Phosphonate Herbicides

COMMERCIAL PRODUCTS

fosamine ammonium

glyphosate (Brands include Round-Up and Glyfonox)

HIGHLIGHTS

Most commonly used herbicide in U.S.

Many reported poisonings

Actual toxicity likely from surfactant

Read label to ascertain possible additional ingredients

SIGNS & SYMPTOMS

GI symptoms predominate

Cardiovascular, respiratory, renal systems may be affected

Can be measured in plasma

TREATMENT

Decontaminate skin and eyes

Consider GI decontamination

Control seizures

Consider hemodialysis in cases of renal failure

No known antidote

CHAPTER 13

Other Herbicides

Many herbicides are now available for use in agriculture and for lawn and garden weed control. This chapter discusses herbicides other than the chlorophenoxy compounds, nitro- and chloro-phenols, arsenicals and dipyridyls, which are subjects of separate chapters. Many modern herbicides kill weeds selectively by impairing metabolic processes that are unique to plant life. For this reason, systemic toxicity in mammals is generally low. Nonetheless, some pose a significant risk of poisoning if not handled appropriately, and may result in eye, skin and mucous membrane irritation.

Herbicides mentioned in this chapter should be handled and applied only with proper personal protective equipment and careful attention to hygienic measures that minimize personal contact. Many formulations contain adjuvants (stabilizers, penetrants, surfactants) that may have significant irritating and toxic effects in addition to the primary herbicide. A number of premixed products may be combination formulations with additional active ingredients that are more toxic than the principal herbicide. Therefore, it is important to read the label to identify each active ingredient and its associated toxicities. Good hygienic practice should not be disregarded because only the primary pesticide is reported to have a high LD_{50} in laboratory animals.

Healthcare professionals should have a general understanding of the metabolism and health effects of these compounds after human exposures. This knowledge is necessary to properly assess acute and chronic exposures. Generally, water-soluble herbicides are not retained in body tissues for long periods of time, as were the previously used lipophilic organochlorine insecticides such as DDT. Most of the water-soluble herbicides are primarily excreted, mainly in the urine, within 1-4 days.

This chapter follows a slightly different format than the other chapters in this book. Glyphosate is discussed separately since it is a widely used herbicide. It has been studied extensively and is the subject of numerous publications in the medical literature. The remaining herbicides in the chapter are summarized in a table. A notable inclusion in the table is propanil, an anilide herbicide. Propanil was previously described as having low toxicity; however, data from Sri Lanka have documented significant acute toxicity with the development of methemoglobinemia, including several fatalities.[1,2]

The rat acute oral LD_{50} is given as a rough index of potential lethal toxicity (If several values are reported by various sources, the lowest is recorded here). Adverse effect information given is drawn from many sources, including reregistration eligibility decisions (REDs), product labels, textbooks and published reports. The listing cannot be considered inclusive, either of herbicide products or of effects.

PHOSPHONATE HERBICIDES

Glyphosate is the most commonly used herbicide in the United States; it is used as weed control on numerous agricultural crops and is also registered for home use.[3] The advent of genetically modified seed producing plants resistant to glyphosate allows the planting of crops such as corn that can tolerate widespread application of glyphosate. The National Poison Data System (NPDS) uses 63 generic categories to classify pesticides. In 2010, among reported human exposures to pesticides, glyphosate ranked

eighth.[4] Although Round-Up is the most well-known brand of glyphosate, note that some products with the same brand name may include additional active ingredients. Always read labels carefully.

Toxicology

Glyphosate is marketed in the United States as **isopropylamine salt**. Glyphosate and related compounds have a specific mechanism of action inhibiting the enzyme responsible for synthesizing phenylalanine, tyrosine and tryptophan, which is an enzyme system that is not present in humans.[5,6] Given the plant-specific mechanism of action, there is theoretically a low risk for acute human toxicity. Indeed, glyphosate has low acute toxicity in mammals, with a rat LD_{50} in the range of 4,300 mg/kg. Despite this, there have been a number of reports in the medical literature of acute glyphosate-related poisoning. Most, if not all, of the symptoms may actually be related to the organic surfactant with which glyphosate is combined. Most moderate to severe symptomatic cases have been associated with intentional (suicidal) ingestion.[3,7,8]

Another formulation of glyphosate is **glyphosate-trimesium**, which is not marketed in the United States. Two fatalities have been reported associated with glyphosate-trimesium exposure.[9]

Signs and Symptoms of Poisoning

Gastrointestinal symptoms predominate, including mouth and throat pain, nausea, vomiting, diarrhea and abdominal discomfort, and are usually self limiting. More severe signs and symptoms may be seen in cases of intentional oral exposures. Cardiovascular, respiratory and renal systems may be affected; and signs and symptoms include tachypnea, dysrhythmias, hypotension, non-cardiogenic pulmonary edema, hypovolemic shock, oliguria and respiratory failure. Seizures and depressed level of consciousness may also occur. Death was often caused by severe hypotension and respiratory failure.[3,8] Hyperkalemia may occur as a complication of renal failure.[3,7]

One study assessed patients prospectively following a report of glyphosate ingestion. Of the 601 cases, most were either asymptomatic (27%) or with minor symptoms (64%). Approximately 5.5% had moderate to severe poisoning, and 3.2% of the patients died.[8] In another series of acutely poisoned patients, 42% had medical complications of some type, with metabolic acidosis (37%) and respiratory failure (28%) being the most common. A late complication in 12% of patients was pancreatitis.[3]

Confirmation of Poisoning

Glyphosate can be measured in the plasma, with levels above 734 µg/mL being measured in fatal cases.[8]

Treatment of Glyphosate Toxicosis

1. Provide supportive treatment, as there is no known antidote.

2. Decontaminate the skin with soap and water as outlined in **Chapter 3, *General Principles***. Treat eye contamination by irrigating the exposed eye(s) with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, specialized medical treatment in a healthcare facility is indicated.

3. If ingested, consider gastrointestinal decontamination as outlined in **Chapter 3**.
4. Control seizures using benzodiazepines. See **Chapter 3** for specific medications and dosages.
5. In cases of severe poisoning resulting in acute renal failure, consider hemodialysis to correct acidosis and hyperkalemia.[7]

Potential Effects of Other Herbicides

The potential effects of a variety of other herbicides are summarized in the following multi-page table.

POTENTIAL EFFECTS OF OTHER HERBICIDES

Chemical Class	Generic Name	Examples of Proprietary Names	Acute Oral LD_{50} mg/kg	Known or Suspected Adverse Effects
Acetamides	Metolachlor	Dual, Pennant	2,780	Irritating to eyes and skin. Methemoglobinemia has been reported in a mixed herbicide ingestion with the urea derivative metobromuron; however, it is likely that the latter was the cause of the methemoglobinemia.
Anilides	Alachlor	Lasso, Alanox	1,800	Mild irritant, vomiting. Occasionally hypotension and CNS depression.[10]
	Propachlor	Ramrod, Bexton, Prolex	710	Dermal irritant and sensitizer.
	Propanil	DPA, Chem Rice, Propanex, Riselect, Stam, Stampede	>2,500	Despite the relatively high LD_{50} in rats, this compound has caused significant methemoglobinemia, reduced consciousness and respiratory depression.[1,2]
Benzamide	Pronamide	Kerb, Rapier	8,350	Moderately irritating to eyes.

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POTENTIAL EFFECTS OF OTHER HERBICIDES, continued				
Chemical Class	**Generic Name**	**Examples of Proprietary Names**	**Acute Oral LD_{50} mg/kg**	**Known or Suspected Adverse Effects**
Benzoic, Anisic Acid derivatives	Trichloro-benzoic acid	TCBA, Tribac, 2,3,6-TBA	1,500	Moderately irritating to skin and respiratory tract.
	Dicamba	Banvel	2,700	
Benzonitriles	Dichlobenil	Casoron, Dyclomec, Barrier	>4,460	Minimal toxic, irritant effects.
Benzothiadiazinone dioxide	Bentazone	Basagran	>1,000	Generally described as irritating to eyes, GI tract and respiratory tract. Some reports of acute renal failure and respiratory failure have been reported with ingestion of large amounts.[11,12]
Carbamates and Thiocarbamates (herbicidal)	Asulam	Asulox	>5,000	Some are irritating to eyes, skin, and respiratory tract, particularly in concentrated form. Some may be weak inhibitors of cholinesterase.
	Terbucarb	Azac, Azar	>34,000	
	Butylate	Sutan	3,500	
	Cycloate	Ro-Neet	2,000	
	Pebulate	Tillam, PEBC	921	
	EPTC	Eptam, Eradicane	1,630	
	Diallate	Di-allate	395	
	Triallate	Far-go	1,675	
	Thiobencarb	Bolero, Saturn	1,300	
Chloropyridinyl	Triclopyr	Garlon, Turflon	630	Irritating to skin and eyes.

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POTENTIAL EFFECTS OF OTHER HERBICIDES, continued				
Chemical Class	**Generic Name**	**Examples of Proprietary Names**	**Acute Oral LD_{50} mg/kg**	**Known or Suspected Adverse Effects**
Cyclohexenone derivative	Sethoxydim	Poast	3,125	Irritating to skin and eyes.
Dinitroaminobenzene derivative	Butralin	Amex, Tamex	12,600	May be moderately irritating, particularly to the GI tract following ingestion.[13] These herbicides do not uncouple oxidative phosphorylation or generate methemoglobin.
	Pendi-methalin	Prowl, Stomp, Accotab, Herbodox, Go-Go-San, Wax Up	>5,000 2,250	
	Oryzalin	Surflan, Dirimal	>10,000	
Fluorodinitrotoluidine compounds	Benfluralin	Benefin, Balan, Balfin, Quilan	>10,000	May be mildly irritating. These herbicides do not uncouple oxidative phosphorylation or generate methemoglobin.
	Ethalfluralin	Sonalan	>10,000	
	Fluchloralin	Basalin	1,550	
	Trifluralin	Treflan	>10,000	
Nicotinic idisopropylamine derivative	Imazapyr	Arsenal	>5,000	Irritating to eyes and skin. Impaired consciousness, respiratory distress and severe vomiting occurs with large quantity (>100 mL) ingestion.[14] Does not contain arsenic.
Oxadiazolinone	Oxadiazon	Ronstar	>3,500	Minimal toxic and irritant effects.
Picolinic acid compound	Picloram	Tordon, Pinene	8,200	Irritating to skin, eyes, and respiratory tract. Low systemic toxicity.

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POTENTIAL EFFECTS OF OTHER HERBICIDES, continued				
Chemical Class	**Generic Name**	**Examples of Proprietary Names**	**Acute Oral LD_{50} mg/kg**	**Known or Suspected Adverse Effects**
Triazines	Ametryn	Ametrex, Evik, Gesapax	1,750	Systemic toxicity is unlikely unless large amounts have been ingested. There is one report in the literature of metabolic acidosis following massive ingestion of prometryn.[15] Some triazines are moderately irritating to the eyes, skin and respiratory tract.
	Atrazine	Aatrex, Atranex, Crisazina	1,780	
	Desmetryn	Semeron	1,390	
	Metribuzin	Sencor, Lexone, Sencoral, Sencorex	1,100	
	Prometryn	Caparol, Gesagard, Prometrex	5,235	
	Propazine	Milo-Pro, Primatol, Prozinex	>7,000	
	Simazine	Gesatop, Princep, Caliber 90	>5,000	
	Terbuthy-lazine	Gardoprim, Primatol M	2,000	
	Tertutryn	Ternit, Prebane, Terbutrex	2,500	
	Prometon	Gesafram 50, Pramitol 25E	2,980	Some formulations of prometon are strongly irritating to eyes, skin and respiratory tract.
Triazole	Amitrole, aminotriazole	Amerol, Azolan, Azole, Weedazol	>10,000	Minimal systemic toxicity. Slight irritant effect.
Uracils	Bromacil	Hyvar	5,200	Irritant to skin, eyes and respiratory tract.
	Lenacil	Venzar	>11,000	Moderately irritating.
	Terbacil	Sinbar	>5,000	

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POTENTIAL EFFECTS OF OTHER HERBICIDES, continued				
Chemical Class	**Generic Name**	**Examples of Proprietary Names**	**Acute Oral LD_{50} mg/kg**	**Known or Suspected Adverse Effects**
Urea derivatives	Chlorimuron ethyl	Classic	>4,000	Systemic toxicity is unlikely unless large amounts have been ingested.
	Chlorotoluron	Dicuran, Tolurex	>10,000	Chlorimuron ethyl has been associated with asthma.[16]
	Diuron	Cekiuron, Crisuron, Dailon, Direx, Diurex, Diuron, Karmex, Unidron, Vonduron	>5,000	Many substituted ureas are irritating to eyes, skin and mucous membranes.
	Ebuthiuron	Spike, Tebusan	644	
	Flumeturon	Cotoran, Cottonex	8,900	
	Isoproturon	Alon, Arelon, IP50, Tolkan	1,826	
	Linuron	Afalon, Linex, Linorox, Linurex, Lorox, Sarclex	1,500	
	Methabenz-thiazuron	Tribunil	5,000	
	Metobromuron	Pattonex	2,000	Metobromuron has been associated with methemoglobinemia.[17]
	Metoxuron	Deftor, Dosaflo, Purivel, Sulerex	3,200	
	Monolinuron	Aresin	2,100	
	Monuron	Monuron	3,600	
	Neburon	Granurex, Neburex	>11,000	
	Siduron	Tupersan	>7,500	
	Sulfometuron-methyl	Oust	>5,000	

Confirmation of Poisoning

Although there are analytical methods for residues of many of the herbicides mentioned in this chapter, and for some of the mammalian metabolites generated from them, these procedures are not generally available to confirm human absorption of the chemicals. Prior exposure must be determined from a recent history of occupational exposure or accidental or deliberate ingestion.

Treatment of Toxicosis from Other Herbicides

1. Decontaminate skin promptly by washing with soap and water. Treat contamination of the eyes immediately by prolonged flushing with copious amounts of clean water. If dermal or ocular irritation persists, medical attention should be obtained without delay.

2. Ingestions of these herbicides are likely to be followed by vomiting and diarrhea because of the irritant properties of most of the toxicants. Management depends on: (a) the best estimate of quantity originally ingested, (b) the time elapsed since ingestion and (c) the clinical status of the subject.

   If large amounts of herbicide have been ingested and the patient is seen within an hour of the ingestion, consider gastrointestinal decontamination as outlined in **Chapter 3, *General Principles***. GI decontamination may be effective in limiting irritant effects and reducing absorption of most or all of these herbicides.

3. If serious dehydration and electrolyte depletion have occurred as a result of vomiting and diarrhea, monitor blood electrolytes and fluid balance and administer intravenous infusions of glucose, normal saline, Ringer's solution or Ringer's lactate to restore extracellular fluid volume and electrolytes. Follow this with oral nutrients as soon as fluids can be retained.

4. Use supportive measures to manage excessive exposures to these herbicides. With the exception of treating methemoglobinemia associated with some of these herbicides, there are no specific antidotes for poisoning by most of these compounds. In the case of suicidal ingestions, particularly, the possibility must always be kept in mind that multiple toxic substances may have been swallowed, especially if the patient's condition deteriorates in spite of good supportive care.

5. Antidotal therapy for methemoglobinemia is methylene blue.

Dosage of Methylene Blue

- ***1-2 mg/kg of 1% methylene blue, slow IV, in symptomatic patients. Additional doses may be required.***

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