REVIEW ARTICLE

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Glyphosate Poisoning

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Abstract

Glyphosate is used extensively as a non-selective herbicide by both professional applicators and consumers and its use is likely to increase further as it is one of the first herbicides against which crops have been genetically modified to increase their tolerance. Commercial glyphosate-based formulations most commonly range from concentrates containing 41% or more glyphosate to 1% glyphosate formulations marketed for domestic use. They generally consist of an aqueous mixture of the isopropylamine (IPA) salt of glyphosate, a surfactant, and various minor components including anti-foaming and colour agents, biocides and inorganic ions to produce pH adjustment.

The mechanisms of toxicity of glyphosate formulations are complicated. Not only is glyphosate used as five different salts but commercial formulations of it contain surfactants, which vary in nature and concentration. As a result, human poisoning with this herbicide is not with the active ingredient alone but with complex and variable mixtures. Therefore, It is difficult to separate the toxicity of glyphosate from that of the formulation as a whole or to determine the contribution of surfactants to overall toxicity. Experimental studies suggest that the toxicity of the surfactant, polyoxyethyleneamine (POEA), is greater than the toxicity of glyphosate alone and commercial formulations alone. There is insufficient evidence to conclude that glyphosate preparations contain-

ing POEA are more toxic than those containing alternative surfactants. Although surfactants probably contribute to the acute toxicity of glyphosate formulations, the weight of evidence is against surfactants potentiating the toxicity of glyphosate.

Accidental ingestion of glyphosate formulations is generally associated with only mild, transient, gastrointestinal features. Most reported cases have followed the deliberate ingestion of the concentrated formulation of Roundup®[1] (41% glyphosate as the IPA salt and 15% POEA). There is a reasonable correlation between the amount ingested and the likelihood of serious systemic sequelae or death. Advancing age is also associated with a less favourable prognosis. Ingestion of >85mL of the concentrated formulation is likely to cause significant toxicity in adults. Gastrointestinal corrosive effects, with mouth, throat and epigastric pain and dysphagia are common. Renal and hepatic impairment are also frequent and usually reflect reduced organ perfusion. Respiratory distress, impaired consciousness, pulmonary oedema, infiltration on chest x-ray, shock, arrythmias, renal failure requiring haemodialysis, metabolic acidosis and hyperkalaemia may supervene in severe cases. Bradycardia and ventricular arrhythmias are often present pre-terminally. Dermal exposure to ready-to-use glyphosate formulations can cause irritation and photo-contact dermatitis has been reported occasionally; these effects are probably due to the preservative Proxel® (benzisothiazolin-3-one). Severe skin burns are very rare. Inhalation is a minor route of exposure but spray mist may cause oral or nasal discomfort, an unpleasant taste in the mouth, tingling and throat irritation. Eye exposure may lead to mild conjunctivitis, and superficial corneal injury is possible if irrigation is delayed or inadequate.

Management is symptomatic and supportive, and skin decontamination with soap and water after removal of contaminated clothing should be undertaken in cases of dermal exposure.

Glyphosate [*N*-(phosphonomethyl) glycine] is an organic compound containing phosphorus (figure 1) that is used extensively as a non-selective herbicide by both professionals and amateurs. It has been marketed since 1974 and its use is likely to increase further as it is one of the first herbicides against which crops have been genetically modified to increase their tolerance.

Commercial glyphosate-based formulations range from concentrates containing 41% or more glyphosate to 1% glyphosate formulations marketed for domestic use. They generally consist of an aqueous mixture of the isopropylamine (IPA) salt of glyphosate, a surfactant, and various minor components including anti-foaming and colour agents, biocides and inorganic ions to produce pH adjustment.[1]

Glyphosate's popularity is attributable to its plant-specific mechanism of action, its inactivation on contact with soil and its suitability for 'no-till' conservation of crops. In addition, its relative lack of volatility and soil migration and rapid biotic degradation give it a favourable environmental safety profile. Glyphosate is metabolised by several bacteria in soil to give phosphorus and sarcosine which is then converted to glycine and ammonia by sarcosine oxidase. The alternative metabolic pathway involves the formation by glyphosate oxidoreductase of aminomethylphosphonic acid (AMPA), which is also the metabolite formed in humans.

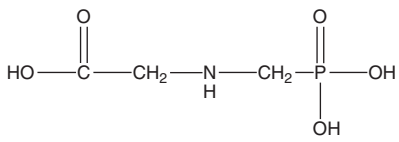

Fig. 1. Chemical structure of glyphosate [*N*-(phosphonomethyl) glycine].

1. Epidemiology

In the 3-year period 2001–03, there were 13 318 reports to the American Association of Poisons Control Centers Toxic Exposure Surveillance System relating to glyphosate exposure.[2-4] Of these, 3622 involved children <6 years of age. There was a 'moderate' outcome in 291 patients, a 'major' (life-threatening) outcome in 18 (0.14%) and five patients died.

Several case series of glyphosate ingestions have been published[5-9] with mortalities ranging from 8% to 16%. Of the 377 cases reported in these four series, 38 died.

Goldstein et al.[1] analysed 815 glyphosate-related reports to the California Environmental Protection Agency Pesticide Illness Surveillance Program for the years 1982–97. Most involved topical irritation of the eye (n = 399), skin (n = 250), upper airways (n = 7), or combinations of these sites (n = 32) without systemic symptoms. Of the 187 systemic cases, only 22 were classified as probably or definitely related to glyphosate exposure alone. With the exception of one intentional ingestion, all of these cases involved incidental topical or inhalation exposure, and a causal relationship to the reported systemic symptoms remains open to question.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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2. Mode of Action

Glyphosate is primarily a competitive inhibitor of the critical enzyme of the shikimate pathway, 5-enolpyruvylshikimate-3-phosphate synthase,[10] which is responsible for the synthesis of an intermediate in the biosynthesis of phenylalanine, tyrosine and tryptophan but is not present in mammalian species, including humans. The shikimate pathway produces aromatic amino acids and a large number of secondary products, including lignins, flavonoids, and tannins in plants and some micro-organisms.[11] Glyphosate is very mobile within plants, with preferential transport to metabolic sinks such as meristematic tissues. It is relatively slow acting, so that it is transported throughout plants before growing tissues are killed. For this reason, it is very effective in controlling perennial weeds in which roots must be killed to prevent regrowth. Although some of the phytotoxicity of glyphosate is a result of reduced pools of aromatic amino acids, most of its herbicidal effect appears to be the result of a general disruption of metabolic pathways through deregulation of the shikimate pathway.[11]

3. Mechanisms of Toxicity

The mechanisms of toxicity of glyphosate formulations are complicated. Not only is glyphosate used as five different salts but commercial formulations of it contain surfactants that vary in nature and concentration and are known by a variety of names. The salts, IPA, Na^+ and NH_3, are probably equipotent as the counterion does not appear to contribute much to toxicity. However, there are new agricultural products that contain K^+ ion, which could increase the toxicity of the formulation if ingested in substantial amounts. The evidence base for the suggestion that products containing glyphosate trimesium are more toxic than other glyphosate salts is limited.[12] Moreover, it is believed that all formulations containing the trimesyl salt have now been withdrawn. Thus, human poisoning with this herbicide is not with the active ingredient alone but with complex and variable mixtures. Therefore, it is difficult to separate the toxicity of glyphosate from that of the formulation as a whole or to determine the contribution of surfactants to overall toxicity.

Although glyphosate is a phosphorus-containing compound, it does not inhibit acetylcholinesterase.

3.1 Glyphosate

3.1.1 Acute Toxicity

Numerous acute toxicity studies have been performed to determine the LD_{50} of glyphosate and herbicide formulations containing glyphosate as an active ingredient.[13] Glyphosate has very low toxicity by the oral (>5000 mg/kg bodyweight [bw]) and dermal (>2000 mg/kg bw) routes but is markedly more toxic by the intraperitoneal route (134–545 mg/kg bw).

Based upon animal studies, some investigators suggest that glyphosate may enhance adenosine triphosphatase activity and uncouple mitochondrial oxidative phosphorylation,[14-17] although this has been disputed by Tominack et al.[7] who identified some unexplained inconsistencies in Olorunsogo's data. "For example, the resting respiratory rates (state 4) were inconsistent in all the glyphosate-treated rats, with the post-ADP (adenosine 5′-diphosphate) rates higher (and more normal) than the pre-ADP rates. This phenomenon does not occur in uncoupled mitochondria. Furthermore, there is no relationship between dose of glyphosate given in the range of the sublethal to lethal doses (30–120 mg/kg) and respiratory control ratios (oxygen consumption in the presence of ADP/oxygen consumption in the absence of ADP) in isolated mitochondria. Finally, no data on the effect of adding pure glyphosate (which is not metabolised in animals or humans) on the oxidative phosphorylation of normal mitochondria were present. Likewise, the clinical picture in this survey of patients ingesting up to 500mL of a 41% glyphosate preparation is inconsistent with oxidative uncoupling. Tachypnea and tachycardia, the expected effects of poisoning with agents that uncouple oxidative phosphorylation, were not consistently seen and no cases of significant hyperpyrexia were encountered". It is probable that the surfactant in Roundup® formulations is responsible for uncoupling oxidative phosphorylation.

In rats, glyphosate decreased hepatic cytochrome P450 and mono-oxygenase activities and the intestinal activity of aryl hydrocarbon hydroxylase.[18]

At high concentrations *in vitro* glyphosate has been shown to inhibit acetylcholinesterase,[19] although there is no evidence for significant acetylcholinesterase inhibition in mammals *in vivo*.

3.1.2 Chronic Toxicity

In repeat-dose studies in experimental animals, the toxicity of glyphosate tends to be non-specific, failure to gain weight being the most frequent observation. Since very high dietary concentrations were used in some of these studies, this effect may have been due to unpalatability and reduced calorie intake.[20] There is no evidence of carcinogenic or teratogenic potential and little evidence of genotoxicity in a variety of *in vitro* tests.[20]

3.2 Surfactants

In general, surfactants interfere with the walls of mitochondria, destroying the proton gradient required for energy production. The poorly responsive multiple organ failure observed following surfactant ingestion are consistent with these effects. The amine surfactants are strongly alkaline and, therefore, corrosive in their pure forms. However, adjustment to a neutral pH is routinely performed when they are co-formulated with glyphosate.

Surfactants in concentrations of up to 50% are added to nearly all glyphosate preparations available for land use; formulations for

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aquatic use are generally surfactant-free due to aquatic toxicity of the surfactants. They serve several purposes: they primarily act as wetting agents, promote uniform spreading of the herbicide on the leaf surface and assist the penetration of glyphosate into the leaf.

3.2.1 Polyoxyethyleneamine

The most widely used surfactants are tertiary amines comprising a nitrogen atom bonded to two polyoxyethylene (C_2H_4O) groups and one long-chain alkyl group. The polyoxyethylene groups are hydrophilic and increasing their number in a molecule increases the hydrophilicity of the surfactant. These groups are also referred to by synonyms including ethylene oxide and ethoxylate. The hydrophobic alkyl group is derived from tallow, a mixture of fats obtained from cows and pigs, consisting of two-thirds stearin and palmitin and one-third olein. The latter react with a nitrogen source to produce primary alkylamines which, in turn, react with polyoxyethylene to produce polyoxyethyleneamine.

Manufacturers use several terms to refer to this class of surfactants, including polyoxyethyleneamine (POEA), ethoxylated tallow amine, polyethoxylated tallow amine, tallow amine, alkoxylated fatty amine and tallow alkyl amine ethoxylate. These all refer to the same group of compounds (although the last two terms may technically refer to a compound containing any of a number of hydrophilic polymer chains, based on the general formula [$C_nH_{2n}O$], as opposed to C_2H_4O as above). Thus, 'polyoxyethyleneamine' or any of its synonyms does not refer to a single chemical entity, but rather to a group of compounds. The chain length and degree of saturation of the alkyl groups can vary, as can the chain length of the polyoxyethylene groups. It is likely that the surfactant used in a particular glyphosate preparation consists of molecules with polyoxyethylene chains of roughly similar lengths as this is an important means of tailoring the surface-active properties. However, the surfactant probably contains a mixture of molecules substituted with different alkyl groups, as they are derived from tallow, which is itself a mixture.

The concentration of polyoxyethyleneamine ranges from <1% in ready-to-use glyphosate formulations to 21% in some concentrated professional products.

3.2.2 Surfactants Derived from Plant Fats

The carbon chains contained in tallow are identical to those extracted from other sources, such as cocoa, peanuts, and cotton or palm oil, although the tallow may contain different impurities. Therefore, it seems likely that ethoxylated cocoamine (another term used by manufacturers to describe the surfactants of several glyphosate products) is toxicologically equivalent to tallow amine.

3.2.3 Other Surfactants

Other surfactants used in glyphosate-containing herbicides include alkyl polyoxyphosphate amine (generally used in a concentration of around 13%), polyethoxylated alkyl etheramine (7.5%), trimethylethoxypolyoxypropylammonium chloride (up to 13%), ethoxylated phosphate ester (9.5%), polyethoxysorbitan monolaurate (3%), alkyl polysaccharide (0.5–5% in amateur products and up to 50% in professional products) and substances such as polyethylene glycol and polyethoxylated fatty alcohol, generally present in low concentrations.

3.2.4 Do Surfactants Contribute to the Toxicity of Glyphosate Formulations?

The main controversy regarding the toxicity of glyphosate formulations is whether their toxicity is due to the herbicide itself or to their co-formulants, notably surfactants.

Animal experiments suggest that the toxicity is due primarily to the surfactant, since it has an oral LD_{50} of 1200 mg/kg,[20] as opposed to >5000 mg/kg for glyphosate[13] and for its formulations.[13,20]

Adam et al.[21] investigated the toxicity of Roundup® in rats. They also tested separately solutions of 41% glyphosate isopropylamine, 18% POEA, and a mixture of 41% glyphosate isopropylamine and 18% POEA (i.e. the two major ingredients of Roundup®, without the other formulation additives). Each batch of eight rats were observed for 6 hours after dosing to detect immediate toxicity and again at 24 hours. The animals were then sacrificed if still alive. Two of the eight rats given POEA died, whereas none of the other animals succumbed. Oral administration of POEA also caused more severe diarrhoea (seven of eight animals at 6 hours; eight of eight animals at 24 hours) than in those administered glyphosate alone. POEA also caused more damage to the gastrointestinal tract and lungs.

Baba et al.[22] investigated the toxicity of glyphosate, surfactant and Roundup® (41% glyphosate/15% surfactant) in seven rats and obtained oral LD_{50} values at 72 hours post-administration of 5957 mg/kg, 661 mg/kg and 5337 mg/kg, respectively. The authors concluded that the toxic effects of Roundup® were more related to the surfactant than glyphosate.

Tai et al.[23] administered glyphosate, surfactant or Roundup® (41% glyphosate/15% surfactant) to five beagle dogs by continuous intravenous infusion. Glyphosate increased myocardial contractility, possibly in response to a glyphosate-induced increase in pulmonary artery pressure. In contrast, the surfactant and Roundup® both reduced myocardial contractility and cardiac output suggesting that the cardiac depressant effect of Roundup® was due to the surfactant, rather than to glyphosate.

Sawada and Nagai[9] reported 56 cases of human poisoning with Roundup® (41% glyphosate isopropylamine/15% POEA), and two cases of poisoning due to products containing a shampoo and a spreading agent (not specified), but not glyphosate. The clinical features were very similar, suggesting that the features of Roundup® poisoning were due to the surfactant.

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3.2.5 Do Surfactants Potentiate the Toxicity of Glyphosate?

Martinez et al.[24] obtained an oral LD_{50} for Roundup® (18% glyphosate/7% POEA) of approximately 1600 mg/kg of glyphosate when combined with 560 mg/kg POEA. They compared this to published LD_{50} values for the individual substances and suggested that the combination of glyphosate and POEA resulted in greater toxicity than would be expected by the addition of the two substances, i.e. that there was potentiation. The same group[25] also compared the same Roundup® preparation to 7% POEA alone. Both caused similar respiratory features but those produced by POEA alone were less severe. The authors suggested that the combination of POEA with glyphosate potentiated pulmonary toxicity. However, neither study was designed appropriately to confirm the existence of a synergistic interaction, no statistical analysis was carried out and no group was treated with glyphosate alone.

Potentiation of the toxicity of glyphosate and POEA in combination has not been observed in other studies.[21] Tai et al.[23] suggested that in terms of cardiotoxicity, glyphosate and the surfactant had an opposite, rather than synergistic effect.

In the study described in section 3.2.4 by Baba et al.[22] that investigated the toxicity of glyphosate, surfactant and Roundup® (41% glyphosate/15% surfactant) in seven rats and obtained oral LD_{50} values at 72 hours post-administration of 5957 mg/kg, 661 mg/kg and 5337 mg/kg, respectively, graphical analysis indicated that the interaction between glyphosate and surfactant was antagonistic. The authors concluded that it was unlikely that the toxicity of glyphosate was potentiated by mixing with surfactant.

3.2.6 Are Polyoxyethyleneamines More Toxic Than Other Surfactants?

As there are very few human case reports of exposure to glyphosate preparations that are stated to contain surfactants other than POEA, it cannot yet be concluded that non-POEA preparations do not cause the features associated with POEA ingestions.

3.2.7 Summary

Experimental studies suggest that the toxicity of the surfactant, POEA, is greater than the toxicity of glyphosate alone. There is insufficient evidence to conclude that glyphosate preparations containing POEA are more toxic than those containing alternative surfactants. Although surfactants probably contribute to the acute toxicity of glyphosate formulations, the weight of evidence is against surfactants potentiating the toxicity of glyphosate; indeed, the reverse has been suggested. The evidence base for the suggestion that products containing glyphosate trimesium are more toxic than formulations containing other glyphosate salts is very limited, but cannot be dismissed.

4. Toxicokinetics

The existing knowledge of the toxicokinetics of glyphosate is mainly derived from animal studies and has been reviewed recently.[20] Only some 30% is absorbed after oral administration to rats.[20,26] Peak plasma concentrations of glyphosate are attained at 1–2 hours[20,26,27] and decline quickly.[26] Initial distribution is mainly to the small intestine, colon, kidney and bone.[27] Very little glyphosate undergoes biotransformation, the vast majority being rapidly excreted unchanged in the urine.

A similar pattern of absorption, metabolism and elimination after ingestion is seen in humans, although the data are limited. Two poisoned patients reached peak plasma glyphosate concentrations within 4 hours, the concentrations being almost undetectable by 12 hours.[28] Severe poisoning is associated with plasma glyphosate concentrations >1000 mg/L[28] and, occasionally, concentrations as high as 1600 mg/L have been encountered.[29] However, as toxicity may not be due to glyphosate itself, the clinical predictive value of these concentrations is limited.

In another case, the high ratio of glyphosate to AMPA in serum at 8 hours and 16 hours post-ingestion (126 : 1 and 147 : 1, respectively) and the ratio of the total amounts in the patient's urine (148 : 1) strongly indicate that very little glyphosate is metabolised.[30]

Dermal absorption of glyphosate by monkeys is poor; only some 2% of the applied amount is absorbed over 24 hours.[31,32] Absorption through human (cadaver) skin is little better and was <1% after application of Roundup® diluted to spray strength.[20,33]

Absorption after inhalation does not appear to have been studied but would not be expected to be significant.

Urinary glyphosate concentrations were evaluated in 48 farmers, their spouses, and their 79 children (4–18 years of age). Sixty per cent of farmers had detectable concentrations of glyphosate in their urine on the day of application. The geometric mean concentration was 3 μg/L, the maximum value was 233 μg/L, and the highest estimated systemic dose was 0.004 mg/kg. Farmers who did not use rubber gloves had higher geometric mean urinary concentrations than did other farmers (10 vs 2.0 μg/L). For spouses, 4% had detectable concentrations in their urine on the day of application. Their maximum value was 3 μg/L. For children, 12% had detectable glyphosate in their urine on the day of application, with a maximum concentration of 29 μg/L. All but one of the children with detectable concentrations had helped with the application or were present during herbicide mixing, loading, or application. None of the systemic doses estimated in this study approached the US Environmental Protection Agency reference dose for glyphosate of 2 mg/kg/day.[34]

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5. Clinical Features

In human poisoning, it is not always possible to determine which glyphosate formulation, and in particular which surfactant, was ingested. Accidental ingestion of glyphosate is generally associated with only mild, transient gastrointestinal features,[6,35] although a 6-year-old died shortly after ingesting a 'small amount' of a herbicide containing glyphosate trimesium 326 g/L (33%).[12] Most reported cases relate to the deliberate ingestion of the concentrated formulation of Roundup® (41% glyphosate as the IPA salt and 15% POEA), which has resulted in the development of severe features.[6,7]

5.1 Ingestion

Nausea, vomiting and diarrhoea are the only likely features following ingestion of glyphosate ready-to-use amateur formulations. Small amounts of the concentrated formulation have not caused severe systemic effects in adults[6,7] but may cause burning in the mouth and throat, hypersalivation, nausea, vomiting and diarrhoea.[5] In contrast, ingestion of >85mL of the concentrated formulation is likely to cause significant toxicity in adults.[6] Gastrointestinal corrosive effects with mouth, throat and epigastric pain and dysphagia are common in these circumstances,[7,36] with predominantly gastric and oesophageal rather than duodenal damage.[36] Small bowel infarction has been reported, probably secondary to hypotension.[37] Lower gastrointestinal corrosive injury is rare,[6] although Delcenserie et al.[38] described a 44-year-old man who developed acute colitis 1 week after consuming an unknown amount of glyphosate-contaminated wine.

Table I lists proposed criteria for classification of severity of poisoning resulting from glyphosate formulation ingestion.

Among 50 patients who ingested glyphosate concentrate (estimated mean volume 182 ± (SD) 202mL; n = 44) nearly half exhibited grade 1 gastric injury (oedema and hyperaemia of the mucosa) at endoscopy with grade 1 oesophagitis in one-third of cases.[36] Duodenal injury was relatively uncommon, with 14% of cases showing grade 1 duodenitis and only one patient a more severe (grade 2a, superficial ulceration) lesion. In this study, patients with grade 2 or 3 (multiple ulcerations with necrosis) oesophageal lesions were more likely to have ingested >200mL glyphosate concentrate and were also more likely to manifest severe systemic sequelae including gastrointestinal haemorrhage, hypotensive shock (not always in association with hypovolaemia) or aspiration pneumonia. The latter complication is particularly likely if laryngeal corrosive injury occurs during ingestion.[39]

Aspiration contributes to ventilatory insufficiency in severely poisoned patients[7] but non-cardiogenic pulmonary oedema (adult respiratory distress syndrome) is the underlying pathological process in some cases.[6,37]

Table I. Proposed criteria for the classification of the severity of poisoning resulting from ingestion of glyphosate formulations[6,7]

Asymptomatic
Absence of symptoms and abnormal clinical or laboratory findings
Mild
Short-lived (<24h) buccal or alimentary tract features
Moderate (at least one of the following)
Buccal ulceration
Endoscopically confirmed oesophagitis
Alimentary tract features lasting >24h
Gastrointestinal haemorrhage
Transient hypotension
Transient oliguria
Transient renal impairment
Transient acid-base abnormalities
Transient hepatic damage
Severe (at least one of the following)
Hypotension requiring intervention
Loss of consciousness
Recurrent convulsions
Renal failure requiring replacement therapy
Respiratory abnormalities requiring endotracheal intubation
Cardiac arrest
Death

Yang et al.[40] described acute bronchospasm requiring ventilation, bronchodilators and corticosteroids in a 55-year-old male who committed suicide by ingesting 500mL Roundup®. His clinical course was complicated by pneumomediastinum, tension pneumothorax and subcutaneous emphysema and he died on day 62 from sepsis.

Renal and hepatic impairment (increased transaminase activities) and/or impaired consciousness are not uncommon in more severe cases[5,37] and usually reflect reduced organ perfusion, although a direct toxic effect of glyphosate or surfactant may contribute. Similarly hypovolaemia is an important factor in cases complicated by cardiogenic shock and/or acidosis, although direct toxicity may contribute.[41] Glyphosate/surfactant-induced myocardial depression may also occur.[42]

Other reported features include dilated pupils,[7,35,41] convulsions,[7] confusion,[6] a neutrophil leucocytosis,[5,6] fever[5] and increased serum amylase activity.[6] In one series of 131 cases of glyphosate/surfactant ingestion,[5] metabolic acidosis (standard bicarbonate <22 mmol/L) was present in 48%. Electrocardiographic abnormalities occur in up to 20% of cases, usually sinus tachycardia and/or nonspecific ST-T wave changes,[5] although sinus bradycardia and atrioventricular block[9] are recognised. Stella and Ryan[37] recently reported a case in which broad complex tachycar-

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dia (140 beats/min) was a presenting feature following ingestion of 1L glyphosate concentrate, although this patient also developed marked metabolic acidosis (pH 7.25, HCO_3 13 mmol/L) with a serum potassium concentration of 8.2 mmol/L. Bradycardia and ventricular arrhythmias may occur as the pre-terminal events.[6,7,35,41]

5.1.1 Prognosis

There is a reasonable correlation between the amount of glyphosate ingested, the severity of damage[6] and the likelihood of serious systemic sequelae[6,7] or death.[5,7] Tominack et al.[7] reported concordance between the estimated ingested volume and outcome, recording a mean ingested volume of glyphosate concentrate of 263 ± 100mL by 11 fatal cases compared with 120 ± 112mL by 86 survivors. Similarly, in their series of 131 ingestions, Lee et al.[5] estimated a mean (±SD) volume ingested of 122 ± 12mL by survivors compared with 330 ± 42mL by those who died ($p < 0.001$). When a large quantity is ingested, death typically ensues within 72 hours.[5] However, not all cases are consistent with this prediction and atypical cases are recognised.[6,35] For example, Temple and Smith[35] described a 43-year-old female who died some 24 hours after ingesting 200–250mL Roundup® concentrate and in whom the principal postmortem findings were pulmonary oedema and acute tubular necrosis. She had been found semi-comatose and covered in vomitus and deteriorated rapidly, the features being dominated by hypotension, metabolic acidosis, anuria and hyperkalaemia. Gastrointestinal haemorrhage and corrosion were not reported. The same authors described another patient who experienced only vomiting despite apparently consuming 1L of Roundup® concentrate.[35] A 34-year-old woman died shortly after consuming some 150mL of a herbicide containing glyphosate trimesium 0.28 g/L (as pure glyphosate).[12] The speed with which death followed ingestion in this case may indicate a greater risk from trimesium salts compared with others.

Other features significantly ($p < 0.001$) more likely in patients who die than in those who survive include: the development of respiratory distress, impaired consciousness, pulmonary oedema, shock, arrhythmias, renal failure requiring haemodialysis and the presence of infiltrates on chest x-ray.[5] Stella and Ryan[37] suggested that the triad of pulmonary oedema, metabolic acidosis and hyperkalaemia are also poor prognostic indicators. Advancing age is also associated with a less favourable prognosis.[5,7]

5.2 Skin Exposure

Skin contact with ready-to-use glyphosate formulations can cause irritation[32] and contact dermatitis has been reported occasionally;[43] these effects are probably due to the preservative, Proxel® (benzisothiazolin-3-one), which is to be phased out in the European Union shortly. Severe skin burns are rare.[44] A 78-year-old woman developed severe chemical burns on her legs, knees and lumbar area after kneeling on ground recently sprayed with a 41% glyphosate, 15% POEA mixture and wearing clothing that had been placed on the same ground 'for some time' prior to being worn. A burning sensation developed in the exposed skin and was followed several hours later by the appearance of erythematous macules that developed into bullae within 24 hours. Complete resolution without scarring occurred after 4 weeks of conventional treatment.

Transfer by contaminated hands to the face led to swelling and paraesthesiae in one case and periorbital oedema in another.[35] The same authors also reported generalised pompholyx in a man who was accidentally drenched with horticultural-strength Roundup®.[35] Although photosensitivity to glyphosate was claimed to have developed in a 64-year-old man,[45] the authors later concluded that the responsible agent was not glyphosate but a co-formulant.[46]

Cutaneous exposure to a glyphosate-containing herbicide (formulation not specified) has been postulated as contributing to Parkinsonism.[47] A previously healthy 54-year-old man was exposed on his trunk, arms, legs and face to glyphosate drift whilst spraying a garden on a windy day. Despite washing the herbicide off some 30 minutes later, he developed conjunctival hyperaemia and a generalised rash 6 hours after exposure. A week later, blisters developed that resolved over 15 days following treatment with oral antihistamines. One month after exposure the patient displayed rigidity of the limbs. A year later he developed a resting tremor of his left arm and also complained of impaired short-term memory. Clinical assessment at this stage confirmed other features of Parkinsonism with paucity of facial expression, global akinesia, rigidity and cogwheeling. Brain magnetic resonance imaging revealed bilateral hyperdense lesions in the globus pallidus and substantia nigra. Clinical improvement ensued with levodopa therapy. The authors proposed that glyphosate may have contributed to the neurological pathology by virtue of its chemical similarity with glycine, a co-factor required for activation of the *N*-methyl-D-aspartate (NMDA) receptor, which controls excitatory actions in the central nervous system and is also involved in memory and learning. However, glyphosate does not possess NMDA activity clinically.

5.3 Inhalation

Inhalation is a minor route of exposure,[13] but spray mist may cause oral or nasal discomfort, an unpleasant taste in the mouth, tingling and throat irritation.

A single case of acute pneumonitis alleged to be due to inhalation of Roundup® in a warm, confined space over a 4-hour period has been reported.[48] Within a few days pharyngeal and laryngeal burns developed. However, the worker involved also used diesel fuel as a cleaning agent over the same period. Whether the features

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were due to glyphosate including POEA or to some other cause was subsequently debated but not resolved.[49,50]

5.4 Eye Exposure

Eye contact may lead to mild conjunctivitis, and superficial corneal injury is possible if irrigation is delayed or inadequate. One man who accidentally rubbed Roundup® into one eye developed chemosis, palpitations, raised blood pressure, headache and nausea.[35] Permanent eye damage is most unlikely.[51]

6. Management

6.1 Ingestion

Management is symptomatic and supportive. As ingestion of ready-to-use consumer products is unlikely to cause systemic toxicity, gut decontamination is unnecessary. Gastric lavage may be considered if a life-threatening amount of a concentrated glyphosate formulation has been ingested within 1 hour (unless there is evidence of buccal irritation or burns) but there is no evidence that this procedure reduces absorption of either glyphosate or POEA. Alternatively, if there is no buccal irritation or burns, oral activated charcoal, 50–100g for an adult, may be considered.

Hypotension secondary to fluid loss should be treated conventionally with appropriate use of crystalloids, colloids and blood products. Dopamine or dobutamine may be required in severe cases. Early upper alimentary endoscopy should be considered in patients with features suggesting significant gastrointestinal corrosive effects.

Intubation and mechanical ventilation are likely to be required in the most severely poisoned. Significant acidosis that persists despite adequate oxygenation and perfusion should be corrected by intravenous sodium bicarbonate. An electrocardiogram should be performed in all symptomatic cases.

New formulations containing the potassium salt of glyphosate may present a large load of oral potassium. Clinical experience with these formulations is limited. Pending further experience, careful monitoring of potassium concentrations is appropriate following ingestion of potassium salt formulations.

6.2 Skin Exposure

Thorough skin decontamination is the priority with removal of contaminated clothing and washing with soap and water management is otherwise symptomatic and supportive. Severe lesions should be managed as chemical burns.

6.3 Inhalation

Removal from exposure is the priority. Management is otherwise symptomatic and supportive.

6.4 Eye Exposure

Eye contamination should be managed as a chemical exposure with attention particularly to adequate irrigation.

7. Conclusions

The deliberate ingestion of concentrated glyphosate-containing formulations results in severe toxicity and death in some 10–15% of cases, depending on the amount ingested. There is still controversy as to the precise mechanisms of toxicity of the formulations, particularly the role of the surfactant POEA in inducing toxicity. It is unclear also whether non-POEA containing formulations are less (or even more) toxic than POEA-containing formulations.

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