HEALTH RISK ASSESSMENT: GLYPHOSATE

Prepared as part of a Ministry of Health
contract for scientific services

by

Dr Rob Lake

October 2014

Client Report FW14022

HEALTH RISK ASSESSMENT: GLYPHOSATE

Dr Rob Lake
Manager
Risk and Response Group
ESR

Matt Ashworth
Project Leader

Jefferson Fowles and Peter Cressey
Peer Reviewers

CONTENTS

LIST OF TABLES

GLOSSARY

Acute toxicity	1. *Adverse effects* of finite duration occurring within a short time (up to 14 d) after administration of a single *dose* (or *exposure* to a given *concentration*) of a test substance or after multiple doses (exposures), usually within 24 h of a starting point (which may be exposure to the *toxicant*, or loss of reserve capacity, or developmental change, etc.) 2. Ability of a substance to cause *adverse effects* within a short time of dosing or *exposure*
ADI	Acceptable daily intake, a measure of the amount of a specific substance in food or drinking water that can be ingested (orally) on a daily basis over a lifetime without an appreciable health risk
Adverse effect	A change in biochemistry, physiology, growth, development morphology, behaviour, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to other environmental influences
ARfD	Acute reference dose, an estimate of the amount a substance in food or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risks to the consumer on the basis of all known facts at the time of the evaluation
Dermal	Cutaneous, pertaining to the skin
Dose	Total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue
Dose response	Association between dose and the incidence of a defined biological effect in an exposed population
Dose response assessment	Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose–response assessment is the second of four steps in risk assessment
Exposure assessment	Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.
Harm	An adverse effect. Damage or adverse effect to a population, species, individual organism, organ, tissue, or cell
Hazard identification	The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first

	stage in hazard assessment and the first of four steps in risk assessment.
Incidence	Number of occurrences of illness commencing, injury, or of persons falling ill, during a given period in a specific population usually expressed as a rate
Injury	Any physical harm or damage serious enough to warrant medical treatment by a health professional either at the scene or in a hospital or primary care practice.
Irritant	Producing inflammation or irritation
Necrosis	Morphological changes indicative of cell death
No observed adverse effects level (NOAEL)	Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure
Ocular	Pertaining to the eye
Oral	Pertaining to or via the mouth
Permanent harm	An adverse effect from which the subject does not recover
Risk characterisation	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.
Toxicological endpoints	An observable or measurable biological event or chemical concentration (e.g., metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure

SUMMARY

The purpose of this report is to develop a generic health risk assessment for glyphosate. This report only considers domestic, non-occupational, routine and incidental exposure to glyphosate formulations.

Formulations containing glyphosate are available to the general public for weed control purposes. The herbicidal active ingredient in these formulations is usually the isopropyl ammonium salt. The most well-known brand name is Roundup, but there are at least sixteen other glyphosate containing products on the New Zealand market. These products are generally described as mixtures of glyphosate and other "inert" ingredients, principally surfactants.

In New Zealand, Roundup is available to consumers as a concentrate (40% glyphosate) or ready to use (approximately 1% glyphosate solution). The concentrate is widely available in containers of up to 1L (with a child resistant cap).

Long-term animal studies and human epidemiological studies do not indicate a risk of serious illness (e.g. cancer) from chronic glyphosate exposure. The focus in this assessment is on acute exposure to glyphosate concentrate.

Adverse health effects from acute poisoning events will be dose-related. Severe health effects and fatalities do occur, and generally result from intentional ingestion of larger volumes (>100 mL) by adults, whereas ingestion of volumes <50 mL is likely to be asymptomatic. However, estimated exposures for young children suggest that adverse health effects in the form of gastrointestinal distress are likely from ingestion of <50 mL and ingestion of volumes up to 100 mL has the potential to cause moderate to severe adverse health effects in children. Products on the New Zealand market include warnings to keep the product away from children, and also include childproof caps.

The risk of severe systemic effects from dermal exposure appears to be low, and case reports indicate that when local effects, such as irritation, burning or swelling, do occur they resolve within days.

Given the large toxicological database, the lack of chronic exposure-related toxicity, and the high doses required to achieve acute effects, Roundup formulations appear to present a low level of toxicological risk to consumers, except for risk following ingestion of more than 50 mL of concentrated glyphosate formulations.

1. INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for glyphosate. This report will only consider domestic, non-occupational, routine and incidental exposure to glyphosate formulations available to the public as concentrate (approximately 40% glyphosate by volume).

Exposure scenarios have been considered for the most common or likely exposure events to assess the health risk for vulnerable groups.

In this report the term "glyphosate" refers to the active ingredient in herbicide formulations, while "glyphosate formulation" refers to the generic product concentrate. Where the term "Roundup" is used, it is because the information derives from studies using that specific product. It is assumed that information on Roundup also applies to other glyphosate formulations.

It is assumed that use of dilute glyphosate formulations (approximately 1% by volume) for their intended purpose is unlikely to result in adverse health effects. Intentional oral exposure by adults intending self-harm is also not considered. The literature has been reviewed to gather information on two scenarios:

- Accidental ingestion (particularly by children) of glyphosate formulation concentrate; and,
- Accidental dermal exposure by adults and children of glyphosate formulation concentrate.

The literature evaluating potential toxicity of glyphosate and glyphosate formulations both *in vivo* and *in vitro* is vast. We have relied on critical reviews for the most part to assess health effects, and concentrated on studies that provide information on exposures.

1.1 Consumer Product Description – Glyphosate herbicides

The herbicidal properties of glyphosate were discovered by Monsanto Company scientists in 1970. Herbicide formulations containing glyphosate, such as Roundup, non-selectively inhibit plant growth through interference with the production of essential aromatic amino acids by inhibition of the enzyme enolpyruvylshikimate phosphate synthase, which is responsible for the biosynthesis of chorismate, an intermediate in phenylalanine, tyrosine, and tryptophan biosynthesis. This pathway for biosynthesis of aromatic amino acids is not shared by members of the animal kingdom, making blockage of this pathway an effective inhibitor of amino acid biosynthesis exclusive to plants (Williams et al 2000).

Formulations containing glyphosate are available to the general public for weed control purposes. The herbicide is usually present as the isopropyl ammonium salt. Previously some formulations contained a trimethylsulfonium salt of glyphosate (glyphosate trimesium) but these have been removed from the market after suggestions that their acute mammalian toxicity is higher than the isopropyl ammonium salt (Bradberry et al 2004). The most well-known brand name is Roundup, but there are at least sixteen other glyphosate containing products on the

New Zealand market.[1] These products are generally described as mixtures of glyphosate and other "inert" ingredients.

In New Zealand, Roundup is available to consumers as a concentrate (40% glyphosate) or ready to use (approximately 1% glyphosate solution).[2] The concentrate is widely available in containers of up to 1 L (with a child resistant cap) from garden centres, while larger volumes (up to 1000 L) can also be purchased.[3] A handler certificate for larger volumes is not required as long as glyphosate is not applied to water, but for domestic use, storage of volumes of greater than 1 L would seem unlikely.[4]

Specific information on the ingredients of glyphosate formulations available in New Zealand is limited. A study of acute poisoning cases from South Korea has reported that the glyphosate formulations available in that country are made up of: glyphosate 15–43% volume, surfactant 6–16% volume, water 40–50% volume, and a few percent volume of artificial colouring agents, antifoaming agents, and supplementary agents (Seok et al 2011). Of the formulations consumed by poisoning cases, the most common (55% of cases) surfactant was polyoxyethylene tallow amine (POEA) at approximately 15% by volume. Other types and mixtures of polyoxyethylene alkyl amine surfactants made up most of the remaining formulations.

---

[1] http://www.nzchemicalsuppliers.co.nz/list/search?search=glyphosate accessed 5 May 2014
[2] http://roundup-garden.co.nz/ accessed 9 May 2014
[3] http://www.ravensdown.co.nz/nz/products/pages/agrochemicals/herbicides/glyphosate-g360.aspx accessed 29 May 2014
[4] http://www.epa.govt.nz/Publications/ER-IS-33-2.pdf accessed 29 May 2014

2 HAZARD IDENTIFICATION

2.1 Previous Assessments

2.1.1 Systemic toxicity

Many organisations have conducted risk assessments of glyphosate, including Health Canada, the US Environmental Protection Agency (USEPA) and the World Health Organization (WHO). An updated risk assessment was published in 2000 (Williams et al 2000). This review considered the active ingredient glyphosate, the formulation Roundup, the most common surfactant POEA, and the major breakdown product of glyphosate, aminomethylphosphonic acid (AMPA).

The oral absorption of glyphosate and AMPA is low, and both compounds were eliminated essentially unmetabolised. After oral administration in rats approximately 30% is absorbed, peak plasma concentrations are reached after 1-2 hours, and decline quickly (Bradberry et al 2004). Data from humans are limited, but results from two patients indicated that peak plasma concentrations of glyphosate were reached after 4 hours, and had become undetectable after 12 hours (Bradberry et al 2004).

In vitro percutaneous (through the skin) absorption of glyphosate through human skin was no more than 2% when applied for up to 16 hours, either as concentrated Roundup or as a diluted spray solution. Studies in rhesus monkeys showed similar results, with a maximum of 2.2% of an applied dose (undiluted Roundup or diluted glyphosate) absorbed after time periods of up to seven days. A further *in vitro* dermal penetration study on human skin with Roundup (formulated or at spray dilution) showed even lower absorption (<0.2% over 2 days) (Williams et al 2000).

A review of glyphosate and non-cancer health outcomes supported the absence of adverse health effects (Mink et al 2011). Cohort, case–control and cross-sectional studies on glyphosate and non-cancer outcomes evaluated a variety of endpoints, including non-cancer respiratory conditions, diabetes, myocardial infarction, reproductive and developmental outcomes, rheumatoid arthritis, thyroid disease, and Parkinson's disease. The review found no evidence of a consistent pattern of positive associations indicating a causal relationship between any disease and exposure to glyphosate.

The same authors later considered cancer outcomes (Mink et al 2012). It was stated that the review found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate. This conclusion has been backed up by a review of genotoxicity studies which concluded that glyphosate and glyphosate formulations did not present significant genotoxic risk (Kier and Kirkland 2013). Most assays evaluating the genotoxic effect of glyphosate showed negative results; positive results from some DNA damage endpoints using high or toxic dose levels suggested that this was a result of cytotoxicity rather than DNA interaction.

A prospective cohort study of glyphosate exposure and cancer incidence in the US Agricultural Health Study (AHS) compiled information from 57,311 licensed pesticide

applicators in Iowa and North Carolina (De Roos et al 2005). Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes studied. There was a suggested association with multiple myeloma incidence that should be followed up as more cases occur in the AHS. However, the validity of this latter finding has been challenged (Farmer et al 2005).

A critical analysis of studies of developmental and reproductive outcomes in humans and animals after glyphosate exposure concluded that there was no solid evidence linking glyphosate exposure to adverse outcomes at environmentally realistic exposure concentrations (Williams et al 2012). The review included exposure estimates from biomonitoring of workers following normal application practices. The estimated exposures were more than 500-fold less than the oral reference dose for glyphosate set by the US Environmental Protection Agency.

2.1.2   Influence of surfactant

Numerous studies have suggested that the toxicity of glyphosate containing herbicide formulations derive from the surfactant rather than the active ingredient. Studies on rats have found that adverse health effects from preparations containing surfactant POEA alone, or surfactant and glyphosate, were greater than from glyphosate alone (Adam et al 1997). The administration of intravenous lipid emulsion to attenuate surfactant toxicity in patients with acute glyphosate intoxication has been shown to reduce the incidence of certain symptoms (hypotension, arrhythmia) (Gil et al 2013; Han et al 2010).

2.1.3   Local toxicity

Roundup has been rated "severe" for eye irritation and "slight" for skin irritation from animal studies (Williams et al 2000). However, studies with humans have found little evidence for long term dermal or ocular health effects.

Contact challenges with 346 volunteers have been used to assess the irritation (single application and 21 day cumulative), sensitisation, photoirritation (24 hours with intermittent ultraviolet irradiation) and photosensitisation effects of glyphosate (isopropylamine salt, surfactant not specified) (Maibach 1986). The test material was a 10% v/v dilution of the herbicide Roundup, which contained 41% glyphosate (i.e. a 4% glyphosate solution). Water was used as the control, and all-purpose liquid cleaner, liquid dishwashing liquid, and baby shampoo were tested in parallel. No positive skin tests were found or irritation reported by subjects exposed to Roundup. It was concluded that Roundup had less irritant potential that the cleaner or dishwashing liquid, and was comparable with the baby shampoo.

A review of ocular effects in 1513 cases of Roundup exposure reported to a certified regional centre of the American Association of Poison Control Centres from 1993 to 1997 found that most exposures resulted in either no injury (21%) or transient minor symptoms (70%) (Acquavella et al 1999). There was temporary injury in 2% of cases. None of the reported exposures resulted in permanent change to the structure or function of the eye.

There have been occasional reports of temporary adverse effects on skin after exposure. A case report of skin toxicity from a glyphosate formulation described chemical burns on the trunk and legs of a 78 year old Italian woman who appeared to have lain on ground recently sprayed with herbicide, and then put on clothes which had lain on the same ground (Amerio et al 2004). Complete resolution of symptoms was observed after four weeks of treatment. It was reported that the woman had been exposed to glyphosate concentrate. Three cases of dermal effects have been described from New Zealand (Temple and Smith 1992). Roundup concentrate accidentally rubbed into the eye of one person caused periorbital oedema and chemosis (swelling) which resolved the next day. Another case wiped his face with double strength Roundup which led to a swollen face and paraesthesia (tingling, burning) which settled down after 48 hours. The third case was accidentally drenched by horticultural strength Roundup and developed pompholyx (a form of eczema) which required treatment.

2.2   Observations in Humans

2.2.1   Incident surveillance and epidemiological studies

Where available the specific product ingested is given below. It is likely that summary reports of glyphosate poisoning refer to glyphosate formulations.

2.2.1.1 New Zealand

Four cases of glyphosate formulation poisoning in New Zealand were reported in 1991 (Menkes et al 1991). All appeared to be intentional, and one case was fatal. Two of these cases were also reported in the 1992 paper summarised below. The other two cases ingested an estimated 235 mL and 50-100 mL of Roundup Concentrate, and recovered after approximately 2 weeks and 3 days respectively. Symptoms for these cases were diarrhoea, vomiting and lethargy, and vomiting and abdominal pain, respectively.

A further report on glyphosate formulation poisoning in New Zealand was published by the National Poisons Information Centre in 1992 (Temple and Smith 1992). Several cases had been reported to the Centre during the previous ten years (six are described in detail). Three cases of dermal exposure to Roundup concentrate were self-limiting and responded well to symptomatic and supportive care (see above). One non-fatal case of Roundup concentrate ingestion (1 L) vomited almost immediately, responded well to treatment and was discharged after four days. The remaining two cases were fatal, one of which had ingested petrol along with the Roundup. The other fatal case had ingested approximately 200-250 mL of Roundup concentrate, vomited, and then failed to respond to treatment and died after approximately 24 hours.

In New Zealand, data on hazardous substance exposure incidents is collated in the Hazardous Substances Surveillance System (HSSS) by the Massey University Centre for Public Health Research (CPHR). For the period 2006 to 2011, 5827 hospitalisation incidents were reported to HSSS. Of these, four events concerning

glyphosate (not further specified) were reported (1 in 2006, 2 in 2008, 1 in 2009).[1] A further 18 incidents were reported for Round Up (1 in 2007, 4 in 2008, 1 in 2009, 9 in 2010, 3 in 2011).

Information was provided by the New Zealand National Poisons Centre[2] on the 20 substances accounting for most calls to the centre for each year during the period from 2008 to 2012. Glyphosate does not occur amongst these top 20 substances, but Roundup was the subject of approximately 50 calls each year.

2.2.1.2 United States

The American Association of Poison Control Centers (AAPCC) supports the United States network of 56 poison centres.[3] The association publishes an annual report including summary statistics of all exposures reported to the poison centres during a calendar year. In 2012, 3464 single exposures of glyphosate (not further specified) were reported, including two fatalities (both intentional suicides). Of the exposures where the age of the person was known, most (1949/3065, 63.6%) were adults 20, or more, years of age, but the next highest age group was young children five, or less, years of age (875/3065, 28.5%). Most exposures were reported as being unintentional (3257/3455, 94.2%).

2.2.1.3 United Kingdom

The UK National Poisons Information Service Annual Report for 2010/2011 contains the following information about glyphosate.[4] Accidental exposure was the predominant method of poisoning. Of the 2194 accidental adult exposures, 283 were exposed to glyphosate or glyphosate trimesium herbicides (not further specified). For the 257 cases with a specific age recorded, the age group most frequently affected was of 40–49 year olds, with an overall male predominance. The majority of patients accidentally exposed to glyphosate were allocated severity grades of minor (58%) or asymptomatic (28%).

Among accidental exposures the most frequently reported symptoms were those affecting the gastrointestinal tract (87 cases, or 30.7%), eye (71) and skin (65). Common gastrointestinal features include nausea and vomiting (29 cases) followed by burning sensation or pain of mouth/ throat (17) and abdominal pain (13). Eye irritation/pain (52 cases) and skin irritation (47) were the most common features in their respective categories. The majority of deliberate self-harm exposures (42 cases) were graded asymptomatic (40%) or minor (32%), with moderate (14%), severe (7%) and fatal (7%) exposures less common. Gastrointestinal features were the most common in deliberate self-harm cases, with 18 cases presenting with either nausea, vomiting, abdominal pain or diarrhoea. The next two most common organ categories involved were cardiovascular (11 cases) and respiratory (five).

---

[1] The National Minimum Dataset (NMDS) is the national collection of public discharge and clinical information for inpatients and day patients. It is important to note that hospital events recorded in the NMDS represent individual events rather than individual people. The number of events will be higher than the number of people, because one person can contribute numerous unique hospital events to the dataset.

[2] http://www.poisons.co.nz/index.php Accessed 23 January 2014

[3] http://www.aapcc.org/ Accessed 25 November 2013

[4] http://www.npis.org/NPISAnnualReport2010-11.pdf accessed 7 May 2014

2.2.1.4 Japan

Data concerning clinical cases of pesticide poisoning from 1998 to 2002 from 65 hospitals affiliated with the Japanese Association of Rural Medicine have been reported (Nagami et al 2005). A total of 346 cases were located, which was estimated to represent 1.5-2.5% of all cases across Japan. Suicides accounted for 70% of the located cases, followed by accidental exposures during spraying work (16%) or accidental ingestion (8%). Of the 15 cases of glyphosate (not further specified) poisoning reported, 13 recovered, 1 died, and there was one unspecified outcome.

2.2.1.5 Taiwan

A study of 97 cases of glyphosate poisoning (11 fatalities) in Taiwan between 1986 and 1988 reported that the average amount ingested by survivors was 120 ± 112 mL, while non-survivors ingested 263 ± 100 mL (range 150-500 mL) (Tominack et al 1991). The product ingested was described as a glyphosate surfactant herbicide concentrate containing the isopropylamine salt of glyphosate and a non-ionic tallow amine surfactant.

A review of 93 cases of acute poisoning with a glyphosate-surfactant herbicide treated at a hospital in Taiwan between 1980 and 1989 found that the average amount of Roundup concentrate ingested by non survivors was 184 ± 70 mL (range 85-200 mL) (Talbot et al 1991). However, larger amounts (500 mL) were ingested by some patients who experienced only mild to moderate symptoms. The product involved was determined to be genuine Monsanto Roundup in 90 of the 93 cases, while the remainder were local equivalent products. Accidental exposure after dermal contact with spray or consumption of sprayed food (6 cases) was asymptomatic.

A retrospective study of 131 glyphosate-surfactant herbicide intoxication cases at a hospital between 1988 to 1995 was conducted to identify predictors for mortality (Lee et al 2000). Eleven of the 131 patients died. The estimated intakes were: survivors 122 ± 12 mL, while for fatalities the estimated intakes were 330 ± 42 mL (p = <0.001).

A case-control study used glyphosate-surfactant herbicide intoxicated patients admitted to the emergency departments of two hospitals in Taiwan between 1996-2003 and 2000-2003 (Lee et al 2008). Fifty eight patients were enrolled, and 17 died. The purpose of the study was to identify pre-existing conditions that could contribute to a predictive model of mortality. In this study, the amount ingested was not associated with survival; the amount ingested by survivors is reported as mean 112 ± 114 mL standard deviation, while fatalities ingested 129 ± 138 mL (p = 0.62).

An analysis of glyphosate-surfactant herbicide exposures reported to the Taiwan National Poison Control Centre between 1986 and 2007 identified 2186 relevant cases (Chen et al 2009). The products were described as commercial formulations. Most (92.5%) were oral exposure, and suicide attempts (74.6%). Following oral exposure the majority of patients either exhibited mild effects (64.9%) or were

asymptomatic (10.1%). The case fatality rate was 7.2%. Shock and respiratory failure caused most fatalities.

2.2.1.6 Korea

A case series of 107 patients (2 fatalities) resulting from suicide attempts using glyphosate formulations has been reported from Korea. This study examined in detail the effect of the surfactants used in the formulations. It was found that the volume of surfactant ingested was strongly correlated with the appearance and severity of symptoms (Seok et al 2011).

2.2.1.7 France

A case series of glyphosate poisoning cases in France described clinical symptoms as well as blood concentrations (Zouaoui et al., 2013). The materials ingested were several different concentrate formulations, including Roundup, Pistol EV, Verdys, and Glyper. The 13 cases (including six fatalities) reported to the laboratory in Limoges from 2002-2009 were described, and for 10 of these symptoms were able to be recorded (the remaining 3 cases, all fatalities, were forensic cases). Following an acute intoxication by glyphosate, the clinical signs most frequently described were oropharyngeal ulceration (5/10) (sore throat, dysphagia), erosion of the gastro-intestinal mucous membrane (2/10) (gastric pains, blood vomiting) and vomiting (3/10). The principal disturbed biological parameters were: high lactate (3/10) and acidosis (7/10). The more severe symptoms reported were: respiratory distress (3/10), cardiac arrhythmia (4/10), hyperkaleamia, impaired renal function (2/10), hepatic toxicity (1/10), altered consciousness (3/10) and haemodynamic complication which in some cases necessitated a mechanical ventilation and intubation. In fatalities, cardiovascular shock (3/10), cardiorespiratory arrest, haemodynamic disturbance, intravascular disseminated coagulation (1/10) and multiple organ failure were observed. This information suggests that symptoms are a result of local corrosion and associated shock (possibly enhanced by the surfactant) rather than systemic effects from glyphosate.

2.2.1.8 Sri Lanka

A fatality rate from glyphosate poisoning of 7.7% has been widely quoted based on retrospective studies from Taiwan, Korea and Japan. A prospective study of acute glyphosate poisoning conducted in Sri Lanka between 2002 and 2007 identified 601 patients (19 deaths) of which 216 were admitted to hospital (Roberts et al 2010). The majority of cases had ingested a concentrated formulation (36% w/v glyphosate) and the severity of symptoms was correlated (p=0.0072) to the estimated volume ingested:

* asymptomatic (median 50 mL, interquartile range 25-90 mL)
* minor (median 58 mL, interquartile range 25-100 mL)
* moderate to severe (median 53 mL, interquartile range 25-125 mL)
* fatal (median 200 mL, interquartile range 75-350 mL)

The case fatality rate in this study (3.2%) was lower than previous reports.

2.2.1.9 Case Reports

A case report has described a 51 year old man from San Diego who intentionally ingested about 240 mL of Roundup (Sampogna and Cunard 2007). The case was considered significant because despite not having a history of renal disease, he developed acute renal failure.

Vomiting is one of the symptoms of acute glyphosate ingestion – this may reduce the amount available for absorption, as has been observed in a reported case in Japan where the serum glyphosate levels were lower than expected given the apparent amount of Roundup ingested (Hori 2003).

A fatality from ingestion of approximately 300 mL of Roundup has been described from the United Kingdom (Beswick and Millo 2011). Two fatalities in Australia have been reported, where the ingested amounts of glyphosate concentrate were 1 L and 500 mL (Stella and Ryan 2004). A further fatality from Thailand was estimated to have ingested approximately 550 mL of Roundup concentrate (Sribanditmongkol et al 2012).

2.2.1.10   Inhalation studies

There are few data on the effects of inhalation as an exposure route. The 1994 report by the International Programme on Chemical Safety described a number of studies on workers that estimated inhalation exposure, but absorption data were lacking.[1] Estimated exposures for agricultural spray workers suggested a factor of approximately 1000 between exposure and the no observable effect level (NOEL, based on inhalation studies with rats).

Dermal and inhalation exposures are potentially important for farming populations. The Family Farm Study in the United States examined urinary glyphosate concentrations for farmers and their families before, during and after glyphosate applications (Acquavella et al 2004). Sixty percent of farmers had detectable levels of glyphosate in their urine on the day of application. The geometric mean (GM) concentration was 3 ppb, the maximum value was 233 ppb, and the highest estimated systemic dose was 0.004 mg/kg. Farmers who did not use rubber gloves had higher GM urinary concentrations than did other farmers (10 ppb vs. 2.0 ppb). For spouses, 4% had detectable levels in their urine on the day of application. Their maximum value was 3 ppb. For children, 12% had detectable glyphosate in their urine on the day of application, with a maximum concentration of 29 ppb. 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 U.S. Environmental Protection Agency reference dose for glyphosate.

However, the Family Farm Study relates to occupational exposure which is outside the scope of this assessment.

---

[1] http://www.inchem.org/documents/ehc/ehc/ehc159.htm#SectionNumber:10.1 accessed 12 May 2014

2.2.1.11   Summary

Glyphosate formulation ingested by people is rapidly excreted within hours largely unchanged. Acute poisoning results in a variety of gastrointestinal effects including vomiting, which will reduce exposure. The effects of acute ingestion range from asymptomatic to fatal. This is partly related to the amount ingested, although pre-existing conditions also play a role in determining outcome.

Fatalities due to ingestion of glyphosate formulations have been reported for volume in the range 75-1000 mL. For an adult weighing 70 kg and assuming a density for glyphosate formulations of approximately one, these volumes equate to fatal doses in the range 1.1-14.3 g/kg bw. Assuming a glyphosate content for formulations of 40%, the fatal dose range equates to 440-5720 mg/kg bw of glyphosate.

Dermal absorption is very low. Dermal exposure can result in skin effects such as oedema in a small proportion of cases.

Exposure through inhalation appears to be minimal, although there are few studies on which to base this conclusion. Studies of agricultural spray workers, for whom inhalation exposure could be expected to be significant, indicate that their exposure is well below the reference dose.

3 DOSE RESPONSE

3.1 Acute Dermal Toxicity

Dermal LD_{50} values in animal studies for Roundup were >5000 mg/kg. The LD_{50} for POEA was >1260 mg/kg for dermal exposure (Williams et al 2000).

As humans may be exposed to Roundup, rather than POEA in isolation, the dermal LD_{50} will be used as the critical effect level for assessment of human dermal exposure. While the actual LD_{50} is not known, a conservative approach will be taken and the upper dose limit used in dermal toxicological studies (5000 mg/kg) will be used as a surrogate for the LD_{50}. It should be noted that no mortality and no adverse effects were noted at this level of exposure for either Roundup or glyphosate (Joint FAO/WHO Meeting on Pesticide Residues 2006; Mensink and Janssen 1994) and 5000 mg/kg bw can be considered to be an acute NOAEL for dermal exposure.

3.2 Oral Systemic Toxicity

3.2.1 Acute

Animal studies

Oral LD_{50} values in animal studies for Roundup were >5000 mg/kg. The LD_{50} for POEA was 1200 mg/kg for oral exposure (Williams et al 2000).

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) considered setting an acute reference dose (ARfD) for glyphosate, but concluded it was not necessary, due to its low acute toxicity (Joint FAO/WHO Meeting on Pesticide Residues 2006).

Observations in humans

The study of acute ingestion cases in Taiwan indicates that where dose could be estimated, the odds ratio (OR) for severe symptoms or death compared to a non-severe exposure was dose dependent (Chen et al 2009). Using a dose of ≤50 mL commercial glyphosate-surfactant formulation as a reference, the OR for severe/death exposure was 3.2 at 51-100 mL, 4.7 at 101-150 mL, 5.3 at 151-200 mL, 5.9 at 201-300 mL, and 11.4 at ≥301 mL.

A similar dose response relationship for glyphosate concentrate is suggested by the study from Sri Lanka (Roberts et al 2010):

- asymptomatic (median 50 mL, interquartile range 25-90 mL)
- minor (median 58 mL, interquartile range 25-100 mL)
- moderate to severe (median 53 mL, interquartile range 25-125 mL)
- fatal (median 200 mL, interquartile range 75-350 mL)

The French case series study determined blood glyphosate concentrations with a mean value of 61 mg/L (range 0.6–150 mg/L) and 4146 mg/L (range 690–7480 mg/L) respectively in mild–moderate intoxication and fatal cases (Zouaoui et al 2013). In the severe intoxication case for which blood has been sampled, the blood

glyphosate concentration was found at 838 mg/L. Death was usually associated with larger ingested volumes (500 mL in one patient) and high blood glyphosate concentrations.

More serious symptoms (e.g. respiratory distress, cardiac arrhythmia, hyperkaleamia, impaired renal function, hepatic toxicity) appear unlikely to result from ingestions of less than 100 mL of glyphosate concentrate formulation in adults (Chen et al 2009; Roberts et al 2010). Fatality is very unlikely.

Available reports of the effect of ingestion of glyphosate formulations suggest that adults ingesting volumes of <50 mL are likely to be asymptomatic (Chen et al 2009; Roberts et al 2010). After oral administration in rats, rabbits, laying hens and lactating goats, absorption of glyphosate from the gastrointestinal tract has been estimated as 15-36% (Williams et al 2000).[1] For a 70 kg adult, 50 mL of 40% glyphosate concentrate represents an exposure of 286 mg/kg bw, equating to an internal dose of 103 mg/kg bw, assuming 36% absorption.

As a significant amount of human-specific information on the acute toxicity of glyphosate formulations is available, this information will be used to assess the significance of estimates of human exposure.

3.2.2 Chronic

The US Environmental Protection Agency has established a reference dose for systemic toxicity of glyphosate of 1.75 mg/kg bw/day.[2,3] This value was based on a maternal NOAEL of 175 mg/kg bw/day for reduced foetal weight and minor foetal skeletal defects in a rabbit developmental toxicity study. An uncertainty factor (UF) of 100 was applied.

JMPR established a lower acceptable daily intake (ADI) of 1.0 mg/kg bw/day for glyphosate, based on a NOAEL for salivary gland alterations in a long-term rat study (Joint FAO/WHO Meeting on Pesticide Residues 2006). A safety factor of 100 was applied. The ADI was a group ADI covering glyphosate and its major metabolite, AMPA.

It should be noted that the current report only considers the potential for accidental acute exposure to glyphosate formulation.

---

[1] http://www.inchem.org/documents/pds/pds/pest91_e.htm#2.1.1 accessed 30 May 2014
[2] 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.
[3] http://npic.orst.edu/factsheets/glyphotech.html#reg accessed 14 May 2014

4   EXPOSURE ASSESSMENT

4.1   Exposure Scenarios for Glyphosate Concentrate Formulations in New Zealand

For the purposes of this health risk assessment we considered three exposure scenarios:

1. Dermal exposure during preparation and/or use by adults;
2. Dermal exposure following spilling of container contents by children; and
3. Acute poisoning through accidental ingestion by children.

4.2   Dermal exposure

Dermal exposure to glyphosate concentrate formulation may occur through spillage, most likely during preparation of dilutions for use. Dermal exposure will cause skin effects in a small proportion of cases (perhaps 2%, (Acquavella et al 1999)). Such effects appear to resolve quickly (within days).

Dermal exposure was determined using the formulae:

$$A_{der} = C_{der} \times T_{der} \times Area_{der} \text{ x } BIO_{derm} \text{ x } N_{events}$$

$$U_{derm\,pot} = \frac{A_{der} \text{ x } F_{absorp}}{BW}$$

Where:

Concentration in the product (g/mL)	C_{der}
External exposure to skin (g/event)	A_{der}
Potential dermal uptake rate (g/kg BW/day)	$U_{derm\,pot}$
Thickness of the film layer on skin (default = 0.01cm)	T_{derm}
Surface area of skin exposed (cm^2)	$AREA_{derm}$
Bioavailability for dermal exposure (default = 1)	BIO_{derm}
Number of events per period (usually, events/day)	N_{events}
Average bodyweight	BW
Factor to quantify absorption	F_{absorp}

As the relevant limit derived from animal dermal toxicological studies was for the dose applied to skin, the factor to quantify absorption in the equation above is set to 1.

4.2.1.1 Adults

There is potential for concentrated glyphosate formulation to be spilled on the skin during preparation of dilutions for spraying. For the current study, it was considered that a 'worst case, spillage may result in both hands being exposed to concentrated glyphosate formulation. The hands make up approximately 5.2% of the adult body surface area, with the median body surface area for adults being in the range 1.8-2.0 m^2, depending on age (US Environmental Protection Agency 2011). Using a highest median body surface area of 2.0 m^2, the corresponding hand surface area would be 0.104 m^2 or 1040 cm^2.

For a glyphosate concentrate containing 40% glyphosate, an adult with a body weight of 70 kg and an assumed 2.0% dermal absorption:

A_{der} = 0.4 x 0.01 x 1040 x 1 x 1 = 4.2 g/event

$U_{derm\ pot}$ = 4.2 x 1/70 = 0.06 g/kg BW/event or 60 mg/kg BW/event

4.2.1.2 Children

Concentrated glyphosate formulations are sold in child-resistant packaging (CRP) and there should be little opportunity for dermal exposure of children to glyphosate, other than the small amounts associated with spray drift. However, CRP cannot be assumed to be a completely effective risk management measure.

It is assumed that spilling of glyphosate formulation concentrate will be more likely in the young (2-3 years). Exposure will be limited, to some extent, by the volume of material in retail packages (usually 250 mL or 1 L). It has been assumed that a serious spillage may affect up to one-third of a young child's body surface area (mean total body surface area = 0.61 m^2 for a 2-3 year old child (USEPA 2008).

Using a median body weight for a 2-3 year old child of 13.6kg (USEPA 2008) and other parameters as given above gives:

A_{der} = 0.4 x 0.01 x 6100/3 x 1 x 1 = 8.1 g/event

$U_{derm\ pot}$ = 8.1 x 1/13.6 = 0.6 g/kg BW/event or 600 mg/kg BW/event

4.3   Accidental ingestion

As discussed above, CRP should mitigate the risk of accidental ingestion of concentrated glyphosate formulations by children. However, while the majority of the literature on human glyphosate ingestion relates to adult intentional ingestion, accidental ingestion by children has been reported.

There is a lack of data on the amounts ingested by children in accidental glyphosate formulation poisonings. One study was located, which estimated the amount of caustic substances consumed as between 1-100 mL for ingestion (Melek et al 2008). While glyphosate formulations are not caustic, it is plausible that accidental ingestion

of glyphosate formulations will involve similar volumes. Based on this study, two volumes were assessed; a median volume of 50 mL and a high volume of 100 mL of glyphosate concentrate formulation.

Exposures were assessed for median and 5th percentile body weight 2-3-year-olds, with body weights taken from the USEPA child specific exposure factors handbook table 8-3 (USEPA 2008).

The ingestion exposure dose is a normalisation of the amount of a substance taken in by ingestion per unit body weight, the equation for calculation of this value is shown below:

$$Ingestion\ exposure\ dose\ = \frac{C\ \times IR\ \times EF}{BW}$$

Where:

C = contaminant concentration in g/mL

IR = ingestion volume (mL)

EF = exposure factor (the proportional absorption of contaminant)

BW = body weight (kg)

The exposure factor (EF) is used to convert an ingested dose to an internal dose. However, the critical effect levels that will be used for risk characterisation are derived from ingested doses and an EF of one was used that maintain consistency between exposure estimates and critical effect levels.

Exposure estimates for ingestion of glyphosate concentrate by children 2-3 years are summarised in Table 1.

Table 1:   Estimated exposure to glyphosate from ingestion of glyphosate concentrate (40% glyphosate) by children aged 2-3 years

Ingested volume (mL)	Body weight percentile	Body weight (kg)	Exposure (g)	Exposure (mg/kg body weight)
50	5th	10.9	20	1830
50	50th	13.6	20	1470
100	5th	10.9	40	3670
100	50th	13.6	40	2940

5   RISK CHARACTERISATION

The risk of serious illness (e.g. cancer) from chronic glyphosate exposure is very low, based on the information in Section 2.1.1. The focus in this assessment is on acute exposure to glyphosate concentrate formulation.

5.1   Acute Dermal Exposure

Risks associated with acute dermal exposure scenarios were assessed using a margin of exposure (MoE) approach. The MoE is calculated from the animal critical effect level divided by the estimated human exposure (EFSA 2005). For the acute dermal exposure scenarios in the current study a LD_{50} has been used as the acute critical effect level. Estimated human exposures are those derived in section 4.2 of this report.

Margins of exposure for acute dermal exposure scenarios are summarised in Table 2.

Table 2:   Summary of acute dermal exposure scenarios for concentrated glyphosate formulations and associated margins of exposure

Exposure scenario	Estimated exposure (mg/kg bw)	Critical effect level (mg/kg bw)	Margin of exposure
Adult exposure (hands) while preparing glyphosate formulation dilution	60	5000	83
Dermal exposure of a 2-3 year old child, accidentally spilling concentrated glyphosate formulation	600	5000	8

bw = body weight

Although the critical effect level used to determine the MoEs shown in Table 2 relates to a serious toxicological point of departure (50% mortality in test animals), it should be noted that the critical effect level of 5000 mg/kg bw is a limit value and no mortality was observed following dermal exposure at this dose level. Additionally, none of the studies of acute glyphosate toxicity following dermal application reported any clinical signs or treatment-related changes at necropsy and the dose of 5000 mg/kg bw is effectively a NOAEL for acute dermal exposure. It is probably that the true LD_{50} is considerably greater than 5000 mg/kg bw or that glyphosate is essentially non-toxic by the dermal route of exposure. Consequently, the MoEs derived and shown in Table 2, should be considered to be lower bound estimates.

There is currently no international consensus on what magnitude of MoE represents an acceptable level of exposure, although an MoE of 100 (equivalent to a safety factor of 100) should probably be considered a minimum (World Health Organization

2009). While the actual MoEs are likely to be higher than those shown in Table 2, it is not currently possible to quantitatively assess the risks to human health due to dermal exposure to concentrated glyphosate formulations. However, the low dermal absorption of glyphosate formulations (Williams et al 2000) and reports of no systemic adverse health effects following dermal exposure (Maibach 1986; Talbot et al 1991) suggest that the risks associated with acute exposure by this route are low. However, effects following dermal exposure cannot be completely discounted and a case report identified neurological impairment (reduced finger flexion and sensation with reduced nerve conduction) following prolonged accidental exposure to a glyphosate formulation (Mariager et al 2013).

5.2 Acute Oral Exposure (Ingestion)

The estimated glyphosate exposure for an adult from 50 mL of glyphosate concentrate formulation has been estimated to be 286 mg/kg bw. Acute ingestion of this amount of glyphosate is likely to be asymptomatic. Adults ingesting 50-100 mL (286-572 mg/kg bw for a 70 kg adult and a glyphosate content of 40% in the concentrated formulation) are likely to experience minor to moderate symptoms of gastrointestinal distress, including oropharyngeal ulceration (sore throat, dysphagia), erosion of the gastro-intestinal mucous membrane (gastric pains, blood vomiting), and vomiting. Fatalities have been associated with ingestion of volumes of concentrated glyphosate formulations of greater than 200 mL (1140 mg/kg bw for a 70 kg adult and a glyphosate content of 40% in the concentrated formulation)

The lower body weight of children provides higher exposures on a body weight basis than those for adults, as shown in Table 1, with exposures resulting from ingestion of 50 or 100 mL of concentrated glyphosate formulation resulting in glyphosate exposures in the range 1830-3670 mg/kg bw. Although there is a shortage of data on the effects of acute ingestion by young children, the estimated exposures suggest that ingestion of 50-100 mL of concentrated glyphosate formulation by a young child could result in moderate to severe adverse health effects. The possibility of such a dose being fatal cannot be excluded.

5.3 Local Effects

Case reports indicate that concentrated glyphosate formulations can result in irritation, burning or swelling following dermal or ocular exposure. However, when symptoms occur, they generally resolve within days.

6   CONCLUSIONS

No conclusions can be drawn from the quantitative risk characterisation for dermal exposure to glyphosate formulations, but qualitative information suggests that it is unlikely that systemic toxicological effects would result from this route of exposure. Exposure of the skin or eyes to glyphosate formulations may result in local dermal or ocular irritation which will resolve within days.

For acute oral exposure to glyphosate formulations, ingestion of less than 50 mL by adults is unlikely to cause symptoms or harm. Ingestion of larger volumes (50-100 mL) by adults is likely to result in minor to moderate symptoms, while much larger volumes (>200 mL) may result in fatality.

Acute oral exposure of children to 50 mL of glyphosate formulation generates an estimated exposure higher than the estimated exposure for adults ingesting 200 mL of glyphosate formulation, and this exposure may cause fatality in adults. Consequently children ingesting 50 mL or more of glyphosate formulation are likely to suffer significant adverse health effects.

7 REFERENCES

Acquavella JF, Weber JA, Cullen MR et al. 1999. Human ocular effects from self-reported exposures to Roundup® herbicides. *Human and Experimental Toxicology* 18 (8): 479-86

Acquavella JF, Alexander BH, Mandel JS et al. 2004. Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. *Environmental Health Perspectives* 112 (3): 321-6

Adam A, Marzuki A, Rahman HA et al. 1997. The oral and intratracheal toxicities of ROUNDUP and its components to rats. *Veterinary and Human Toxicology* 39 (3): 147-51

Amerio P, Motta A, Toto P et al. 2004. Skin toxicity from glyphosate-surfactant formulation. *Journal of Toxicology. Clinical Toxicology* 42 (3): 317-9

Beswick E, Millo J. 2011. Fatal poisoning with glyphosate-surfactant herbicide. *Journal of the Intensive Care Society* 12 (1): 37-9

Bradberry SM, Proudfoot AT, Vale JA. 2004. Glyphosate poisoning. *Toxicological Reviews* 23 (3): 159-67

Chen YJ, Wu ML, Deng JF et al. 2009. The epidemiology of glyphosate-surfactant herbicide poisoning in Taiwan, 1986-2007: A poison center study. *Clinical Toxicology* 47 (7): 670-7

De Roos AJ, Blair A, Rusiecki JA et al. 2005. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environmental Health Perspectives* 113 (1): 49-54

EFSA. 2005. Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic (Request No EFSA-Q-2004-020). *EFSA Journal* 282 1-31

Farmer DR, Lash TL, Acquavella JF. 2005. Glyphosate results revisited. *Environmental Health Perspectives* 113 (6): A365-6; author reply A6-7

Gil HW, Park JS, Park SH et al. 2013. Effect of intravenous lipid emulsion in patients with acute glyphosate intoxication. *Clinical Toxicology* 51 (8): 767-71

Han SK, Jeong J, Yeom S et al. 2010. Use of a lipid emulsion in a patient with refractory hypotension caused by glyphosate-surfactant herbicide. *Clinical Toxicology* 48 (6): 566-8

Hori Y. 2003. Glufosinate poisoning and analysis using biological samples. *Japanese Journal of Forensic Toxicology* 21 (1): 1-19

Joint FAO/WHO Meeting on Pesticide Residues. 2006. *Pesticide Residues in Food - 2004. Part II. Toxicological Evaluations*. Geneva: World Health Organization

Kier LD, Kirkland DJ. 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. *Critical Reviews in Toxicology* 43 (4): 283-315

Lee CH, Shih CP, Hsu KH et al. 2008. The early prognostic factors of glyphosate-surfactant intoxication. *American Journal of Emergency Medicine* 26 (3): 275-81

Lee HL, Chen KW, Chi CH et al. 2000. Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication: A review of 131 cases. *Academic Emergency Medicine* 7 (8): 906-10

Maibach HI. 1986. Irritation, sensitization, photoirritation and photosensitization assays with a glyphosate herbicide. *Contact Dermatitis* 15 (3): 152-6

Mariager TP, Madsen PV, Ebbehoj NE et al. 2013. Severe adverse effects related to dermal exposure to a glyphosate-surfactant herbicide. *Clinical Toxicology* 51 (2): 111-3

Melek M, Edirne Y, Cobanoglu U et al. 2008. An analysis of corrosive substance ingestion of children in eastern Turkey. *Eastern Journal of Medicine* 13 1-6

Menkes DB, Temple WA, Edwards IR. 1991. Intentional self-poisonin with glyphosate-containing herbicides. *Human and Experimental Toxicology* 10 (2): 103-7

Mensink H, Janssen P. 1994. *Glyphosate*. Environmental Health Criteria 159. Geneva: World Health Organization

Mink PJ, Mandel JS, Lundin JI et al. 2011. Epidemiologic studies of glyphosate and non-cancer health outcomes: a review. *Regulatory Toxicology and Pharmacology* 61 (2): 172-84

Mink PJ, Mandel JS, Sceurman BK et al. 2012. Epidemiologic studies of glyphosate and cancer: a review. *Regulatory Toxicology and Pharmacology* 63 (3): 440-52

Nagami H, Nishigaki Y, Matsushima S et al. 2005. Hospital-based survey of pesticide poisoning in Japan, 1998--2002. *International Journal of Occupational and Environmental Health* 11 (2): 180-4

Roberts DM, Buckley NA, Mohamed F et al. 2010. A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning. *Clinical Toxicology* 48 (2): 129-36

Sampogna RV, Cunard R. 2007. Roundup intoxication and a rationale for treatment. *Clinical Nephrology* 68 (3): 190-6

Seok SJ, Park JS, Hong JR et al. 2011. Surfactant volume is an essential element in human toxicity in acute glyphosate herbicide intoxication. *Clinical Toxicology* 49 (10): 892-9

Sribanditmongkol P, Jutavijittum P, Pongraveevongsa P et al. 2012. Pathological and toxicological findings in glyphosate-surfactant herbicide fatality: a case report. *American Journal of Forensic Medicine and Pathology* 33 (3): 234-7

Stella J, Ryan M. 2004. Glyphosate herbicide formulation: A potentially lethal ingestion. *EMA - Emergency Medicine Australasia* 16 (3): 235-9

Talbot AR, Shiaw MH, Huang JS et al. 1991. Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. *Human & Experimental Toxicology* 10 (1): 1-8

Temple W, Smith N. 1992. Glyphosate herbicide poisoning experience in New Zealand. *New Zealand Medical Journal* 105 173-4

Tominack RL, Yang GY, Tsai WJ et al. 1991. Taiwan National Poison Center survey of glyphosate--surfactant herbicide ingestions. *Journal of Toxicology. Clinical Toxicology* 29 (1): 91-109

US Environmental Protection Agency. 2011. *Exposure Factors Handbook: 2011 Edition.* 7 August 2014. http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf

USEPA. 2008. *Child-Specific Exposure Factors Handbook. EPA/600/R-06/096F.* Wasington DC: US Environmental Protection Agency

Williams AL, Watson RE, DeSesso JM. 2012. Developmental and reproductive outcomes in humans and animals after glyphosate exposure: a critical analysis. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 15 (1): 39-96

Williams GM, Kroes R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regulatory Toxicology and Pharmacology* 31 (2 Pt 1): 117-65

World Health Organization. 2009. *Principles and methods for the risk assessment of chemicals in food.* Environmental Health Criteria 240. Geneva: World Health Organization

Zouaoui K, Dulaurent S, Gaulier JM et al. 2013. Determination of glyphosate and AMPA in blood and urine from humans: About 13 cases of acute intoxication. *Forensic Science International* 226 (1-3): e20-e5