Information, Inc (2013) Research report on global and China glyphosate industry, 2013–2017. https://www.giiresearch.com/report/cri273672-research-report-on-global-china-glyphosate.html

Goldman L Tran N (2001) The impact of toxic substances on the poor in developing countries. http://documents.worldbank.org/curated/en/707331468763840793/pdf/34661.pdf

Greim H, Saltmiras D, Mostert V, Strupp C (2015) Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Crit Rev Toxicol 45(3):185–208. https://doi.org/10.3109/10408444.2014.1003423

Guyton KZ, Loomis D, Grosse Y, El Ghissasi F, Benbrahim-Tallaa L, Guha N, Scoccianti C, Mattock H, Straif K (2015) Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazonon and glyphosate. Lancet Oncol 16(5):490–491. https://doi.org/10.1016/S1470-2045(15)70134-8

Hakim D (2017) Monsanto weed killer roundup faces new doubts on safety in unsealed documents. The New York Times. https://www.nytimes.com/2017/03/14/business/monsanto-roundup-safety-lawsuit.html

Heap I, Duke SO (2018) Overview of glyphosate-resistant weeds worldwide. Pest Manag Sci 74(5):1040–1049. https://doi.org/10.1002/ps.4760

Henderson AM, Gervais JA, Luukinen B, Buhl K Stone D (2010) Glyphosate technical fact sheet. National Pesticide Information Center, Oregon State University Extension Services http://npic.orst.edu/factsheets/archive/glyphotech.html

Herbert LT, Vázquez DE, Arenas A, Farina WM (2014) Effects of field-realistic doses of glyphosate on honeybee appetitive behavior. Exptl Biol 217:3457–3464. https://doi.org/10.1242/jeb.109520

IARC Director (2018) IARC response to criticisms of the monographs and the glyphosate evaluation. International Agency for Research on Cancer http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_response_to_criticisms_of_the_Monographs_and_the_glyphosate_evaluation.pdf

International Agency for Research on Cancer (2017) Some Organophosphate Insecticides and Herbicides. International Agency for Research on Cancer, Lyon, France http://monographs.iarc.fr/ENG/Monographs/vol112/mono112.pdf. p. 32

International Agency for Research on Cancer (2006) IARC monographs on the evaluation of carcinogenic risk to humans: preamble. World Health Organization International Agency for Research on Cancer, Lyons, France. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

International Agency for Research on Cancer (2017) Some organophosphate insecticides and herbicides. International Agency for Research on Cancer, Lyon, France. http://monographs.iarc.fr/ENG/Monographs/vol112/mono112.pdf. pp 321–399

Kelland K (2017) In glyphosate review, WHO cancer agency edited out 'non-carcinogenic' findings. Reuters: Health News, October 19, 2017 https://www.reuters.com/article/us-who-iarc-glyphosate-specialreport/in-glyphosate-review-who-cancer-agency-edited-out-non-carcinogenic-findings-idUSKBN1CO251

Kelley MA, Flocks JD, Economos J, McCauley LA (2013) Female farmworkers' health during pregnancy; health care providers' perspectives. Workplace Health Saf 61(7):308–313. https://doi.org/10.1177/216507991306100706

Kier LD (2015) Review of genotoxicity biomonitoring studies of glyphosate-based formulations. Crit Rev Toxicol 45(3):209–218. https://doi.org/10.3109/10408444.2015.1010194

Kier LD, Kirkland DJ (2013) Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol 43(4): 283–315. https://doi.org/10.3109/10408444.2013.770820

Kimmel GL Kimmel CA Williams AL DeSesso JM (2013) Evaluation of developmental toxicity studies of glyphosate with attention to cardiovascular development. Crit Rev Toxicol, 2013; 43(2): 79–95. https://doi.org/10.3109/10408444.2012.749834

Kremer RJ, Means NE (2009) Glyphosate and glyphosate-resistant crop interactions with rhizosphere microorganisms. Eur J Agron 31:153–161

Krüger M, Schledorn P, Schrödl W, Hoppe HW, Lutz W, Shehata AA (2014) Detection of glyphosate residues in animals and humans. J Environ Anal Toxicol 4:210. https://doi.org/10.4172/2161-0525.1000210

McClellan RO (2016) Evaluating the potential carcinogenic hazard of glyphosate. Crit Rev Toxicol 46(sup1):1–2. https://doi.org/10.1080/10408444.2016.1234117

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW (2001) Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomark Prev 10(11): 1155–1163

Mesnage R, Defarge N, Spiroux de Vendômois J, Séralini GE (2015) Potential toxic effects of glyphosate and its commercial formulations below regulatory limits. Food Chem Toxicol 84:33–153

Meyer H, Hilbeck A (2013) Rat feeding studies with genetically modified maize—a comparative evaluation of applied methods and risk assessment standards. Environ Sci Europe 25:33. https://doi.org/10.1186/2190-4715-25-33

Mirande L, Haramboure M, Smagghe G, Saret P, Schneider M (2010) Side-effects of glyphosate on the life parameters of Eriopis connexa (Coleoptera: Coccinelidae) in Argentina. Commun Agric Appl Biol Sci 75:367–372

Morris A, Murrell EG, Klein T, Boden BH (2016) Effect of two commercial herbicides on life history traits of a human disease vector, *Aedes aegypti*, in the laboratory setting. Ecotoxicology 25:863–870. https://doi.org/10.1007/s10646-016-1643-9

Mortensen DA, Egan JF, Maxwell BD, Ryan MR, Smith RG (2012) Navigating a critical juncture for sustainable weed management. Bioscience 62(1):75–84. https://doi.org/10.1525/bio.2012.62.1.12

National Toxicology Program (2016) Summary minutes NTP Board of Scientific Counselors June 15–16, 2016. https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2016/june/minutes201606_508.pdf. pp 11–12

Neumann G Kohls S Landsberg E Stock-Oliveira Souza K Yamada T Römheld V (2006) Relevance of glyphosate transfer to non-target plants via the rhizosphere. Z Pflanzenk Pflanzen 963–969

Newman MM, Hoilett N, Lorenz N, Dick RP, Liles MR, Ramsier C, Kloepper JW (2016) Glyphosate effects on soil rhizosphere-associated bacterial communities. Sci Total Environ 543(2016): 155–160

Polansek T (2017) Monsanto, U.S. farm groups sue California over glyphosate warnings. Reuters https://www.reuters.com/article/us-usa-pesticides-monsanto/monsanto-u-s-farm-groups-sue-california-over-glyphosate-warnings-idUSKBN1DF1LR

Portier CJ (2017) Open letter: Review of the Carcinogenicity of Glyphosate by EChA, EFSA and BfR. https://www.nrdc.org/sites/default/files/open-letter-from-dr-christopher-portier.pdf

Portier CJ, Armstrong BK, Baguley BC, Bauer X, Belyaev I et al (2017) Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). J Epidem Comm Health 70(8) http://jech.bmj.com/content/70/8/741

Rao P, Arcury TA, Quandt SA, Doran A (2004) North Carolina Growers' and extension agents' perceptions of Latino farmworker pesticide exposure. Human Organ Summer 63(2):151–161. https://doi.org/10.17730/humo.63.2.qdyhan8n1ngkf2rk

Reeves M, Schafer KS (2003) Greater risks, fewer rights: U.S. farmworkers and pesticides. Int J Occup Env Heal 9(1):30–39. https://doi.org/10.1179/107735203800328858

Rodriguez AS (2017) Public comment request for hearing on glyphosate. https://oehha.ca.gov/media/downloads/proposition-65//united_farm_workers.pdf

Rosenblatt J (2018) Monsanto judge says expert testimony against roundup is 'shaky'. Bloomberg. https://www.bloomberg.com/news/articles/2018-03-14/monsanto-judge-says-expert-testimony-against-roundup-is-shaky

Sanchís J Kantiani L Llorca M Rubio F Ginebreda A Fraile J Garrido T Farré M (2012) Determination of glyphosate in groundwater samples using an ultrasensitive immunoassay and confirmation by on-line solid-phase extraction followed by liquid chromatography coupled to tandem mass spectrometry. Anal Bioanal Chem 2012 402(7): 2335–2345 https://doi.org/10.1007/s00216-011-5541-y

Santos MJG, Ferriera MFL, Cachada A, Duarte AC, Sousa JP (2012) Pesticide application to agricultural fields: effects on the reproduction and avoidance behavior of Folsomia candida and Eisenia andrei. Ecotoxicology 21(8):2113–2122. https://doi.org/10.1007/s10646-012-0963-7

Saska P, Skuhrovec J, Lukáš J, Chi H, Tuan SJ, Honěk A (2016) Treatment by glyphosate-based herbicide alters life history parameters of the rose-grain aphid *Metopolophium dirhodum*. Sci Rep 6: 27801. https://doi.org/10.1038/srep27801

Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, Hennequin D, de Vendomois JS (2012) Long term toxicity of a roundup herbicide and a roundup-tolerant genetically modified maize. Food Chem Toxicol 50:4221–4231. https://doi.org/10.1016/j.fct.2012.08.005

Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, Hennequin D, de Vendômois JS (2014) Republished study: long-term toxicity of a roundup herbicide and a roundup-tolerant genetically modified maize. Environ Sci Eur 26(1):14. https://doi.org/10.1186/s12302-014-0014-5

Smith L Biggs A Lucas F (2017) Letter to Dr. Christopher wild congress of the United States house of representatives committee on science, space, and technology https://science.house.gov/sites/republicans.science.house.gov/files/documents/12.08.2017_SST-IARC.pdf

Smith-Roe S (2016) Glyphosate research scoping. National Toxicology Program, NTP Board of Scientific Counselors Meeting, June 15–16, 2016 https://usrtk.org/wp-content/uploads/2016/09/NTP-Glyphosate-presentation-2016-BOSC-glyphosate_508.pdf

Soil Association, (2016) The impact of glyphosate on soil health: the evidence to date. https://www.soilassociation.org/media/7202/glyphosate-and-soil-health-full-report.pdf

Sol Balbuena M, Tison L, Hahn M, Greggers U, Menzel R, Farina WM (2016) Effects of sublethal doses of glyphosate on honeybee navigation. J Exptl Biol 218:2799–2805. https://doi.org/10.1242/jeb.117291

Solomon KR (2016) Glyphosate in the general population and in applicators: a critical review of studies on exposures. Crit Rev Toxicol 46(sup1):21–27. https://doi.org/10.1080/10408444.2016.1214678

Straif K Loomis D Guyton K Grosse Y et al. (2014) Future priorities for the IARC monographs. The Lancet Oncology 15. www.thelancet.com/oncology Vol 15 June 2014; https://doi.org/10.1016/S1470-2045(14)70168-8

Thompson HM, Levine SL, Doering J, Norman S, Manson P, Sutton P, von Mérey G (2014) Evaluating exposure and potential effects on honeybee brood (Apis mellifera) development using glyphosate as

an example. Int Environ Assess Manag 10(3):463–470. https://doi.org/10.1002/ieam.1529

Transparency Market Research (2014) Glyphosate market for genetically modified and conventional crops—global industry analysis, size, share, growth, trends and forecast 2013–2019. https://www.transparencymarketresearch.com/glyphosate-market.html

U.S. Right to Know (2017) The Monsanto papers: roundup (glyphosate) cancer case key documents and analysis. https://usrtk.org/pesticides/mdl-monsanto-glyphosate-cancer-case-key-documents-analysis/

United States Environmental Protection Agency (1985) EPA reg #524–308: Roundup; glyphosate; pathology report on additional kidney sections. Document No. 004855. Washington (DC): Office of Pesticides and Toxic Substances, United States Environmental Protection Agency. http://www.ep.gov/pesticides/chemicalsearch/chemical/foia/cleared-reviews/reviews/03601-206.pdf

United States Environmental Protection Agency (1986) Glyphosate; EPA Registration No. 524–308; Roundup; additional histopathological evaluations of kidneys in the chronic feeding study of glyphosate in mice. Document No. 005590. Washington (DC): Office of Pesticides and Toxic Substances, United States Environmental Protection Agency" http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/cleared-reviews/ Glyphosate 83 reviews/103601/103601–211.pdf

United States Environmental Protection Agency (2017) EJ 2020 glossary. https://www.epa.gov/environmentaljustice/ej-2020-glossary

US Right to Know (2016) USDA avoids analyzing glyphosate residues on food annual reports. https://usrtk.org/pesticides/usda-avoids-analyzing-glyphosate-residues-on-food-for-annual-report/

Vereecken H (2005) Mobility and leaching of glyphosate: a review. Pest Manag Sci 61(12):1139–1151

Verrell P, Van Buskirk E (2004) As the worm turns: Eisenia tetida avoids soil contaminated by a glyphosate-based herbicide. Bull Environ Contam Toxicol 72:219–224

Viano H, Heseltine E, Wilbourn J (1994) Priorities for future IARC monographs on the evaluation of carcinogenic risks to humans. Environ Health Perspect 102(6–7):590–591

Waldman P Stecker T Rosenblatt J (2017) Monsanto was its own ghostwriter for some safety reviews. Academic papers vindicating its Roundup herbicide were written with the help of its employees. Bloomberg. https://www.bloomberg.com/businessweek

Williams GM, Aardema M, Acquavella J, Berry C, Brusick D, Burns MM, Camargo JLV et al (2016a) A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. Crit Rev Toxicol 46(sup1):3–20. https://doi.org/10.1080/10408444.2016.1214677

Williams GM, Berry C, Burns M, de Camargo JLV, Greim H (2016b) Glyphosate rodent carcinogenicity bioassay expert panel review. Crit Rev Toxicol 46(sup1):44–55. https://doi.org/10.1080/10408444.2016.1214679

Young B (2018) Managing weeds for the future. Corn and Soybean Digest http://www.cornandsoybeandigest.com/resistance-management/managing-weeds-future

Zailer JG Heigl F Reuss L Grabmaier A (2014) Glyphosate herbicide affects belowground interactions between earthworms and symbiotic mycorrhiza. Sci Rep 4 https://archive.org/stream/pubmed-PMC4087917/PMC4087917-srep05634#page/n5/mode/2up https://doi.org/10.1038/srep05634

Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO MEETING ON PESTICIDE RESIDUES

Geneva, 9–13 May 2016

SUMMARY REPORT

Issued 16 May 2016

Edited versions of these evaluations and general considerations will be published in the report of the May 2016 JMPR. They are reproduced here so that the information can be disseminated quickly. These drafts are subject to technical editing.

A Joint Meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization (WHO) Core Assessment Group on Pesticide Residues (JMPR) was held at WHO Headquarters, Geneva (Switzerland), from 9 to 13 May 2016. Diazinon, glyphosate and malathion were placed on the agenda by the JMPR Secretariat, based on the recommendation of the last session of JMPR to re-evaluate these compounds given the number of new studies that had become available since their last full assessments.

The following extracts of the results of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) are provided to make them accessible to interested parties at an early date.

More information on the work of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) is available at:

http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmpr/jmpr-rep/en/

http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/

1. *Evaluation of data for acceptable daily intake (ADI) and acute reference dose (ARfD) for humans*

1.1 Diazinon (22)

Diazinon is an insecticide with a wide range of insecticidal activity. Several epidemiological studies on cancer outcomes following occupational exposure to diazinon were available. The review of these studies provided no convincing evidence of a positive association between exposure to diazinon and non-Hodgkin lymphoma (NHL), but there was weak evidence of a positive association between leukaemia and exposure to diazinon and between lung cancer and exposure to diazinon from one large cohort study only. In studies submitted, diazinon was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. Overall, these studies provided no convincing evidence of genotoxic effects, and the Meeting concluded that diazinon was unlikely to be genotoxic. The Meeting concluded that diazinon is unlikely to pose a carcinogenic risk to humans from exposure through the diet. After considering all previously evaluated data and the new studies, the Meeting established an ADI of 0–0.003 mg/kg body weight, based on inhibition of acetylcholinesterase activity as the most sensitive end-point. The Meeting reaffirmed the ARfD of 0.03 mg/kg body weight established by the 2006 JMPR based on acute (neuro)toxicity in rats.

1.2 Glyphosate (158)

Glyphosate is a broad-spectrum systemic herbicide. Several epidemiological studies on cancer outcomes following occupational exposure to glyphosate were available. The evaluation of these studies focused on the occurrence of NHL. Overall, there is some evidence of a positive association between glyphosate exposure and risk of NHL from the case–control studies and the overall meta-analysis. However, it is notable that the only large cohort study of high quality found no evidence of an association at any exposure level. Glyphosate has been extensively tested for genotoxic effects using a variety of tests in a wide range of organisms. The overall weight of evidence indicates that administration of glyphosate and its formulation products at doses as high as 2000 mg/kg body weight by the oral route, the route most relevant to human dietary exposure, was not associated with genotoxic effects in an overwhelming majority of studies conducted in mammals, a model considered to be appropriate for assessing genotoxic risks to humans. The Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures. Several carcinogenicity studies in mice and rats are available. The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses. In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet. The Meeting reaffirmed the group ADI for the sum of glyphosate and its metabolites of 0–1 mg/kg body weight on the basis of effects on the salivary gland. The Meeting concluded that it was not necessary to establish an ARfD for glyphosate or its metabolites in view of its low acute toxicity.

1.3 Malathion (49)

Malathion is an insecticide used to control insects on agricultural crops and stored commodities and for vector control. Several epidemiological studies on cancer outcomes in relation to occupational exposure to malathion were available. Overall, there is some very weak evidence of a positive association between malathion exposure and NHL; however, it is notable that the only large cohort study of high quality found no evidence of an association at any exposure level. The evidence is suggestive of a positive association between occupational exposure to malathion and risk of aggressive prostate cancer; however, the evidence base is limited to the one large cohort study. The Meeting concluded that there is some evidence that malathion is carcinogenic in rats and mice. However, the formation of nasal adenomas was due to a local irritancy caused by prolonged exposure to high concentrations of malathion absorbed via inhaled food particles. Scenarios of prolonged, direct and excessive exposure of human nasal tissue to malathion or malathion metabolites following ingestion of residues is unlikely, and therefore these tumours would not occur in humans following exposure to malathion in the diet. Malathion has been extensively tested for genotoxicity, including studies in exposed workers. The Meeting noted that there are numerous reports that malathion can induce oxidative damage in cells, and these results suggest that the observed genotoxic effects occur secondary to the formation of reactive oxygen species, which will exhibit a threshold. Based on consideration of the results of animal bioassays, genotoxicity assays and epidemiological data, the Meeting concluded that malathion and its metabolites are unlikely to pose a carcinogenic risk to humans from exposure via the diet. The current Meeting reaffirmed the ADI of 0–0.3 mg/kg body weight. The margins of exposure between this ADI and the doses causing cancer in mice and rats are 5000-fold and 1200-fold, respectively. The current Meeting also reaffirmed the ARfD of 2 mg/kg body weight. The Meeting concluded that the metabolite malaoxon is approximately 30-fold more toxic than malathion. On this basis, a 30-fold potency factor should be applied to the residue levels for use in both the acute and chronic dietary exposure estimates for malaoxon, and these should be added to the dietary exposures for malathion and compared with the ARfD and ADI for malathion, respectively.

2. General considerations

2.1 General considerations on the evaluation of genotoxicity studies

A large number of genotoxicity studies were evaluated during the present meeting. These were identified through direct submission to JMPR, searches of the publicly available literature and requests to the International Agency for Research on Cancer (IARC) Monographs Secretariat and industry groups. The studies evaluated included unpublished (primarily guideline) studies submitted to support pesticide registration as well as peer-reviewed studies published in the scientific literature. The number, quality and relevance of studies differed widely for each chemical and necessitated that a somewhat different approach be used to evaluate each pesticide. As a general strategy, the studies were separated into categories based largely on phylogenetic relevance and significance of the genetic

relation to cancer outcomes. An additional study on prostate cancer, which was not included in the IARC Monographs, was also identified.

The pre-agreed evaluation process shown in Fig. 1 was used to (1) select compound/cancer site combinations to include in this evaluation; (2) screen papers for inclusion/exclusion in this evaluation (Tier 1 screening criteria); and (3) evaluate the information available for risk assessment. In this process, it was noted that there were stand-alone analyses for specific subtypes of non-Hodgkin lymphoma (NHL). The risk for subtypes of NHL was not evaluated separately, as there was insufficient evidence (too few studies or small numbers of cases); the risk for other haematopoietic and lymphoid tumours was also not evaluated separately, as the positive associations identified by IARC were for total NHL.

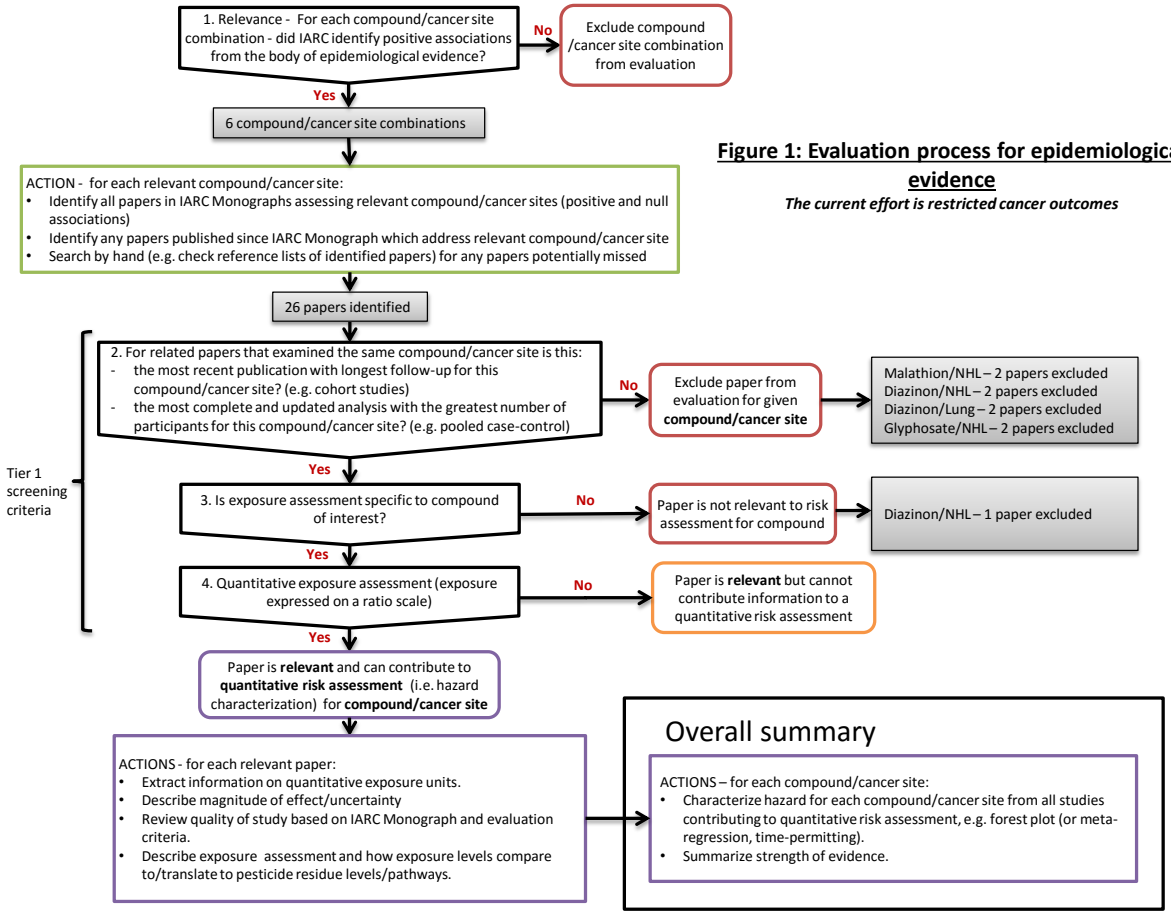


Figure 1: Evaluation process for epidemiological evidence

The current effort is restricted cancer outcomes

Evaluation of evidence for the compound/cancer site associations

Several aspects of each study and of all studies combined were considered in this evaluation, including factors that decrease the level of confidence in the body of evidence, such as risk of bias, unexplained inconsistency and imprecision; and factors that increase the level of confidence, such as large magnitude of effect, dose–response and consistency. The findings for each study were

end-point measured. The categories used were human biomonitoring, in vivo mammals, in vitro mammalian cells, in vitro bacteria, phylogenetically distant organisms, metabolites in vivo and metabolites in vitro. The evaluation was conducted for the pesticide active ingredient, its formulation products and prominent metabolites, as data were available. For the three pesticides evaluated, the human biomonitoring studies were most often confounded by exposures to other pesticides or considered to have other limitations. Among the genotoxicity studies, in vivo studies in mammals were given the greatest weight, compared with cell culture studies or investigations in phylogenetically distant organisms. Studies of gene mutations and chromosomal alterations were also given more weight than studies measuring other less serious or transient types of genotoxic damage. With regard to route of exposure, studies in which chemicals were administered by the oral route were considered to be of most relevance for evaluating low-level dietary exposures.

Following an evaluation and weighting of the studies, taking the criteria described above and the quality of the studies into account, an overall weight of evidence approach was used to reach conclusions about the genotoxicity of the individual pesticides. An important aspect of the evaluation was whether the genotoxic effect would be likely to occur in humans exposed to low levels of the pesticide present as residues in food.

The Meeting recommended that a guidance document be developed for the evaluation of genotoxicity studies, taking the experience gained from this meeting into account.

2.2 Methods for the evaluation of epidemiological evidence for risk assessment

Identification of compound/cancer sites and screening of papers

There is a large body of literature regarding pesticide exposures and non-cancer outcomes (neurodevelopmental, neurodegenerative and reproductive outcomes, among other health outcomes), but the assessment of the epidemiological evidence on diazinon, glyphosate and malathion was restricted to studies of cancer outcomes. This restriction was partly driven by feasibility reasons: a clinically relevant adverse effect size (or an acceptable level of risk) for a non-cancer outcome must be defined, and the methodologies for hazard identification and characterization based on observational epidemiological findings of non-carcinogenic adverse effects are less well established than those for cancer.

The IARC Monographs on malathion, diazinon and glyphosate referred to a total of 45 epidemiological studies. Databases were searched for any relevant articles published after the studies cited in these Monographs using the following search terms: [(diazinon OR glyphosate OR malathion) AND cancer] and [(diazinon OR glyphosate OR malathion) AND (NHL OR lymphoma OR leukemia OR “lung cancer” OR “prostate cancer”)] in PubMed (limited to Humans; published in the last 5 years) and Scopus (limited to 2014–2016). Two studies published since the publication of the IARC Monographs that evaluated at least one of malathion, diazinon or glyphosate were identified in

summarized in tables, and risk estimates for non-quantitative exposure assessment (predominantly ever versus never use) were summarized in forest plots.

Evaluation of information available for risk assessment/hazard characterization

To evaluate overall evidence for dose–response relationships, risk estimates were plotted against quantitative exposure measures (for studies that had used these). The most commonly used quantitative exposure metric was days of use per year. Where studies had used other quantitative exposure metrics (e.g. lifetime days of exposure), data were requested from the authors on median "days of use per year" for the participants in each of the original exposure categories, although this information was not always forthcoming. These additional data allowed the translation and plotting of risk estimates from different studies on the same exposure scale (days of use per year).

NC STATE EXTENSION

EPA Concludes Glyphosate Is Not Likely to Be Carcinogenic to Humans

— Written By N.C. Cooperative Extension

By Patrick Maxwell, M.S. and Travis Gannon, Ph.D.

In December 2017, the US Environmental Protection Agency (EPA) released the draft human health risk assessment for glyphosate, the active ingredient in Roundup. The human health assessment concluded that "glyphosate is not likely to be carcinogenic to humans" and found "no other meaningful risks to human health" when used in accordance with label instructions.

Findings from the human health assessment align with nearly every major regulatory body in the world including Canada , Europe , Germany and the United Nations ; however, the EPA conclusion contradicts the World Health Organization's International Agency for Research on Cancer (IARC), who classified glyphosate as a "Class 2A probable carcinogen to humans" in 2015. The IARC decision generated considerable attention and fueled concerns over human health risks associated with glyphosate use around the globe. Unlike other regulatory agencies, IARC disclosed little about its review process, making it difficult to determine how IARC arrived at its decision. Yet, as part of litigation proceedings, many IARC 'draft' documents surfaced and when

compared with the published reports, several critical edits were identified by Reuters and Forbes calling the legitimacy of the IARC classification into question.

By its own description, IARC is a hazard-based organization meaning they evaluate the possibility of something causing cancer and not the probability. Hence, IARC does not consider potential exposure levels, which is a drastically different approach compared to the EPA. Moreover, it's important to put the IARC grouping system into context. IARC classifies substances in five categories, based on the strength of evidence for their carcinogenicity. While the IARC system is valuable for its simplicity, it only conveys how strong the evidence is that a substance causes cancer and substances in the same group can vary widely in their propensity to increase the risk of developing cancer.

For obvious reasons, the human health assessment generated enormous attention; however, a second component (the ecological risk assessment and supporting documents) have not yet been released. Nevertheless, the EPA commented on the ecological assessment suggesting, "there is potential for effects on birds, mammals, and terrestrial and aquatic plants". While the updated 'draft' has yet to be released, the preliminary ecological risk assessment released in 2015 raised concerns, one of which was the uncertainty surrounding toxicity data for a class of surfactants (polyethoxylated tallow amines) used in select glyphosate formulations (e.g. Roundup). While it may seem inconsequential, the vast majority of toxicity studies used technical material (glyphosate alone) and not a commercial formulation. This creates a dilemma for the EPA as the bulk of toxicity data for glyphosate may not fully characterize the hazard end products (commercial formulations) may present.

In the digital age, the ability to search for and disseminate information has allowed society to connect on a scale once inconceivable. While few can argue the benefits the internet provides, it undoubtedly played a role in the negative public perception around pesticides and the IARC classification of glyphosate as a probable carcinogen is no exception. Today, an individual may encounter anti-pesticide articles based on faulty science and/or personal agendas disguised as a legitimate source that may lead them to form a negative sentiment towards the topic. Scientists can dispute false claims and publish peer-reviewed research, but the reality is that less of those articles will gain traction compared to flashy headlines, like "Glyphosate is Killing Your Child".

For years, glyphosate has generated contentious debate and although the EPA findings will not satisfy all sides, it illustrates the immense responsibility that falls on the agency. People are quick to criticize the agency, yet all the data they use to formulate their conclusions are grounded in science and publically accessible. Ultimately, the allegations leveled against IARC demonstrate the necessity for subjectivity and transparency in the regulatory decision-making process. Finally, EPA is scheduled to publish their proposed registration review decision for glyphosate in 2019 which will outline any proposed mitigation measures, if needed.

Updated on Feb 27, 2018

This page can also be accessed from:
go.ncsu.edu/readext?506902 Links to: http://go.ncsu.edu/readext?506902

Editorial

Conflicting views on the potential carcinogenicity of glyphosate: how did we get here and what should we do?

John M. DeSesso[1,2], Amy Lavin Williams[1], Richard Reiss[1]

[1]Exponent, Inc., Alexandria, Virginia, USA; [2]Georgetown University School of Medicine, Washington, DC, USA

Correspondence to: Dr. John M. DeSesso. 1800 Diagonal Road, Suite 500, Alexandria, VA 22341, USA. Email: jdesesso@exponent.com.

Provenance: This is a Guest Editorial commissioned by the Section Editor Xin Liu (Institute of Occupational Disease Prevention, Jiangsu Provincial Center for Disease Prevention and Control, Nanjing, China).

Comment on: Tarazona JV, Court-Marques D, Tiramani M. Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. Arch Toxicol 2017;91:2723-2743.

Received: 09 September 2017; Accepted: 13 September 2017; Published: 10 October 2017.

doi: 10.21037/jphe.2017.09.03

View this article at: http://dx.doi.org/10.21037/jphe.2017.09.03

The advent of the internet and the information age has allowed the public to become keenly aware of the perceived dangers to health from polluted air and water, pesticide residues in foods, and global warming. Much of the available information on the worldwide web is not vetted, resulting in opinions that are based on anecdotal, emotional and alarming misinformation that runs counter to well-established, science-based medical knowledge. If the ensuing sense of trepidation in the public goes unchecked in social media, it provides the impetus for misguided social activism such as the anti-vaccine movement (due to fears of autism) or the notion that wearing a brassiere or using an underarm antiperspirant contributes to a woman's risk of breast cancer. It is incumbent on the scientific community to debunk the myths and untruths that surround many of the false health claims that have seduced segments of the public. Accomplishing this effectively is a daunting task that begins through interactions with the public and the clear communication of health risk information based on the totality of relevant, credible data.

Communication difficulties arise when recognized scientific expert organizations assess the potential health effects of a substance that is of particular interest to the public and announce completely different conclusions. This occurred recently with glyphosate, the most widely used herbicide in the world. The International Agency for Research on Cancer (IARC), an arm of the World Health Organization, prepared a monograph on glyphosate and glyphosate-based formulations, which concluded that glyphosate was a Group 2A substance, and thus, is probably carcinogenic to humans (1). The IARC assessment (announced in 2015) triggered a thorough re-evaluation of glyphosate by the European Union's European Food Safety Authority (2,3), which in contrast, concluded that glyphosate is unlikely to be carcinogenic in humans and, thus, did not require a cancer classification. This controversy has spilled over into the regulatory and scientific literature (4-8) and has resulted in several communications between representatives supporting IARC [e.g., (9,10)] and EFSA (11,12) defending their respective conclusions.

Due to the stark contrast in the conclusions of IARC and EFSA regarding the carcinogenic potential of glyphosate, we explored the differences in the basis for each organization's conclusion. This analysis showed that the first major difference between the assessments performed by IARC and EFSA pertains to the body of data evaluated by each of the two groups. For the purpose of transparency, IARC restricts its evaluations to data that have been published (or are accepted for publication) in the open scientific literature. If government agencies have published data in reports that are accessible to the public, they may also be considered. But not all the best data are necessarily reported in the peer-reviewed literature. Epidemiological (human) studies—typically, case-control or cohort studies—are often published and thus, readily available to the public in the peer-reviewed literature. However, some chemical manufacturers may have conducted these

types of studies and submitted to regulatory agencies as proprietary reports, which often are not readily available to the public. Nonclinical (animal) toxicology and safety data can also be made available to the scientific public through the publication of results in the open scientific literature. Nevertheless, a much larger proportion of the nonclinical toxicology and safety data for a chemical is generated in contract research organizations (CROs), which are considered proprietary information, and while submitted to regulatory bodies to meet testing requirement, often not available to the public. While these types of studies are typically not published, they are performed under a set of standards called Good Laboratory Practices (GLPs) to meet guidelines for design and quality that have been set by various international regulatory agencies. Additionally, the amount of data collected in guideline studies is often far greater than that provided in published studies and is typically of higher quality with regard to experimental group sizes and the breadth of investigation (e.g., requirement for a dose-response design; histopathology of 35+ tissues from all animals in high dose and control groups; toxicokinetic data for subchronic and chronic/carcinogenicity studies). In contrast to IARC, EFSA considers the entire corpus of credible and relevant scientific data, regardless of the publication status, provided that they meet the criteria for scientific quality, such as those outlined by GLPs.

It is our opinion that this approach, of considering the entire body of data although it may not all be publicly available in the peer-reviewed literature, is more robust—particularly when much of the highest quality data are generated by GLP, but unpublished. It is important to note that published research often emanates from academic laboratories and is typically of very high quality with regard to insightful, cutting-edge mechanistic experiments. Unfortunately, the results of these experiments are often of limited use for safety evaluations. In contrast, the results of experiments performed according to guidelines that have been promulgated by regulatory agencies for safety evaluations are typically not of interest to the general scientific community (especially when the results are negative) and usually are not published in the open literature. These latter studies are often the source of dose-response data as well as being the studies upon which effect levels are defined. Thus, IARC's process of using only publicly available studies, while transparent, provides an incomplete body of data for evaluation.

The second major difference between the assessments of these two organizations relates to their work products. IARC clearly states in its Preamble that: "*The (IARC) Monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the Monographs identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.*" (13).

Thus, IARC performs a hazard assessment only. Hazard assessment is the first step in the process of assessing actual risks. In addition, IARC seems to rely mainly upon statistical analyses to form its opinions with rather limited interpretations of biological plausibility [see discussion in (10)]. EFSA (and other regulatory bodies), in contrast, generates risk assessments (i.e., an estimate of the likelihood of developing cancer after being exposed). This is a key distinction. Thus, EFSA examines additional and more complete toxicological data by gathering numerous additional studies that have been performed according to regulatory guidelines for the purposes of determining both dose-response relationships and internal exposures achieved by various routes of administration over various durations. They also consider mechanism of action studies. In addition, EFSA carefully evaluates environmental data that measured actual exposures to humans under various scenarios.

Thus, in EFSA's evaluation, the information available from all of the toxicology studies was assembled and considered with the exposure data in their final determination of potential carcinogenic risks to people under a variety of scenarios. The results of this assessment found no basis for classifying glyphosate as a carcinogenic risk to humans (3). Importantly, other regulatory bodies have also re-evaluated glyphosate and have come to the same conclusion that it is not a carcinogenic risk to humans [e.g., (7,14,15)]. We believe that this approach—of considering not only hazard, but also the potential for sufficient exposures to result in actual risks—is the more informative one.

Third, as noted previously, the EFSA assessment was restricted to the evaluation of glyphosate only, whereas the IARC review included consideration of not only glyphosate, the active ingredient, but also of glyphosate-based formulations. This latter category comprises mixtures of glyphosate with various surfactants and excipients. Although some of the additional ingredients, especially the surfactants, have toxicologic properties of their own [e.g., (16,17)], the IARC assessment made no attempt to parse out the effects of other substances present in these mixtures. The rationale for IARC's consideration of glyphosate-based formulations is that people are typically exposed to the

formulated products and not the active ingredient alone. The shortcoming to this approach is that carcinogenic risk can be falsely applied to the active ingredient in a formulation instead of to the actual causative chemical that may be present in the mixture.

Taken together, the preceding assessment shows that the inputs to and written products of IARC and EFSA are actually quite different. Nevertheless, the vocabulary used by both organizations is strikingly similar. Both speak of the carcinogenicity of substances and use the term "carcinogen", although their criteria and meanings differ. Because both EFSA and IARC are held in high regard by the public, both organizations need to be transparent in communicating their assessment approaches and what their conclusions mean in terms of actual risks to the public. In particular, when IARC classifies a substance as "probably carcinogenic to humans (Group 2A)" the public hears that "it causes cancer" and is a reason to worry. Without further clarifying or revamping their assessment process or more clearly communicating to the public what their determinations mean for the average person, IARC may erode its credibility within the scientific community. This, in turn will ultimately result in the Agency's becoming a less reliable source of information to the public.

In closing the IARC reassessment of glyphosate served as a stimulus for multiple regulatory agencies to carefully re-evaluate all of the data available to them in separate risk assessments (3,7,14,15,18). The results of these new risk assessments unanimously concluded that glyphosate does not pose a carcinogenic risk to humans and that there was no cause for classification. We concur with those risk assessments and urge the scientific community to communicate these conclusions regarding glyphosate to the public.

Acknowledgements

None.

Footnote

Conflicts of Interest: While the authors were not compensated for preparing this manuscript, in the past they have worked on issues related to glyphosate that were funded by industry consortia and Monsanto.

References

1. International Agency for Research on Cancer. Some organophosphate insecticides and herbicides: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. Lyon: IARC Monogr Eval Carcinog Risk Chem Hum, 2017;112:321-412.
2. European Food Safety Authority. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance glyphosate.2015a. Available online: http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302
3. European Food Safety Authority. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA J 2015;13:4302.
4. Cressey D. Widely used herbicide linked to cancer. Nature [Internet]. 24 Mar 2015. Available online: https://www.nature.com/news/widely-used-herbicide-linked-to-cancer-1.17181
5. Williams GM, Aardema M, Acquavella J, et al. A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. Crit Rev Toxicol 2016;46:3-20.
6. EU chemicals agency sweeps glyphosate cancer evidence under the carpet. Available online: http://www.greenpeace.org/eu-unit/en/News/2017/EU-chemicals-agency-sweeps-glyphosate-cancer-evidence-under-the-carpet/
7. Glyphosate issue paper: evaluation of carcinogenic potential. Washington DC: EPA's Office of Pesticide Programs. Available online: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf
8. Does Monsanto's Roundup Herbicide Cause Cancer or Not? The Controversy, Explained. Available online: https://www.wired.com/2016/05/monsantos-roundup-herbicide-cause-cancer-not-controversy-explained/
9. Portier CJ, Armstrong BK, Baguley BC, et al. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). J Epidemiol Community Health 2016;70:741-5.
10. Portier CJ, Clausing P. Re: Tarazona et al. (2017): Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. doi: 10.1007/s00204-017-1962-5. Arch Toxicol 2017. [Epub ahead of print].
11. Tarazona JV, Court-Marques D, Tiramani M, et al. Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. Arch Toxicol 2017;91:2723-2743.
12. Tarazona JV, Court-Marques D, Tiramani M, et al.

Response to the reply by C. J. Portier and P. Clausing, concerning our review "Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC". Arch Toxicol 2017. [Epub ahead of print].
13. International Agency for Research on Cancer. Some organophosphate insecticides and herbicides: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. IARC Working Group. Lyon: IARC Monogr Eval Carcinog Risk Chem Hum, 2017;112:9-31.
14. BfR-contribution to the EU-approval process of glyphosate is finalised. Available online: http://www.bfr.bund.de/cm/349/bfr-contribution-to-the-eu-approval-process-of-glyphosate-is-finalised.pdf
15. Re-evaluation Decision RVD2017-01, Glyphosate. Available online: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/registration-decision/2017/glyphosate-rvd-2017-01.html
16. Mesnage R, Bernay B, Séralini GE. Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity. Toxicology 2013;313:122-8.
17. Seok SJ, Park JS, Hong JR, et al. Surfactant volume is an essential element in human toxicity in acute glyphosate herbicide intoxication. Clin Toxicol (Phila) 2011;49:892-9.
18. Opinions of the Committee for Risk Assessment on proposals for harmonised classification and labelling. Available online: https://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance-rev/16901/term

doi: 10.21037/jphe.2017.09.03
Cite this article as: DeSesso JM, Williams AL, Reiss R. Conflicting views on the potential carcinogenicity of glyphosate: how did we get here and what should we do? J Public Health Emerg 2017;1:78.

Virginia Cooperative Extension
Virginia Tech • Virginia State University
www.ext.vt.edu

Glyphosate: Health Controversy, Benefits and Continuing Debate

Author: Ralph Morini, Piedmont Extension Master Gardener
Specialist Reviewer: Jeffrey Derr, Professor of Weed Science, Virginia Tech, Hampton Roads AREC
Specialist reviewer: Penelope Fenner-Crisp, PhD, Retired Sr Science Advisor to the director of EPA Office of Pesticide Programs and Piedmont Extension Master Gardener

Introduction

At a time when alternative facts and fake news are making detectives out of all of us, we probably shouldn't be surprised that conflicting opinions invade our lives as gardeners as well. Glyphosate, the active ingredient in the world's most widely used weed killers, including Monsanto's Roundup, has long been regarded by government agencies including the US Environmental Protection Agency (EPA), as economical, broadly effective, low-toxicity and environmentally benign. In 2015 however, glyphosate was classified as "probably carcinogenic to humans" by the World Health Organization's International Agency for Research on Cancer (IARC). This classification conflicts with the EPA's stated opinion that glyphosate is "not likely to be carcinogenic to humans". Since the IARC's departure from the prevailing governmental posture on the chemical, there has been a proliferation of conflicting opinions on where the truth lies. Let's try to sort the arguments out in layman's terms.

How it works

Glyphosate is applied to leaves and stems and translocates throughout the plant, concentrating in meristem tissue. It blocks the shikimic acid pathway,

preventing plants from making certain amino acids required to produce proteins. needed for growth. Exposure leads to stunted growth, loss of green coloration, leaf wrinkling/malformation, tissue death and plant death generally in 7-21 days.

The absence of this pathway in mammals is the basis for low toxicity claims in humans. Humans and other animals must get these amino acids from their diets since they can't produce them.

The National Pesticide Information Center notes that glyphosate doesn't easily pass through skin. If ingested, it passes quickly without change. It may cause eye/skin and nose/throat irritation and can be toxic if ingested intentionally in very large quantities. This is unsurprising and typical of many commonly used items like aspirin and

table salt, for example. It further notes conflicting studies on whether glyphosate exposure increases cancer rates in humans, including a possible association with Non-Hodgkin Lymphoma, and notes that developmental and reproductive issues have been observed in rats at high doses.

Environmentally, Glyphosate binds to soil, minimizing runoff issues. It is broken down by microbial action with a half-life averaging about 47 days.

History

Glyphosate was patented by Monsanto in 1974 and is the active ingredient in their Roundup herbicide. Today glyphosate is used in many competing herbicide products. Its use as a weed control product took off in the 1990s when Monsanto introduced GMO crops that are resistant to it. Today these crops include corn, soybeans, sugar beets, canola and cotton. Glyphosate is used as a pre-planting treatment and as a maintenance treatment during the growing season. Less well known is its use as a dessicant, sprayed on wheat crops. The practice is to spray Roundup or a similar product on wheat to dry the plants up a couple of weeks prior to harvest. This makes the harvest more uniform and easier on harvesting machinery. There is some dispute about how widespread this practice is in the US. Overall use of glyphosate herbicide products in the US is in excess of 100 million pounds annually.

The IARC Position

On March 20, 2015, IARC published an opinion that called glyphosate "Probably carcinogenic to humans". The studies were an analysis of published and peer reviewed reports, of mostly agricultural exposures in the US, Canada and Sweden performed after 2001. It also reanalyzed EPA studies of tumors in lab mice. According to IARC, the EPA originally classified these results as possibly carcinogenic to humans (1985), but then later reclassed them as presenting "evidence of non-carcinogenicity in humans" (1991) after a review of the tissue slides by an independent panel of expert pathologists. The IARC analysis of this data led to a conclusion of "sufficient evidence of carcinogenicity" that they became a part of the "probably carcinogenic to humans" position noted above.

The EPA Position

In December 2017, the EPA released a "draft" human health risk assessment for glyphosate, concluding that it is "not likely to be carcinogenic to humans" and found "no other meaningful risks to human health" when used according to published directions. The EPA assessment is based on published information plus manufacturer data that is normally withheld from public view to protect proprietary information. While Monsanto offered to provide this data to IARC, they declined to utilize it. The EPA conclusion agrees with virtually every major regulatory body in the world, (IARC, not a regulatory body, excepted) and includes the latest observations of enrollees in the Agricultural Health Study, a collaboration of EPA, National Cancer Institute, National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health. It is the largest ever pesticide study with over 50,000 farmers in North Carolina and Iowa participating over 25+ years. A November 2017 published study update cited "No association apparent between glyphosate and ...Non-Hodgkin Lymphoma. There was some evidence of AML (acute myeloid leukemia) among the highest exposed group that requires confirmation." The EPA draft assessment does state that "there is potential for effects on birds, mammals, and terrestrial and aquatic plants". A "final" opinion is due from EPA in 2019.

Opinions from Other World Regulatory and Advisory Organizations

In March 2015, the European Chemicals Agency (ECHA), the main driver of European Union chemicals regulation, released a report that concluded that there is "no evidence linking glyphosate to cancer in humans, based on the available information" and that "glyphosate should not be classed as a "substance that causes genetic damage or disrupts reproduction".

The same conclusions were reached by the European Food Safety Authority, national authorities in Canada, Japan, Australia and New Zealand, and the Joint Food and Agriculture Organization/World Health Organization on Pesticide Residues. This makes the IARC the only agency with a divergent view.

The Conflict Continues

The IARC position has been undermined by a Reuters journalist who managed to get a copy of the draft report and found 10 significant instances where evidence of non-carcinogenicity of glyphosate in animals were edited out and were replaced with neutral or countervailing statements.

On the flip side, there is reporting that a key EPA official involved in the agency's cancer assessment has a cozy and maybe compromised relationship with Monsanto. There is current court action underway involving hundreds of lawsuits of alleged non-Hodgkin lymphoma sufferers brought by farmers and farm workers. There are also published reports by academic researchers noting correlations between glyphosate exposure and shortened gestational lengths in pregnant women as well as the coincident rise of glyphosate use with the increase of autism since the 1990s. There are no direct causal relationships established, but they add to the emotion around the topic.

Complicating matters is the fact that the cited reports address glyphosate without considering the effects of other chemicals in the herbicide formulation, which need not be identified on the product label. For example, there is evidence that the surfactant in Roundup is toxic to aquatic plant species so glyphosate-based products containing that surfactant are not approved for aquatic weed control. In addition, conventional farmers handle many different chemicals throughout their lifetime. It is difficult to effectively isolate glyphosate's impacts from the many other variables that could affect the study participants' health.

And finally, after 20 plus years of heavy use, there are an increasing number of weeds, 24 species at last count, that are glyphosate resistant. At some point this becomes a major issue for both weed control and the crops that the herbicide has been mated with. What then?

Sorting It Out

An important distinction between IARC and EPA positions is that IARC assesses Hazard. EPA assesses Risk. Hazard means that glyphosate, in this case, is capable of causing cancer under some circumstances. IARC does not determine safe/unsafe exposure levels or attempt to quantify risks. Risk attempts to quantify impact based on level of exposure. The EPA "not likely to be carcinogenic" position is based on use per manufacturer directions.

From a user viewpoint, glyphosate-based herbicides are low toxicity compared to other chemical weed control options. It has had a positive impact in the growth of no-till farming, reducing erosion, runoff and topsoil depletion. It has also helped increase food production in a food short world, while helping control growers' costs.

On the flip side, there are credible individuals and environmental organizations that hold the opinion that glyphosate may be a human carcinogen. Regardless, it is unsettling to know that we unavoidably ingest glyphosate residues in our food and at a minimum, pass it through our bodies. The Non-Hodgkin lymphoma and AML claims by high exposure farm workers are a definite concern, even if their exposure is a lot higher than for us home gardeners.

Then there is the symbiotic relationship between glyphosate, GMO crops and Monsanto's heavy dependence on their related acceptance by society. There is certainly reason for caution in accepting Monsanto's advocacy given their stake in the outcome.

Organic Alternatives

Based on my research, there doesn't seem to be another chemical herbicide that matches glyphosate's combination of effectiveness and low toxicity. So, as chemical week killers go, it is hard to improve on.

There are several organic post-emergence herbicides available for home use. They include acetic acid-based products containing 10-20% acidity vs the 5-7% content of the white vinegar in our kitchens. Other products contain mixtures of plant oils, acetic or other acids, or other chemicals. The products most widely used by organically minded professionals are plant oil mixtures. Clove oil is the basis for many with citric and cinnamon oils also part of different recipes. All these options are contact herbicides. They will burn down above ground plant parts but underground parts like rhizomes, bulbs and roots are unaffected and require repeated applications for control. In addition, acetic acid and the oils have strong scents which some may find objectionable. Ironically, the risk to skin and eyes from contact may be higher with these products than with glyphosate. Many advisors recommend these alternatives for smaller weed control requirements, for example on a patio or pool area.

Corn gluten can be a practical preemergence weed control product

If your need is for preemergence weed control, corn gluten meal may be used on turf and certain other areas. It is a byproduct of corn milling and inhibits germination of crabgrass and certain other weeds. It requires metered application and moisture management, and lasts about 5 or 6 weeks. However, tests indicate that chemical herbicides like pendimethalin are more effective than corn gluten.

Cultural Alternatives

Beyond hand weeding and boiling water, there are a couple of non-herbicidal practices worth mentioning. Using a propane torch to burn weeds, actually to heat them to kill cell function, can be an effective contact weed control method. Obviously, care to prevent the spread of fire beyond the weeds under attack is very important. Specialty weed torches have flames that are nearly invisible and it is not hard to imagine inadvertently lighting up a wooden fence post, or dead plant material among the weeds. Again, the method does not kill the roots of offending plants, only the above ground portion.

For a contained area, solarization is an option. This involves tilling the area to be cleared of weeds and covering it with a sheet of plastic for six weeks in summer. This will raise the soil temperature enough to kill weed seed.

So What About Roundup™?

The IARC opinion lacks the specificity to be of much value, beyond stoking fear. The EPA draft is more substantial and the "not likely to be carcinogenic" characterization is a relatively high bar. However it isn't conclusive and the many outstanding claims of negative health impacts will keep the debate going.

The occasional, proper use of glyphosate products by home gardeners doesn't generate unacceptable risks of toxicity, carcinogenicity or environmental harm, as long as users follow directions for mixing and use. The large scale use of these chemicals in commercial farming does however cause concern for farm workers, the environment and the public at large. Gut level discomfort with the widespread use of glyphosate products on commercial crops and its hidden presence in our food, is understandable in spite of the official view that it is not likely to harm human health. It is this large scale commercial dependence on glyphosate, and other chemical pesticides and fertilizers that is most troubling.

Always read the label! The label is the law.

What does the home gardener do? Aspire to gardening using integrated pest management or organic techniques. Turn to glyphosate and other chemicals, minimally, when there is no effective alternative. Follow directions for mixing and use. Understand that virtually all conventionally grown produce and processed foods may contain trace levels of pesticides such as glyphosate and that the EPA has determined that these amounts don't pose a health risk. And while conventionally grown produce is equally nutritious, organic produce will be closer to chemical free.

And stay tuned. This story is a long way from over...

Sources:

EPA Concludes Glyphosate Is Not Likely to Be Carcinogenic to Humans, NC Cooperative Extension, P Maxwell, M.S., and T Gannon, Ph.D., updated Feb 27, 2018.https://www.turffiles.ncsu.edu/2018/01/epa-concludes-glyphosate-is-not-likely-to-be-carcinogenic-to-humans/?src=rss

IARC Monographs Volume 112: evaluation of five organophosate insecticides and herbicides, World Health Organization, March 20, 2015 http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

European Chemicals Agency's conclusions (https://ec.europa.eu/food/plant/pesticides/glyphosate_en)

In glyphosate review, WHO cancer agency edited out "non-carcinogenic" findings, Kate Kelland, 10/19/2017. https://www.reuters.com/investigates/special-report/who-iarc-glyphosate/

IARC Response to criticisms of the monograph and the glyphosate evaluation, IARC Director, Jan 2018. http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_response_to_criticisms_of_the_Monographs_and_the_glyphosate_evaluation.pdf

EPA Releases Draft Human Health and Ecological Risk Assessments for Glyphosate for Public Comment, The National Law Review, T Backstrom and J Aidala, March 8, 2018.

Glyphosate Fact Sheet, National Pesticide Information Center: http://npic.orst.edu/factsheets/archive/glyphotech.html

Why Regulators conclude glyphosate safe while IARC, alone, claims it could cause cancer, Andrew Porterfield, Genetic Literacy Project, July 24, 2015. https://geneticliteracyproject.org/2015/07/24/why-do-regulators-conclude-glyphosate-safe-while-iarc-almost-alone-claims-it-could-cause-cancer/

Monsanto, EPA Seek to Keep Talks About Glyphosate Cancer Review a Secret, Carey Gillam, Huffington Post, The Blog, January 19, 2018. https://www.huffingtonpost.com/carey-gillam/monsanto-epa-seek-to-keep_b_14250572.html

Glyphosate Exposure in Pregnancy and Shortened Gestational Length: A Prospective Indiana Birth Cohort Study, Pavez, Gerona, Proctor, Friesen, Ashby, Reiter, Lui and Winchester, Environmental Health, March 9. 2018.https://ehjournal.biomedcentral.com/articles/10.1186/s12940-018-0367-0

Challenges for Use of Glyphosate Alternatives in Urban Landscapes, University of Florida, IFAS Extension, May 27, 2016. http://nwdistrict.ifas.ufl.edu/phag/2016/05/27/challenges-for-use-of-glyphosate-alternatives-in-urban-landscapes/

Vinegar: An Alternative to Glyphosate?, Deborah Smith-Fiola and Stanton Gill, University of Maryland Extension, updated 2017. https://extension.umd.edu/sites/extension.umd.edu/files/_docs/programs/ipmnet/Vinegar-

International Agency for Research on Cancer

World Health Organization

20 March 2015

IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides

Lyon, France, 20 March 2015 – The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, has assessed the carcinogenicity of **five organophosphate pesticides**. A summary of the final evaluations together with a short rationale have now been published online in The Lancet Oncology, and the detailed assessments will be published as Volume 112 of the IARC Monographs.

What were the results of the IARC evaluations?

The herbicide **glyphosate** and the insecticides **malathion** and **diazinon** were classified as *probably carcinogenic to humans* (Group 2A).

The insecticides **tetrachlorvinphos** and **parathion** were classified as *possibly carcinogenic to humans* (Group 2B).

What was the scientific basis of the IARC evaluations?

The pesticides **tetrachlorvinphos** and **parathion** were classified as *possibly carcinogenic to humans* (Group 2B) based on convincing evidence that these agents cause cancer in laboratory animals.

For the insecticide **malathion**, there is *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma and prostate cancer. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. Malathion also caused tumours in rodent studies. Malathion caused DNA and chromosomal damage and also disrupted hormone pathways.

For the insecticide **diazinon**, there was *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma and lung cancer. The evidence in humans is from studies of agricultural exposures in the USA and Canada published since 2001. The classification of diazinon in Group 2A was also based on strong evidence that diazinon induced DNA or chromosomal damage.

For the herbicide **glyphosate**, there was *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. On the basis of tumours in mice, the United States Environmental Protection Agency (US EPA) originally classified glyphosate as *possibly carcinogenic to humans* (Group C) in 1985. After a re-evaluation of that mouse study, the US EPA changed its classification to *evidence of non-carcinogenicity in humans* (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is *sufficient evidence of carcinogenicity* in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby.

How are people exposed to these pesticides?

Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on livestock and companion animals, including in pet flea collars. No information was available on use in other countries.

Parathion use has been severely restricted since the 1980s. All authorized uses were cancelled in the European Union and the USA by 2003.

IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides

Malathion is currently used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. Workers may be exposed during the use and production of malathion. Exposure to the general population is low and occurs primarily through residence near sprayed areas, home use, and diet.

Diazinon has been applied in agriculture and for control of home and garden insects. Production volumes have been relatively low and decreased further after 2006 due to restrictions in the USA and the European Union. Only limited information was available on the use of these pesticides in other countries.

Glyphosate currently has the highest global production volume of all herbicides. The largest use worldwide is in agriculture. The agricultural use of glyphosate has increased sharply since the development of crops that have been genetically modified to make them resistant to glyphosate. Glyphosate is also used in forestry, urban, and home applications. Glyphosate has been detected in the air during spraying, in water, and in food. The general population is exposed primarily through residence near sprayed areas, home use, and diet, and the level that has been observed is generally low.

What do Groups 2A and 2B mean?

Group 2A means that the agent is ***probably*** *carcinogenic to humans*. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. *Limited evidence* means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations (called chance, bias, or confounding) could not be ruled out. This category is also used when there is limited evidence of carcinogenicity in humans and strong data on how the agent causes cancer.

Group 2B means that the agent is ***possibly*** *carcinogenic to humans*. A categorization in Group 2B often means that there is convincing evidence that the agent causes cancer in experimental animals but little or no information about whether it causes cancer in humans.

Why did IARC evaluate these pesticides?

The IARC Monographs Programme has evaluated numerous pesticides, some as recently as 2012 (anthraquinone, arsenic and arsenic compounds). However, substantial new data are available on many pesticides that have widespread exposures. In 2014, an international Advisory Group of senior scientists and government officials recommended dozens of pesticides for evaluation. Consistent with the advice of the Advisory Group, the recent IARC meeting provided new or updated evaluations on five organophosphate pesticides.

How were the evaluations conducted?

The established procedure for Monographs evaluations is described in the Programme's Preamble. Evaluations are performed by panels of international experts, selected on the basis of their expertise and the absence of real or apparent conflicts of interest. For Volume 112, a Working Group of 17 experts from 11 countries met at IARC on 3–10 March 2015 to assess the carcinogenicity of **tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate**. The in-person meeting followed nearly a year of review and preparation by the IARC secretariat and the Working Group, including a comprehensive review of the latest available scientific evidence. According to published procedures, the Working Group considered "reports that have been published or accepted for publication in the openly available scientific literature" as well as "data from governmental reports that are publicly available". The Working Group did not consider summary tables in online supplements to published articles, which did not provide enough detail for independent assessment.

What are the implications of the IARC evaluations?

The Monographs Programme provides scientific evaluations based on a comprehensive review of the scientific literature, but it remains the responsibility of individual governments and other international organizations to recommend regulations, legislation, or public health intervention.

Media inquiries: please write to com@iarc.fr. Thank you.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75