GLYPHOSATE

SUMMARY

Background

Glyphosate, commonly known by its original trade name Roundup™ (manufactured by Monsanto), is the world's most widely used herbicide. Glyphosate-based herbicides are manufactured by many companies in many countries.

Glyphosate is sprayed on numerous crops and plantations, including nearly 80% of genetically modified (GM) crops (canola, corn, cotton, soybean, sugar beet); with relatively high levels permitted as residues in food and animal feed. It is used as a pre-harvest desiccant, and because it is a systemic herbicide it cannot be completely removed from food by washing, peeling or processing. It is widely used in home gardens and public places including roadsides. Human exposure is widespread and constantly recurring.

Very aggressive public relations and marketing by its developer, Monsanto, has resulted in the widespread belief that glyphosate is 'safe'. Registration processes have generally supported this attitude, and there are no national or international bans. However, independent scientific studies and widespread poisonings in Latin America (resulting from aerial application) are beginning to reveal the true effects of glyphosate-based herbicides. Now France's Supreme Court has upheld judgements by two previous courts that "Monsanto falsely advertised its herbicide as 'biodegradable' and claimed it 'left the soil clean'" (Anon 2009).

Poisonings

Glyphosate herbicides have been frequently used in self-poisonings and many deaths have occurred, especially in Asia. There have also been many cases of unintentional poisonings amongst users and bystanders. Widespread poisonings have occurred in Latin America as a result of aerial spraying of GM soybean crops, and of coca crops in Colombia—effects being recorded as far as 10 km away from the supposed spray zone. The coca spraying (instigated by a US government funded program to eliminate cocaine production in Colombia) has also resulted in widespread animal deaths and food crop losses. Symptoms of poisoning commonly reported from unintentional exposure include vomiting, diarrhoea, abdominal pain, gastrointestinal infections, itchy or burning skin, skin rashes and infections (particularly prevalent in children), blisters, burning or weeping eyes, blurred vision, conjunctivitis, headaches, fever, rapid heartbeat, palpitations, raised blood pressure, dizziness, chest pains, numbness, insomnia, depression, debilitation, difficulty in breathing, respiratory infections, dry cough, sore throat, and unpleasant taste in the mouth. Other effects reported include balance disorder, reduced cognitive capacity, seizures, impaired vision, smell, hearing and taste, drop in blood pressure, twitches and tics, muscle paralysis, peripheral neuropathy, loss of gross and fine motor skills, excessive sweating, and severe fatigue.

Acute Toxicity

Glyphosate has a low toxicity rating (WHO Table 5) despite the substantial evidence of adverse health effects. Surfactants added to formulated glyphosate products may be more toxic: the surfactant POEA in Roundup is 2 to 3 times more toxic than the glyphosate itself. There are a number of other chemicals added to glyphosate formulations or contaminating them; some are known to be harmful, but many are regarded as trade secrets and it is unknown which might be contributing to the health effects.

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Long-term Toxicity

Recently scientists have found harmful effects on human cells at levels of glyphosate too low to have a herbicidal effect, some at levels similar to those found in food. These effects are amplified by the adjuvants in the Roundup formulation, which assist penetration of the cells by glyphosate. Several researchers have reported that glyphosate appears to accumulate in human cells.

Cancer, genotoxicity, endocrine disruption, reproduction

The International Programme on Chemical Safety (IPCS) and the United States Environmental Protection Agency (US EPA) have declared that glyphosate is not carcinogenic to humans. The US EPA originally classified glyphosate as a Group C "possible human carcinogen", then re-classified it as Group D "not classifiable as to human carcinogenicity", then as Group E "evidence of non-carcinogenicity in humans", and then in 2006 rephrased this as "Group E carcinogen with no evidence of human carcinogenicity".

Yet there is substantial laboratory and some epidemiological evidence that points to the opposite conclusion. Some researchers have concluded that glyphosate and its formulations clearly present a risk of carcinogenic, mutagenic, and reproductive effects on human cells.

Numerous laboratory studies have shown that glyphosate and the Roundup formulation can be genotoxic and endocrine disrupting. One study summarises these effects occurring at doses substantially lower than those used in agriculture, or permitted as residues: at 0.5 mg/kg (40 times lower than levels permitted in soybeans in the US) they were anti-androgenic; at 2 mg/kg they were anti-oestrogenic; at 1 mg/kg they disrupted the enzyme aromatase; at 5 mg/kg they damaged DNA, and at 10 mg/kg there were cytotoxic. These effects can result in crucial outcomes for sexual and other cell differentiation, bone metabolism, liver metabolism, reproduction, development and behaviour, and hormone dependent diseases such as breast and prostate cancer (Gasnier et al 2009).

Studies have demonstrated that glyphosate and/or Roundup cause genetic damage in human lymphocytes and liver cells; bovine lymphocytes; mouse bone marrow, liver, and kidney cells; fish gill cells and erythrocytes; caiman erythrocytes; tadpoles; sea urchin embryos; fruit flies; root-tip cells of onions; and in Salmonella bacteria. Other studies have shown that it causes oxidative stress, cell-cycle dysfunction, and disruption to RNA transcription, all of which can contribute to carcinogenicity.

Laboratory studies have shown that very low levels of glyphosate, Roundup, POEA, and the metabolite AMPA all kill human umbilical, embryonic and placental cells. Roundup can reduce sperm numbers, increase abnormal sperm, retard skeletal development, and cause deformities in amphibian embryos.

Exposure to glyphosate-based herbicides, even at very low doses may result in reproductive and hormonal problems, miscarriages, low birth weights, birth defects, and various cancers—especially haematological cancers such as non-Hodgkin's lymphoma, and hormonal cancers such as breast cancer.

Several epidemiological studies have linked exposure to glyphosate with non-Hodgkin's lymphoma, hairy cell leukaemia, multiple myeloma, DNA damage; and one study with spontaneous abortions and pre-term deliveries.

Neurological

Glyphosate is assumed by regulators to have no neurological effects—the US EPA did not require neurotoxicity studies to be carried out for the registration of Roundup. However there is emerging evidence that glyphosate can affect the nervous system, and in particular areas of the brain associated with Parkinson's disease. In one case study glyphosate exposure was linked to 'symmetrical parkinsonian syndrome'. An epidemiological study of children identified a link with Attention-Deficit/Hyperactivity Disorder (ADHD).

Other effects

Glyphosate damages liver cells and interferes with a number of enzymes important in metabolism.

Environmental Effects

The environmental effects of glyphosate of greatest concern are those that occur at a subtle level, and can result in significant disruption of aquatic and terrestrial eco-systems, including the agro-ecosystem.

Aquatic effects

Glyphosate is water soluble, and is increasingly found in the environment at levels that have

caused significant effects on species that underpin the entire aquatic food chain. Glyphosate and/or Roundup can alter the composition of natural aquatic communities, potentially tipping the ecological balance and giving rise to harmful algal blooms. It can have profound impacts on microorganisms, plankton, algae and amphibia at low concentrations: one study showed a 70% reduction in tadpole species and a 40% increase in algae. Insects, crustaceans, molluscs, sea urchins, reptiles, tadpoles, and fish can all be affected, with vulnerability within each group varying dramatically between species. Effects include reproductive abnormalities, developmental abnormalities and malformations, DNA damage, immune effects, oxidative stress, modified enzyme activity, decreased capacity to cope with stress and maintain homeostasis, altered behaviour, and impaired olfaction that can threaten their survival. Amphibians are particularly vulnerable. Roundup is generally more toxic than glyphosate, especially to fish.

Terrestrial effects

Soil and plant health

As with the aquatic environment, it is the subtle effects causing disruption of the ecosystem that are of greatest concern, particularly effects on the agroecosystem. Glyphosate is toxic to some but not all soil microorganisms, altering microbial community dynamics in ways that are harmful to plants and to ecological balance. It increases microorganisms capable of metabolising the chemical. It can reduce some beneficial organisms such as saprophytic fungi that decompose dead plant material and are important for soil fertility. Numerous studies have shown that glyphosate stimulates the growth of a number of fungal pathogens that cause diseases in many crops. The upsurge in use of glyphosate in no-till agriculture has brought about a resurgence of some diseases. Glyphosate binds micronutrients in the soil and causes micronutrient deficiencies in plants that increase their susceptibility to disease, decrease their vigour, and produce micronutrient-deficient food crops. It can reduce the plant's production of lignin and phenolic compounds, which are also important for disease resistance. It can reduce nitrogen-fixation in legumes such as soybean.

Glyphosate can alter the nutritional composition of foods, for example the protein and fatty acid content of soybeans. It can cause iron deficiency in soybeans, which is a concern for human health as human iron deficiency is widespread.

Earthworms and beneficial insects

Glyphosate has adverse effects on some earthworms; and a number of beneficial insects useful in biological control, particularly predatory mites, carabid beetles, ladybugs, and green lacewings. It can also adversely effect other insects that play an important part in ecological balance such as springtails, wood louse, and field spiders.

Birds and other animals

Glyphosate use may result in significant population losses of a number of terrestrial species through habitat and food supply destruction. There have been reports of numerous deaths of livestock and domestic animals as a result of the aerial spraying of glyphosate in Colombia.

Environmental Fate

Soils

Glyphosate is relatively persistent in soil, with residues still found up to 3 years later in cold climates. It is less persistent in warmer climates, with a half-life between 4 and 180 days. It is bound onto soil particles, and this was once thought to mean that glyphosate is not biologically active within soil, nor will it leach to groundwater. However it is now known that it can easily become unbound again, be taken up by plants or leach out, indicating a greater risk of groundwater contamination. It can reduce nitrogen and phosphate fertility of soils.

Water

Glyphosate is soluble in water, and slowly dissipates from water into sediment or suspended particles. Although it does break down by photolysis and microbial degradation, it can be persistent for some time in the aquatic environment, with a half-life of up to nearly 5 months, and still be present in the sediment of a pond after 1 year.

Residues of glyphosate have been found in a wide range of drains, streams, rivers, and lakes, in many countries including Canada, China, France, Netherlands, Norway, USA, and the UK. Urban use on road and rail sides is contributing significantly to this contamination, with residues being found in sewage sludge and wastewater treatment plants. Contamination of 'vernal pools'—pools that are shallow and disappear in dry weather—are a concern for amphibia, for which these water sources are critical.

Residues have also been found in groundwater in Canada, Denmark, the Netherlands, and USA. They have been detected in the marine environment off the Atlantic Coast of France; and in the rain in Belgium and Canada.

Resistance

Fourteen weeds in 14 countries have developed resistance to glyphosate. Most of this resistance has been caused by the repeated use of glyphosate in GM crops and no-till agriculture. Some has resulted from a gradual evolution of exposed weed species, and some from gene flow from GM crops to weed relatives. The latter has been observed with sugar beet in France, canola in Canada, creeping bentgrass in USA, and also with corn and soybean. Now even Monsanto is recommending the use of other herbicides in addition to glyphosate in Roundup-Ready crops (crops genetically modified to be tolerant of Roundup), to slow the onset of resistance in weeds.

Climate Change effects

A number of glyphosate's adverse effects can be expected to increase with climate change: higher temperatures enhance glyphosate's reduction of chlorophyll and carotenoids in freshwater green algae, increase toxicity to fish, and increase susceptibility to *Fusarium* head scab in cereals.

Alternatives

There are numerous design, mechanical and cultivational practices, as well as some non-chemical herbicides based on plant extracts, that can be used instead of glyphosate herbicides, depending on the weed species and the situation.

Chemical Profile

Common name

Glyphosate

Common trade name

Roundup

Chemical names and form

N-(phosphonomethyl)glycine

Glyphosate is a weak organic acid that consists of a glycine moiety (part of a molecule) and a phosphonomethyl moiety.

Technical grade glyphosate is a colourless, odourless crystalline powder, formulated as water-soluble concentrates and granules.

Most formulations contain the isopropylamine ammonium salt of glyphosate (glyphosate-isopropyl ammonium).

Molecular formula

$C_3H_8NO_5P$

Chemical group

Phosphinic acid

Other related chemicals

Glyphosate, diammonium salt
Glyphosate, dimethylammonium salt (glyphosate dimethylamine)
Glyphosate, ethanolamine salt
Glyphosate, monoammonium salt (glyphosate sel d'ammonium)
Glyphosate, potassium salt
Glyphosate, sesquisodium (or sodium) salt
Glyphosate, trimethylsulfonium salt (glyphosate-trimesium)

CAS numbers

Glyphosate	1071-83-6
Isopropylamine salt	38641-94-0
Monoamine salt	114370-14-8
Diammonium salt	69254-40-6
Sesquisodium salt	70393-85-0
Glyphosate-trimesium	81591-81-3
(Aminomethyl)phosphonic acid	1066-51-9

Trade names

Because glyphosate is so widely used and is off-patent, there are now very many generic formulations—Malaysia alone had 311 registered formulations containing glyphosate in February 2009—so there is a very large number of trade names.

In many cases glyphosate formulations can be identified by the word G360, G450, G510, or G580, preceded by a trader's name. The number indicates the concentration of glyphosate in the formulation, i.e. G360 has 360 g/l of glyphosate.

In some cases only the term 'Herbicide' is used, preceded by a variety of names such as Farmers Own, Growers, Harvest, etc.

Others make a play on the original product 'Roundup' by including 'up' in the name (Bright Up, Conto-Up, Dry-Up, Farm Up, Foldup, Ken-Up, Kleenup, Klin-Up, Move-Up, Set-Up, Sunup, Take-Up, Touch Up, Wes-Up, Zap Up); or the opposite, 'down' (Touchdown, Turndown); or 'round' (Myround, Roundsate, Seround).

Some names are variations of the word glyphosate (Glifosate, Glifosato, Glyfo, Glyfosaat, Glyfosat, Glymax, Glyphogan, Glyphosat, Glyphotis); use the last syllable of glyphosate (Ancosate, Envisate, Farmfosate, Gofosate, Herbisate, Ken-phosate, Masate, Megasate, Narscosate, Pilarsate, Sulfosate, Sulfosato, Supresate, Tecforsate, Vefosate); or use the chemical constituent glycine (Glyacid, Glycel, Glycin). Many more trade names are in local languages.

Many other trade names bear no distinguishable relationship to Roundup or glyphosate. Some of these attempt to present a benign image (Aglow, Ecomax, Esteem, Granny's Herbicide, Lotus, Spirit, S-Star, Vision); but many more do just the opposite (Ammo, Armada, Arrow, Assassin, Avenger, Challenge, Decimate, E-Kill, Fire, Frontier, Harass, Hatchet, Knockout, Monster, Mustang, Pounce, Punch, Q-Weapon, Raider, Rival, Rodeo, Salute, Samurai, Scud, Sentry, Shoot, Siren, Slash, Smash, Squadron, Stampede, Sting, Swing, Thunder, Tomahawk, Trounce, Turbo, Typhoon, Wallop). Others just try to indicate the product kills weeds (Weedact, Weedcut, Weed-go, Weed Hoe, Weedo, Weego).

Some formulations combine glyphosate with other herbicides such as aminopyralid (Broadnet), 2,4-D (Bimasta, Campaign, Evo, Hat-trick, Kontraktor,

Landmaster), dicamba (Fallowmaster), diquat (A-13692B), imazapyr (Tackle, Imasate), MCPA (Fusta, Rapid, Rextor, Panton), metsulfuron-methyl (Fusion), picloram (Fusta), pyrithiobac sodium (Staple Plus, a pre-plant herbicide for glyphosate-resistant soybeans), simazine (Ricochet), terbuthylazine (Folar, Terminate), and triclopyr (Glytron). The formulation Tag G2, registered in New Zealand, contains glyphosate, amitrole, oxyfluorfen, and terbuthylazine.

Inerts and contaminants

Glyphosate formulations may contain a number of so-called 'inert' ingredients or adjuvants, most of which are not publicly known as in many countries the law does not require that they be revealed. Some information is available about formulations sold in the US, and the following list of 'inerts', provided by Cox (2004), can be expected to be found in products in many other countries. The list is not exhaustive.

POEA (polyoxyethylene alkylamine)
This is the most well known inert as it is contained in the original Roundup formulation. Registration data in New Zealand showed Roundup contained 18% POEA (Watts 1994).
- eye irritant, toxic to fish

Propylene glycol
- genetic damage, reduced fertility, and anaemia in laboratory tests

Glycerine
- genetic damage in human cells and laboratory animals
- reduced fertility in laboratory animals

Sodium sulfite
- genetic damage in human cells and laboratory animals

Sodium benzoate
- genetic damage in human cells and laboratory animals
- developmental problems and reduced newborn survival in laboratory animals

Sorbic acid
- severe skin irritant
- genetic damage in laboratory tests

Sodium salt of o-phenylphenol
- skin irritant
- genetic damage and cancer in laboratory animals

Light aromatic petroleum distillate
- reduced fertility, and growth of newborns, in laboratory animals

Methyl p-hydroxybenzoate
- genetic damage in laboratory animals

3-iodo-2-propynyl butyl carbamate
- thyroid damage and decreased growth in laboratory animals

5-chloro-2-methyl 3(2H)-isothiazolone
- genetic damage and allergic reactions in laboratory tests

Other constituents of surfactants recommended for use with Monsanto's Rodeo formulation include:
- polyol fatty acid esters
- polyoxyethyl polyol fatty acid esters
- paraffin base petroleum oil
- propionic acid
- alkylpolyoxyethylene ether
- octylphenoxypolyethoxyethanol – skin and eye irritant
- n-butanol
- compounded silicone
- nonylphenoxypolyethoxyethanol – also used as a spermicide
- silicone antifoam compound
- isopropanol
- polydimethylsiloxane

(Diamond & Durkin 1997)

Impurities found in technical grade glyphosate include *N*-nitroso-*N*-phosphonomethyl-glycine (also called *N*-Nitrosoglyphosate) (US EPA 1993). *N*-nitroso compounds are "genotoxic, carcinogenic to animals, and may play a role in human cancer development" (Hebels et al 2009).

Registration data for Roundup in New Zealand showed the presence of 1% sulphuric acid and trace amounts of phosphoric acid (Watts 1994).

POEA is contaminated with 1,4-dioxane, reported at levels of 0.03% by the US EPA in 1991. This substance causes liver and nasal cancer in laboratory rodents (NTP 2005; Kano et al 2009) and is "reasonably anticipated to be a human carcinogen" (NTP 2005).

It is clear, then, that exposure to a glyphosate-based herbicide entails exposure to a wide range of other chemicals as well as the glyphosate, about which little information is available and the full health effects of which have not been established. Some, such as POEA, are known to

be more acutely toxic than the glyphosate itself. Others are clearly capable of causing serious chronic effects.

Metabolites

The main metabolite of glyphosate is (aminomethyl) phosphonic acid (AMPA).

N-acetyl-glyphosate (also called *N*-acetyl-*N*-(ph osphonomethyl)glycine) is a metabolite formed when glyphosate is applied to genetically modified 'Optimum Gat' soybean (FR 2008). It is assumed by the US EPA (2008) to be "toxicologically equivalent to glyphosate".

N-acetyl-glyphosate is in turn metabolised to *N*-acetyl (aminomethyl)phosphonic acid (*N*-acetyl-AMPA)—which is considered by the US EPA to be of low toxicity and "of limited concern" (FR 2008).

Mode of action in weeds

The commonly accepted explanation of glyphosate's mode of action is as follows: glyphosate inhibits the enzyme 5-enolpyruvyl-shikimate 3-phosphate synthase, which is essential for the formation of aromatic amino acids (phenylalanine, tyrosine, tryptophan) in plants, by what is commonly referred to as the shikimic pathway. Without amino acids the plants cannot make protein; growth ceases, followed by cellular disruption and death. The shikimic pathway is not found in the animal kingdom, hence glyphosate was thought to be "relatively non-toxic to mammals" (Anadón 2009).

However, there may be more to it than that: after glyphosate is absorbed through the foliage, it is translocated within the plant, down to the roots and released into the rhizosphere (soil surrounding the roots) (Kremer & Means 2009), where it disrupts the soil and root microbial community. As much as 80% of glyphosate absorbed after foliar application is translocated to the shoot apex and root tips (Cakmak et al 2009). Glyphosate's herbicidal action is now suggested to be in part due to, on the one hand stimulation of soil-born pathogens which colonise the roots of the plants, and on the other hand the reliance of many plant defences on the shikimic acid pathway—so that the combination of increased pathogens and increased susceptibility to them is an important element in the death of the plant (Johal & Huber 2009). As far back as 1984 Johal & Rahe demonstrated that the death of bean plants treated with glyphosate resulted from parasitisation by fungal root rot pathogens in the growth medium (refer to section on Plant diseases for more on this).

Uses

Glyphosate is believed to be the world's most heavily used pesticide (Duke & Powles 2008b), with over 600 thousand tonnes used annually (CCM International 2009b).

It is a broad spectrum (non-selective), systemic, post-emergence herbicide used to control annual and perennial plants including grasses, sedges, broadleaf weeds and woody plants. It is used for crops, orchards, glasshouses, plantations, vineyards, pastures, lawns, parks, golf courses, forestry, roadsides, railway tracks, industrial areas, and home gardening.

It is used for pre-harvest desiccation of cotton, cereals, peas, beans, and other crops; for root sucker control; and for weed control in aquatic areas.

The sodium salt (Quotamaster) is used as a growth regulator on sugar cane—to hasten ripening, enhance sugar content, and promote earlier harvesting—and on peanuts.

Glyphosate is also used to destroy drug crops grown in Colombia. Since 2000, the USA has been funding the Colombian government to aerial spray crops of coca and opium—in 2006 alone 171,613 hectares were sprayed. The area sprayed has increased every year since 2000, with a 24% increase from 2005 to 2006 (Leahy 2007). The product used is Roundup-Ultra containing 43.9% glyphosate, POEA, and another adjuvant, Cosmo-Flux 411 F.

Weak solutions of the Roundup formulation are used to devitalise some plant material before importation into Australia and New Zealand to reduce biosecurity risks by preventing propagation of the plant material. For example, the New Zealand biosecurity authority requires that the stems of cut flowers and foliage are immersed to within 50 mm of the flower in a 0.5% solution of Roundup for 20 minutes—this reputedly prevents propagation but allows about a week of shelf life (MAF 2002).

Glyphosate is patented as a synergist for mycoherbicides (natural fungi used for biological control of weeds), as it enhances the virulence of the fungi (Johal & Huber 2009).

Glyphosate is applied by a wide-range of methods, including backpack sprayers, aerial spraying, ground broadcast sprayers of various types, shielded and hooded sprayers, wiper applications, sponge bars, injection systems, and controlled droplet applicators.

The main drivers for global glyphosate use in recent years have been no-till farming, biofuels production and, especially, the development of plants genetically modified to be tolerant of glyphosate (CCM International 2009a). The growing of GM corn, cotton, and soybean in the USA is credited with the eight-fold increase in glyphosate use between 1995 and 2005 (Johnson et al 2009).

Genetically modified (GM) crops

The first glyphosate-tolerant crop was soybean, introduced in the United States in 1996 (Dill et al 2008).

Now, over 80% of the current GM crop acreage worldwide is planted in 4 herbicide-tolerant crops, the vast majority of which are tolerant to high levels of glyphosate (a small amount are tolerant to glufosinate ammonium). The crops are soybean, maize, canola, and cotton, grown mainly in USA, Canada, Argentina, Brazil, and Paraguay (Villar & Freese 2008). By 2008 glyphosate-tolerant soybean was grown on 65.8 million ha (53% of global GM crops), maize on 37.3 million ha (30% of global GM), and cotton on 15.5 million ha (12% of global GM) (Yamada et al 2009).

About 95% of Argentina's annual crop of 47 million tonnes of soybean is the GM Roundup Ready soybean; 200 million litres of glyphosate are applied to it every year, mainly by aerial spraying. This monocultural soybean is grown on 42 million acres, accounting for nearly 50% of all farmland in Argentina (Trigona 2009; Valente 2009).

Bolivia also grows soybean; and Australia grows glyphosate-tolerant cotton and canola (ISAAA 2008). By 2007 about 75% of Australia's cotton was glyphosate-tolerant (Werth et al 2008).

In 2008, glyphosate-tolerant sugar beet was introduced in Canada and USA (James 2008).

On 24 June 2009, the U.S. Court of Appeals "reaffirmed its previous decision to uphold a ban on Roundup Ready (RR) alfalfa, because it could cause irreversible harm to organic and conventional crops, damage to the environment, and economic harm to farmers" (CFS 2009). About 100,000 ha of the GM alfalfa was grown in the USA in 2007 (James 2007).

Glyphosate-tolerant wheat and glyphosate-tolerant creeping bentgrass (turf grass for golf courses) have also been developed by Monsanto, but have not been commercialised.

Pioneer Hi-Bred International, a subsidiary of DuPont, has been developing glyphosate-tolerant corn and soybean containing the trait called 'Optimum Gat'. It proposes that the DuPont herbicide Staple Plus (containing glyphosate and pyrithiobac sodium) be used as a pre-plant herbicide, 10 months before planting (US EPA 2008). It also planned to introduce the trait into cotton and other crops (Pioneer 2007). Introduction of the corn is scheduled for 2010 and the soybean for 2011, once regulatory approval has been achieved (Gullickson 2009). However there appears to be some problems with the trait, and Monsanto is now suing DuPont (Monsanto 2009).

Manufacturers

The original manufacturer of glyphosate herbicides was the Monsanto Company of St Louis, Missouri, USA. It still manufactures them under various trade names including the original Roundup. However since the patent on Roundup expired, many other companies in many countries now also manufacture glyphosate-based herbicides. China is the largest producer, with its production capacity accounting for more than 40% of the global total (CCM International 2009b).

Regulatory Status

Glyphosate was first registered in the USA in 1974; it is now registered worldwide and is the most commonly used herbicide, especially on GM crops.

Very little regulatory action has been taken against glyphosate. In May 2009, the Environmental Lawyers Association of Argentina filed a lawsuit in Argentina's Supreme Court for a ban on glyphosate, citing the study by Professor Carrasco's team (reported in the section on Reproductive toxicology). Argentina's defence ministry has banned the planting of glyphosate-tolerant soybean on lands it rents to farmers. Early in 2009 a court order banned crop spraying of soybean fields near Ituzaingó Anexo suburb of the central Argentinean city of Córdoba after

multiple health complaints. The ban now applies to all fields within 1,000 metres of residential areas in the province of Córdoba (Misculin 2009; Trigona 2009).

International regulatory action

None taken to date.

Toxicological Assessment

The toxicity database for glyphosate is considered by the US EPA (2006) to be "complete and without data gaps". However the US EPA did not require developmental neurotoxicity studies; neither did it require studies of its impact on hormones, or studies of inhalation toxicity.

Most of the studies used for registering glyphosate-based herbicides have been carried out on laboratory animals, often using high levels of exposure to demonstrate visible effect. More recent advances in testing using cell cultures have enabled toxicity of low levels of glyphosate to be determined with much higher sensitivity, eliciting the subtle effects that can be of profound importance to the organism. However, the results of these latter studies have generally not been used for registering the herbicides, and therefore registration outcomes do not reflect the potential and actual effects of glyphosate. Both types of studies are reported here.

Absorption and distribution

About 30-36% of glyphosate is absorbed through the gastrointestinal tract in laboratory animals, with 97.5% excreted unchanged in the faeces and urine together with small amounts of the metabolite AMPA. Less than 1% of the absorbed dose remains in the carcass, and this is primarily in the bone according to the US EPA (2006).

Absorption through the skin is said to be "low" (US EPA 1993), less than 3% (EC 2002).

Small amounts of glyphosate can be absorbed through the skin from contaminated clothing: one study showed that absorption from cotton fabric was 0.74%, half of that absorbed from an aqueous solution (1.42%) in the same study (Webster et al 1996).

Glyphosate is poorly metabolised in animals (<0.5%), to AMPA, according to the US EPA (1993). More recently, Anadón et al (2009) found 6.49% metabolism.

Poor absorption and rapid elimination of glyphosate are the reasons usually given for the assumption that normal exposure (i.e. not intentional self-poisoning) to glyphosate is unlikely to result in systemic effects (e.g. Williams et al 2000, an often-cited review).

However, recent independent work has shown that both glyphosate and AMPA were eliminated slowly from plasma and, although bioavailability was only 23.21%, it is likely that glyphosate is distributed throughout the body by the blood's circulation and there may be considerable diffusion of it into tissues to exert systemic effects (Anadón et al 2009).

Although Williams et al (2000) state that glyphosate does not bioaccumulate, recent findings by Professor Carrasco of Argentina indicate that glyphosate might be accumulating in cells (Valente 2009; Trigona 2009; Ho 2009).

Acute toxicity

The International Programme on Chemical Safety (IPCS) regards glyphosate as having very low acute toxicity to laboratory animals (IPCS 1994). However the commonly used surfactant, POEA, is at least four times more toxic than glyphosate.

US EPA (2006) toxicity categories for glyphosate:

- oral = category IV
- inhalation = category: none
- dermal = category IV
- eye irritation = category III
- skin irritation = category IV

The World Health Organisation Recommended Classification by Acute Hazard for glyphosate (WHO 2005):

- Class 5.

Lethal doses

The lethal dose, LD_{50}, is the dose that kills 50% of test animals.

1. Glyphosate
   - Oral LD_{50} rat = >5,000 mg/kg
   - Dermal LD_{50} rabbit = >5,000 mg/kg
   - (US EPA 1993; IPCS 1994)
   - Inhalation LC_{50} rat = >5 mg/l (EC 2002)

2. Roundup
   - Oral LD_{50} rat = >5,000 mg/kg
   - Dermal LD_{50} = >5,000 mg/kg
   - Inhalation LC_{50} rat = 3.18 mg/kg (Williams et al 2000)

3. POEA
- Oral LD_{50} rat = 1,200 mg/kg
- Dermal LD_{50} = >1,260 mg/kg
  (Williams et al 2000)

4. Isopropylamine
- Oral LD_{50} rat = 820 mg/kg (IPCS 1994)

5. AMPA
- Oral LD_{50} rat = 8,300 mg/kg (IPCS 1997)

Acute sublethal effects

Acute effects of glyphosate observed in laboratory studies included breathing difficulties, ataxia, and convulsions. Roundup has caused cardiac depression, mainly due to the surfactant POEA (IPCS 1994).

Skin and eye irritation

FAO (2000) described glyphosate as causing moderate to severe eye irritancy in rabbits. US EPA (2008) described it as a mild skin irritant but not a skin sensitizer.

POEA is severely irritating to the skin and corrosive to the eyes in rabbits (Williams et al 2000).

Sub-chronic toxicity / intermediate

No and Lowest Observed Adverse Effect Levels

The No Observed Adverse Effect Level (NOAEL) is the lowest dose of the chemical given to a test animal at which no harmful effects are observed, and the Lowest Observed Adverse Effect Level (LOAEL) is the lowest dose of the chemical at which a harmful effect is observed.

The sub-chronic NOAELs and LOAELs provided by US EPA (2006) (unless otherwise stated) are:

- 90-day oral toxicity of glyphosate (mouse):
  NOAEL = 1,500 mg/kg/day
  LOAEL = 4,500 mg/kg/day, based on decreased weight
- 90-day oral toxicity of glyphosate (range finding):
  NOAEL = not established
  LOAEL = 50 mg/kg/day, based on increased phosphorous and potassium
- 90-day oral toxicity of AMPA (rat)
  NOAEL = 400 mg/kg/day
  LOAEL = 1,200 mg/kg/day, based on body weight loss and urinary bladder lesions
- 90-day oral toxicity of POEA (rat)
  NOAEL = 36 mg/kg/day, based on decreased body weight and intestinal irritation (Williams et al 2000)
- 21/28-day dermal (rabbit)
  NOAEL = 1,000 mg/kg/day
  LOAEL = 5,000 mg/kg/day, based on slight erythema and oedema in both sexes, and decreased food consumption by females

Systemic effects

Trials in which laboratory animals were subjected to varying doses of glyphosate caused the following symptoms:
- at all dose levels—increased serum glucose; increased blood potassium and phosphorus levels;
- at high doses only—increased blood urea, nitrogen, and serum alkaline phosphatase; red nasal discharge; pancreatic lesions; growth retardation; salivary gland lesions; diarrhoea; changes in the relative weights of kidney, liver, thymus, heart and testes; inflammation of the gastric lining; increased bile acids; dermal exposure resulted in very slight erythema and oedema, decreased food consumption, and decreased serum dehydrogenase. The salivary gland lesions indicate that glyphosate may be weakly mimicking adrenalin (US EPA 1993; IPCS 1994; FAO 2000)

A number of studies have shown adverse effects of glyphosate, and/or formulations of it, on mammalian enzymes:

- Glyphosate (El Demerdash et al 2001) and Roundup (Caglar & Kolankaya 2008) have inhibitory effects on the enzymes lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) in human serum and rat liver. Activities of these enzymes are considered bioindicators for toxicity; and decreased activity of serum AST and ALT are indicators of liver damage, so the studies indicate glyphosate and Roundup cause liver damage.
- Benedetti et al (2004) showed that brief exposure to a Brazilian formulation of glyphosate caused liver damage in rats (fibrosis and leakage of liver enzymes AST and ALP) and they regarded this to be indicative of irreversible damage to liver cells.
- Sublethal doses of Roundup modified liver enzymatic activity (inhibited monoxygenases) in rats (Hietanen et al 1983).
- Glyphosate inhibited acetylcholinesterase (AChE) in human serum, a hallmark of

organophosphate toxicity (El Demerdash et al 2001).
- Maternal exposure to glyphosate caused functional abnormalities in the specific activity of three enzymes found inside cells—isocitrate dehydrogenase, malic dehydrogenase, and glucose-6-phosphate dehydrogenase (G6PD)—in liver, heart, and brain of pregnant rats and their foetuses (Daruich et al 2001). All enzymes are involved in the generation of NADPH (nicotinamide adenine dinucleotide phosphate), which has many essential roles in metabolism.

Ho & Ching (2003) asserted that glyphosate has the potential to disrupt many important enzyme systems that utilise phosphoenol pyruvate, including energy metabolism and the synthesis of key membrane lipids required in nerve cells. Glyphosate acts in plants by preventing the binding of phosphoenol pyruvate to the active site of the enzyme 5-enolpyruvoyl-shikimate-3-phosphate synthetase (EPSPS) and, although this enzyme is specific to plants, phosphoenol pyruvate is a core metabolite in all organisms.

Roundup, at low concentrations of 1-10 mM,[1] damages rat liver cells, including the mitochondrial membranes and nuclei (Malatesta et al 2008). Higher, sublethal, doses of Roundup depress mitochondrial respiratory activity in rat liver cells (Peixoto 2005).

Chronic toxicity

The US EPA's (2006) chronic NOAELs and LOAELs for glyphosate are:

- NOAEL = 500 mg/kg/day
- LOAEL = not established

Williams et al (2000) provided a chronic NOAEL for AMPA in rats of >2.8 mg/kg/day.

General effects

Laboratory trials have shown decreased body weight gain, increased incidence of cataract and lens abnormalities, increased liver weight, and degeneration of the liver and kidney at high doses (US EPA 1993). Kidney effects include interstitial nephritis, proximal tubule epithelial basophilia and hypertrophy (US EPA 2006).

Cancer

Toxicological data on cancer is inadequate and inconsistent. There is still considerable controversy over the carcinogenic potential of glyphosate, as the available evidence does not clearly indicate that glyphosate, and glyphosate-containing products, are not carcinogenic to humans, although that is the conclusion generally reached by regulators. The IPCS (1994) concluded "bioassays in mice and rats did not indicate that technical glyphosate was carcinogenic". It discounted a study that it said constituted evidence of cancer because a more recent study, at higher doses, did not show the same effect.

Glyphosate was originally classified by the US EPA as a 'Group C', 'possible human carcinogen', on the basis of increased incidence of renal tumours in mice. However, after "independent review of the slides, the classification was changed to D on the basis of a lack of statistical significance and uncertainty as to a treatment-related effect". D classification means "not classifiable as to human carcinogenicity" (HSDB 2006). Then, in 1993, the US EPA declared glyphosate as Group E 'evidence of non-carcinogenicity in humans' on the basis of 3 studies on rats and mice. All of these studies showed a variety of carcinogenic effects, but they were considered by the US EPA to be not caused by the glyphosate:

<u>Study 1 (Sprague-Dawley rats, 26 months)</u>
found -
- thyroid C-cell carcinomas in females at high dose levels—discounted by the EPA as not statistically significant and not treatment related;
- interstitial cell testicular tumours at high dose levels—discounted as not treatment-related and within historical incidence.

<u>Study 2 (Sprague-Dawley rat, 2 years)</u> found -
- pancreatic islet cell adenomas in males at low and high doses—discounted because there was no progression to carcinoma, no statistically significant positive dose-related trend, and not treatment-related;
- liver adenomas in males at low and high doses—discounted as not statistically significant, within the historical range, no progression to carcinoma, not treatment related;
- thyroid C-cell adenomas in males and females at mid and high doses—discounted because there was no progression to carcinoma, not statistically significant and no statistically significant dose trend, not treatment-related.

[1] mM means millimolar concentration. 1M = 1 mole/litre; it is the per unit volume available to the species. nM = nanomolar; *u*M = micromolar.

Study 3 (mice 18 months) found -

- slight increase in incidence of renal tubular adenomas in males at high doses—not statistically significant, therefore deemed 'spontaneous' and not treatment-related.

Subsequent reporting of carcinogenicity by the US EPA (2006) omitted any mention of the first study referring only to the other two, and rephrased the classification as "Group E carcinogen with no evidence of human carcinogenicity".

In addition to these studies, Hardell and Eriksson (1999) referred to a study, reported by Stauffer Chemical Company, which found increased incidence of hepatocellular carcinoma, leukaemia, and lymphoma in mice (Pavkov & Turnier 1986).

The US EPA's classification does not take into account recent epidemiological evidence. Increasingly this is suggesting that glyphosate might be causing non-Hodgkin's lymphoma, and possibly other haematological cancers—refer to section 'Health Effects and Poisoning' for details.

Additionally there is increasing toxicological evidence that glyphosate, Roundup, and the metabolite AMPA all have the potential to cause cancer through mechanisms such as genotoxicity, oxidative stress, and interference with hormonal functions.

Genotoxicity / mutagenicity

A pesticide is genotoxic if it causes damage to a gene that could result in cell death, or result in change in the structure or function of the gene. The damage can be mutagenic (heritable) or non-mutagenic. Mutagenic means causing a change in the genetic structure, usually through base-pair substitution (change in amino acid sequence), deletion, or addition of gene fragments, or some other mechanism. Mechanisms involved include causing damage to the chromosome such as loss, breaks or rearrangements of chromosomal segments. It also includes "sister chromatid exchanges", interchanges and re-attachments of strands in the chromosome during DNA replication, and induction (increase) in the frequency of micronuclei (small fragments formed when chromosomes break). One of the main health implications of genotoxicity is cancer.

The US EPA (2006) reported that glyphosate was non-mutagenic in the bacteria *Salmonella typhimurium*, Chinese hamster ovary cells, and rat bone marrow. FAO (2000) also reported it to be non-mutagenic in human lymphocytes (white blood cells) and mouse bone marrow. Both these determinations are based on test results reported by Monsanto (FAO 2000).

However, there are many other studies that did not come from Monsanto which demonstrate glyphosate, Roundup, and/or the metabolite AMPA to be genotoxic. Even some industry papers show this: Hardell & Eriksson (1999) cite a number of papers from the Stauffer Chemical Company (Majeska & Matheson 1982a,b and 1985a,b) showing gene mutations and chromosomal aberrations in mouse lymphoma cells.

Most compelling are the studies that show genotoxicity in human cells:

- Glyphosate caused DNA damage in human liver cells at concentrations of 3 to 7.5 mM, but not in human lymphocytes at 0.2 to 6 mM (Mañas et al 2009a).
- Roundup caused dose-dependent DNA damage in human liver cells, with 50% DNA strand breaks at 5 mg/kg, described by the authors as "residual levels corresponding to 120 nM of glyphosate" (Gasnier et al 2009).
- Glyphosate was genotoxic in normal human cells at concentrations of 4 to 6.5 mM and in human cancer cells (fibrosarcoma) at 4.75 to 5.75 mM (Monroy et al 2005).
- Glyphosate caused a dose-dependent increase in chromosomal aberrations and an increase in sister chromatid exchange in human lymphocytes (Lioi et al 1998a).
- Glyphosate and Roundup caused dose-dependent increases in sister chromatid exchange in human lymphocytes; Roundup had a greater effect (Bolognesi et al 1997).
- Roundup at high concentrations caused an increase in sister chromatid exchange in human lymphocytes (Vigfusson & Vyse 1980).
- In the first data to be published on the potential genotoxicity of the metabolite AMPA, Mañas et al (2009b) have shown that it is clearly genotoxic, causing DNA damage in human liver cells at concentrations of 2.5 to 7.5 mM. It also caused chromosomal damage in human lymphocytes at 1.8 mM.

A variety of tests on animals, bacteria, and plant cells have further demonstrated the genotoxic ability of glyphosate, Roundup and AMPA:

- Glyphosate caused the induction of micronuclei at high doses, possibly through oxidative stress, in mouse bone marrow (Mañas et al 2009a).
- Roundup caused the induction of micronuclei in mouse bone marrow. Both glyphosate and Roundup caused DNA strand breaks in mouse liver and kidney cells (Bolognesi et al 1997).

- Roundup, but not glyphosate, caused dose-dependent formation of DNA adducts in mouse liver and kidney cells (Peluso et al 1998).
- Glyphosate caused chromosomal aberrations and sister chromatid exchange in bovine lymphocytes (Lioi et al 1998b).
- Glyphosate caused sister chromatid exchange in bovine lymphocytes at concentrations of 56 to 1120 *u*M (Siviková & Dianovskỳ 2006).
- Developmental exposure to glyphosate caused mutations in fruit flies (*Drosophila melanogaster*) (Kaya et al 2000).
- Roundup caused DNA damage and micronucleus induction in the gill cells of the neotropical fish *Prochilodus lineatus*, and DNA damage but not micronucleus induction in its erythrocytes, at 10 mg/l concentration (Cavalcante et al 2008).
- Roundup caused dose-dependent DNA damage and micronucleus induction in the erythrocytes of newborn broad-snouted caiman (*Caiman latirostris*) after exposure *in ovo* to concentrations of Roundup of 500 *u*g/egg or higher (Poletta et al 2009).
- Roundup caused micronucleus induction in the erythrocytes of the fish *Tilapia rendalli*, but not in mouse erythrocytes (Grisolia 2002).
- Roundup caused dose-dependent micronuclei induction, nuclear abnormalities, and DNA strand breaks in the erythrocytes of goldfish (*Carassius auratus*) at concentrations of 5, 10 and 15 mg/l (Cavaş & Könen 2007).
- Roundup caused DNA damage in blood, liver and gill tissue of the European eel (*Anguilla anguilla*) at 3.6 mg/l concentration (Guilherme et al 2009).
- Roundup caused DNA damage in bullfrog tadpoles (*Rana catesbeiana*) at concentrations of 6.75 and 27 mg/l, but not at 1.69 mg/l (Clements et al 1997).
- Roundup caused DNA damage in sea urchin embryos (Bellé et al 2007).
- Roundup and Pondmaster, another formulation of glyphosate, "induced a very high frequency of lethals [sex-linked, recessive lethal mutations] in larval spermatocytes and in spermatogonia" of fruit flies (Kale et al 1995).
- Roundup, but not glyphosate, caused chromosomal damage in root-tips cells of onions (*Allium cepa*) (Rank et al 1993).
- Roundup was weakly mutagenic in the bacterium *Salmonella typhimurium* at a concentration of 360 *u*g/plate (Rank et al 1993).
- AMPA caused the induction of micronuclei in mice (Mañas et al 2009b).

In summary, some toxicological studies show glyphosate, Roundup, and/or the metabolite AMPA to be genotoxic and some do not. Using a precautionary approach, the conclusion should be reached that glyphosate appears to have the ability to cause genetic damage that can lead to cancer. This conclusion is supported by the epidemiological reports of DNA damage in people exposed to glyphosate, and cases of lymphocytic cancer, particularly non-Hodgkin's lymphoma, reported in the section 'Health Effects and Poisonings'. Colombian researchers further confirmed the plausibility of the link between glyphosate and haematological cancers such as non-Hodgkin's lymphoma when they studied its effects on human peripheral blood mononuclear cells. They found that both glyphosate and Roundup decreased cell viability in a dose-dependent manner (Reyes et al 2006; Martinez et al 2007), and altered gene expression in the cells (Reyes et al 2007).

Other cancer-causing mechanisms

Cell division dysfunction

The cell cycle, or cell-division cycle, is the series of events that take place in a cell leading to its replication, and underlies the growth and development of all living organisms. Defects in the control of the cell cycle can lead to genetic instability and DNA damage and, therefore, to cancers.

In 2002 Marc et al showed that an 8 mM concentration of Roundup induced a delay in first cell cleavage in sea urchin embryos. Glyphosate alone did not cause the effect but it did in combination with a subthreshold dose of Roundup, indicating a synergistic effect between glyphosate and the Roundup formulation components (possibly the surfactants enabling glyphosate penetration of cells). Cell-cycle dysregulation is a hallmark of tumour cells and human cancer (Marc et al 2004), and Roundup has that hallmark (Marc et al 2002, 2003, 2004). There is "high risk by inhalation for people in the vicinity" of glyphosate being sprayed, since the normal concentration is 500-4000 times higher than the dose that dysregulated the cell-cycle in this study (Marc 2004).

RNA transcription

Transcription is the synthesis of RNA under the direction of DNA by enzymes called RNA polymerases. Disruptions to RNA transcription are also implicated in human cancers.

In 2005 Marc et al, in a study on sea urchin embryos, provided evidence that glyphosate

inhibits RNA transcription at a concentration 25 times below the level that is recommended for commercial spray application. Transcription inhibition was dose-dependent, causing a 50% adverse effect at a concentration of 1 mM equivalent of glyphosate in a Roundup formulation. "Roundup globally inhibited early transcription following fertilization, impeded the specific transcription of the hatching enzyme, and was correlated with a delayed hatching process."

The Richard et al (2005) study summarised below under Endocrine disruption also reported a decrease in mRNA synthesis following exposure to glyphosate or Roundup.

Oxidative stress

Oxidative stress is caused by an imbalance between the production of 'reactive oxygen species' and an organism's ability to detoxify them or repair the resulting damage. Free radicals can be formed as a result, and these damage DNA. Hence, oxidative stress may be a causative factor in cancer as well as neurodegenerative and other diseases.

A number of studies have demonstrated that glyphosate and/or Roundup cause the generation of reactive oxygen species and oxidative stress, in human lymphocytes (Lioi et al 1998a; Pieniążek et al 2004), human skin cells (Gehin et al 2005, 2006), bovine Lymphocytes (Lioi et al 1998b), bullfrog tadpoles (Costa et al 2008), pregnant rats and their foetuses (Beuret et al 2005), rat liver cells (El-Shenawy 2009), mouse kidney cells and liver DNA (Bolognesi et al 1997), and in rice leaves (Ahsan et al 2008). Additionally glyphosate enhanced the genotoxic effect of hydrogen peroxide though an oxidative stress mechanism (Lueken et al 2004). Roundup caused mild oxidative stress in the brain, liver and kidneys of goldfish (Lushchak et al 2009).

Endocrine disruption

The US EPA (2006) reported that "potential estrogen, androgen, and/or thyroid mediated toxicity was not indicated in any test on glyphosate".

However, a number of studies since then have demonstrated that both glyphosate and the Roundup formulation do disrupt both oestrogens and androgens.

US researchers Walsh et al (2000) demonstrated that Roundup, but not glyphosate, significantly disrupted the production of the hormone progesterone in mouse cells, by disrupting expression of the steroidogenic acute regulatory (StAR) protein. The authors concluded that, as the StAR protein is also indispensable for steroidogenesis in the adrenal glands, a disruption in StAR protein expression may potentially affect carbohydrate metabolism, immune system function, and water balance, as well as fertility. It may have an impact on reproduction in humans, other mammals, birds, and amphibians.

In 2000 Lin & Garry found that both Roundup and glyphosate caused the proliferation of MCF-7 human breast cancer cells, but not via an oestrogenic mechanism. Subsequent studies by Richard et al (2005) and Hokanson et al (2007), reported below, may explain the mechanisms by which this could have occurred.

In 2005, a research team from Caen University in France (Richard et al 2005) demonstrated that glyphosate and Roundup, at non-toxic concentrations, affected the enzyme aromatase which is responsible for the synthesis of oestrogen. They found that glyphosate, at dilutions 100 times lower than agricultural rates, inhibited aromatase activity, interacted with the active site of the enzyme, and decreased aromatase mRNA levels. The effects were greater with the Roundup formulation than glyphosate alone. However there appears to be a differential effect on aromatase: although both glyphosate and Roundup reduced aromatase activity once it had entered the cells, prior to this entry into the cells the Roundup (but not glyphosate) actually caused a 40% increase in aromatase activity. A similar differential effect has been observed with lindane and bisphenol-A. The authors concluded that glyphosate has endocrine disrupting effects in mammals, and that the presence of Roundup adjuvants enhances glyphosate bioavailability and/or bioaccumulation in cells, and that these effects could explain premature births and miscarriages observed in epidemiological studies involving women farmers using glyphosate (see section 'Health Effects and Poisonings' for details of these).

In 2007 Hokanson et al demonstrated that a commercial glyphosate formulation ("a 15% home use preparation") dysregulated 680 out of 1,550 genes in MCF-7 human breast cancer cells. They also identified a synergistic effect with oestrogen (17*B*-estradiol). Oestrogen-regulated gene expression is a major factor in the regulation of a number of physiological functions, and the genes affected in this study have implications for tumour formation and growth, immune function,

hypertension, pre-eclampsia (pregnancy-induced hypertension), and foetal growth retardation.

Also in 2007, Benachour et al demonstrated glyphosate-dependent endocrine disruption via aromatase inhibition in human embryonic and placental, and equine testis cells, at non-toxic levels of glyphosate. As little as 0.01% Roundup provoked a significant reduction of 19% of oestrogen production in exposed cells. The authors linked the effects to glyphosate itself, with a synergistic effect provoked by the adjuvants in the formulation. The embryonic cells, which are the most sensitive cells, showed evidence of either bioaccumulation or time-delayed effect, suggesting a cumulative impact of very low doses of glyphosate approximating the Acceptable Daily Intake (0.3 mg/kg). The authors expressed concern that significant levels of glyphosate are likely to reach the placenta and embryo in exposed pregnant women, given that little protective equipment is usually worn with this herbicide. A study by Mose et al (2008) confirmed that glyphosate does cross the placenta: they found 15% of glyphosate in maternal circulation crossed to foetal circulation, although this figure could be higher as 32% of the glyphosate was unaccounted for after the experiment.

Using human liver HepG2 cells, Gasnier et al (2009), found that Roundup (but not glyphosate) inhibited the conversion of androgens to oestrogen, with a non-linear biphasic effect on the aromatase mRNA levels: the greatest effect occurring at medium doses. Effects occurred at 10 mg/l. Lower doses caused linear and dose-dependent disruption of oestrogen- and androgen- dependent transcriptional activity: androgen receptors at 0.5 ppm,[2] and oestrogen receptors at 2 mg/l). Glyphosate alone had no anti-oestrogenic effect but "was clearly anti-androgenic at sub-agricultural and non-cytotoxic dilutions". Most formulations were more anti-androgenic than anti-oestrogenic. The doses used in this study were described by the authors as far below agricultural doses, and the effects occurred within 24 hours of exposure.

The implications of the endocrine-disrupting effects reported above can be profound and far-reaching, involving a range of developmental impacts including sexual and other cell differentiation, bone metabolism, liver metabolism, reproduction, pregnancy, development, behaviour, and hormone-related diseases such as breast and prostate cancer (Gasnier et al 2009).

Reproductive and developmental effects

The US EPA (2006) prenatal developmental and reproductive NOAELs and LOAELs for glyphosate are:

- prenatal developmental (rat)
  NOAEL = 1,000 mg/kg/day
  LOAEL = 3,500 m/kg/day, based on maternal inactivity, mortality, stomach haemorrhage and reduced body weight gain; and increased incidence of foetuses and litters with unossified sternebrae (breast bone) and decreased foetal body weight

- prenatal developmental (rabbit)
  maternal NOAEL = 75 mg/kg/day
  developmental NOAEL = 350 mg/kg/day
  maternal LOAEL = 350 mg/kg/day, based on mortality, diarrhoea, soft stools, and nasal discharge

- 3-generation reproductive (rat)
  reproductive NOAEL = 30 mg/kg/day
  offspring NOAEL = 10 mg/kg/day

Effects suffered by rats (at high doses only) include reduced maternal body weight; decreased total implantations and number of viable foetuses; increased number of early resorptions; reduced litter size; reduced foetal and pup weight; and reduced ossification of the breastbone (US EPA 1993, 2006; IPCS 1994).

Williams et al (2000) provided developmental NOAELs in rats of 400 mg/kg/day for AMPA (based on maternal and foetal body weight effects) and 15 mg/kg/day for POEA (based on decrease in food consumption and mild clinical signs); hence both POEA and AMPA are considerably more developmentally toxic than glyphosate.

Despite the high NOAELs and LOAELs reported for regulatory purposes, independent laboratory studies have shown that glyphosate and Roundup formulations can cause adverse reproductive and developmental effects at much lower dose levels, levels that are relevant to normal human exposure.

The endocrine disrupting actions reported in the preceding section can cause such effects. Additionally, Richard et al (2005) showed that

[2] 800 times lower than the level permitted in some US animal feed, and 40 times lower than levels permitted in soybeans (FR 2000).

glyphosate killed a large portion of human placental cells after 18 hours, at concentrations (0.1%) lower than those recommended for use in agriculture. Roundup was more toxic than its active ingredient, but POEA potentiated the effect of glyphosate and facilitated its penetration of cell membranes.

In 2009 Benachour & Seralini demonstrated that glyphosate, Roundup, POEA, and the metabolite AMPA all cause cell death in human umbilical, embryonic and placental cells, at dilutions far below those used in agriculture. The relative toxicities were as follows: POEA > Roundup > AMPA > glyphosate. Glyphosate alone acted rapidly at concentrations up to 1,000 times lower than recommended agricultural use (Ho & Cherry 2009). Benachour & Seralini concluded "this work clearly confirms that the adjuvants in Roundup formulations are not inert". The study also demonstrated synergistic toxicity between glyphosate, POEA and AMPA. The cell deaths occurred at concentrations of Roundup corresponding to low levels of residues in food: "the proprietary mixtures available on the market could cause cell damage and even [cell] death around residual levels to be expected, especially in food and feed derived from R[oundup] formulation-treated crops".

The cell deaths together with the endocrine disrupting effects reviewed in the previous section could result in pregnancy problems leading to abnormal foetal development, low birth weights, or miscarriages (Benachour et al 2007; Gammon 2009).

As reported in the previous section, glyphosate /Roundup inhibits aromatase, and therefore reduces oestrogen. Low levels in the foetal brain at the time of sex differentiation for the male can result in reduced fertility at puberty or adulthood. Dallegrave et al (2007) found that exposure of rats to Roundup during pregnancy and lactation did result in adverse effects on male reproduction during puberty and adulthood: a decrease in sperm number per epididymis tail and in daily sperm production during adulthood, an increase in the percentage of abnormal sperms and a dose-related decrease in serum testosterone level at puberty, and degeneration of spermatids during both periods. In females the only adverse effect recorded was that of delayed vaginal canal opening. All the doses of Roundup tested were considerably higher than those people are likely to be exposed to: however the effects occurred at even the lowest dose levels used.

A study on semen characteristics in rabbits showed that glyphosate can cause a significant adverse effect on libido, ejaculate volume, and sperm concentration, with increased abnormal or dead sperm (Yousef 1995).

Developmental effects of Roundup were also demonstrated in the studies on sea urchin embryos carried out by Marc et al (2005), in which they found impeded transcription of the hatching enzyme and a delayed hatching process, foreshadowing a potential adverse effect on the developmental process in humans.

Dallegrave et al (2003) found that a glyphosate formulation used in Brazil induced developmental retardation of the foetal skeleton in rats, especially incomplete skull ossification and enlarged fontanel. The rats were exposed to high doses, ranging from 500 to 1,000 mg/kg glyphosate, but the teratogenic effects occurred at all dose levels in a positive dose–response pattern, with the rate of defect at the lowest dose level being double that of the controls.

Most recently a leading Argentinean scientist, Professor Carrasco of the University of Buenos Aires Medical School, demonstrated significant consistent and systematic malformations in amphibian embryos resulting from very low dose exposure to glyphosate, and warned that comparable effects can happen in humans. In the first part of the study amphibian embryos were immersed in a solution of the herbicide 1,500 times weaker than that used in agriculture: the embryos suffered head deformities. In the second part, the embryos were injected with glyphosate, also at 1,500 times dilution: the impact was even more severe, demonstrating that it is the active ingredient, not the adjuvants that are the problem. Effects included reduced head size, genetic alterations in the central nervous system, increased death of cells that help form the skull, deformed cartilage, eye defects, and undeveloped kidneys. Carrasco also stated that the glyphosate was not breaking down in the cells, but was accumulating. The findings lend weight to claims that abnormally high levels of cancer, birth defects, neonatal mortality, lupus, kidney disease, and skin and respiratory problems in populations near Argentina's soybean fields may be linked to the aerial spraying of Roundup (Valente 2009; Trigona 2009; Ho 2009).

Nervous system

US EPA (2006) stated that they did not require neurotoxicity or developmental neurotoxicity studies, and found no evidence of neurotoxicity.

However a study, designed to determine if chronic exposure to low doses of the organophosphate diazinon rendered nerve cells more sensitive to other chemicals subsequently, did show that Roundup especially, but also glyphosate, can affect nerve cells. Both inhibited growth of 'neurite-like structures' (axons or dendrites) even without pre-exposure to diazinon, but higher concentrations were required to cause an effect. Concentrations as low as 10 *u*M for glyphosate alone, and 0.5 nM for Roundup, inhibited growth of neurite-like structures in nerve cells pre-exposed to diazinon (Axelrad et al 2003). The authors reported that a "recent study of glyphosate (formulated as Roundup) exposure in farmers showed a maximum adult plasma/tissue concentration of 17 nM". Thus the level of internal exposure for farmers using Roundup herbicide may be sufficient to affect nerve cells, especially if those farmers have previously been exposed to organophosphate insecticides like diazinon.

A recent study by Anadón et al (2008) identified the possible role of glyphosate in neurodegenerative diseases, especially Parkinson's disease. Glyphosate produced a significant dose-dependent depletion of serotonin and dopamine, also increasing the metabolites of these two neurotransmitters in male rats.

This was followed by a study in 2009 (Astiz et al 2009) that lent further weight to a role in Parkinson's disease. Low doses (subclinical levels) of glyphosate, by itself and in combination with zineb and dimethoate, caused a loss of mitochondrial transmembrane potential in rat brain cells, especially in the substantia nigra region of the brain. The brain is very dependent on mitochondrial energy to maintain normal physiology, and loss of mitochondrial function is associated with many human neurodegenerative disorders. Damage in the substantia nigra is implicated in Parkinson's disease. Additionally, the central nervous system, and particularly the substantia nigra, are highly sensitive to free radical damage which results from oxidative stress—and a number of studies reported earlier show that glyphosate and Roundup cause oxidative stress in various different cells, including brain cells.

Toxic Interactions

Synergistic effects between glyphosate and chlorpyrifos were found on enzyme levels in mosquitofish (Rendón-von Osten et al 2005).

Glyphosate and metsulfuron-methyl were synergistic in their phytotoxic effects on plants; the effect was more pronounced with Roundup (Kudsk & Mathiassen 2004).

Glyphosate and Roundup significantly increased the uptake of mercury by the freshwater flea *Ceriodaphnia dubia* (Tsui et al 2005).

Human Exposure

Exposure guidelines

The US EPA (2006) established an 'incidental oral exposure' and a chronic Reference Dose (RfD) of 1.75 mg/kg/day based on the NOAEL of 175 mg/kg/day in the rabbit developmental study.

- Chronic RfD = 1.75 mg/kg/day (US EPA 2006)
- ADI (acceptable daily intake) = 0.3 mg/kg bw (FAO 2000)
- EU limit for drinking water = 0.1 mg/kg (Buffin & Jewell 2001)
- WHO guideline for drinking water = none set.

Occupational exposure

The US EPA (1993) recommended protective clothing (including protective eyewear) for mixer/loader/applicators. According to US EPA (2006), the "Roundup WeatherMax® label specifies that for application solutions of 30% or greater concentration, mixers, loaders, other handlers and applicators must wear personal protective equipment (PPE) consisting of a long-sleeved shirt, long pants, shoes with socks, and chemical-resistant gloves. If the application solution is 30% or less of the product, applicators must wear PPE consisting of a long-sleeved shirt, long pants, and shoes with socks." Roundup Weathermax contains 48.8% glyphosate as the potassium salt.

A farm family exposure study carried out in Minnesota and South Carolina, USA, found that 60% of the farmers who had applied and/or mixed glyphosate-based herbicides had detectable levels of glyphosate in their urine on the day of application; the mean level was 3 *u*g/l and the maximum 233 *u*g/l. Higher levels were associated with not wearing rubber gloves. As well, 4% of spouses, who had no involvement in the mixing or application, also had detectable levels in their urine (max 3 *u*g/l). The highest estimated systemic dose (i.e. the dose that would have been absorbed into the body) was 0.004 mg/kg (Acquavella et al 2004). Although this

is considerably below the US EPA's reference dose of 2 mg/kg/day, one study reported earlier showed that glyphosate and Roundup can have damaging effects at very much lower exposure levels: Benachour & Seralini (2009) demonstrated that glyphosate, Roundup, POEA, and AMPA all cause cell death in human umbilical, embryonic and placental cells, at 10^5 dilutions.

Another study, comparing urinary levels in mothers, fathers and children in Iowa, USA, found a high incidence in all groups but especially children, with the highest levels of residues (18 *u*g/l) occurring in children (Curwin et al 2007):

	% detection	max conc. (*u*g/l)
father		
• non-farm	66	5.4
• farm	75	18
mother		
• non-farm	65	5.0
• farm	67	11
child		
• non-farm	88	9.4
• farm	81	18

Non-occupational exposure

Non-occupational as exposure to glyphosate is very common, as it is widely used in home gardens, and for the spraying of roadsides, parks and other public places.

Exposure via spray drift is likely to be significant, given the extent of drift reported below and the array of health effects reported in Ecuador up to 10 km away from the aerial application of glyphosate (see section on Poisonings).

Spray drift

Off-target drift of glyphosate can be a considerable problem. Studies report that 10-37% of glyphosate applied to the foliage of weeds drifts to non-target plants (Cakmak et al 2009).

Cox (1998) reported a number of studies showing:

- seedling mortality occurred at 20 m, and sensitive species mortality at 40 m, downwind from glyphosate application with a tractor-mounted sprayer;
- residues have been measured 400 m downwind from ground applications; and 800 m from helicopter applications;
- plant injury has occurred 100 m downwind from fixed wing aerial application;
- one study calculated that buffer zones of 75-1,200 m would be required to protect non-target vegetation;
- Monsanto itself has reported a number of drift incidences after aerial application causing damage to 1,000 trees, 250 acres of corn, and in a third incident 155 acres of tomatoes.

Residues in food and drink

According to the US EPA (2006), uptake of glyphosate and AMPA by plants from the soil is limited, so residues in plants result largely from direct application.

Residue analysis for glyphosate and its metabolite AMPA is difficult and expensive, and is not routinely included in residue analyses. As both are translocated throughout plant tissue, residues are unlikely to be completely removed from produce by washing, peeling or removing the outer leaves. Minimal breakdown of glyphosate occurs in plant tissue and pre-harvest use can result in significant levels of residues; in grains they are not destroyed by milling and much of it remains in the bran, nor are they lost during baking. Residues in malting barley are transferred to beer. Use of glyphosate on forage and animal feed can result in residues in the kidneys of animals, also residues in meat, milk and eggs. Residues are stable for up to one year in plant material and in water, and two years in animal products, in storage. In the wild, residues of glyphosate can persist for a long time (45 mg/kg found in lichens 270 days after application). Sampling of wild berries after forest spraying operations showed that residues remained above 0.1 mg/kg for the 61 days during which samples were taken (Roy et al 1989; Agriculture Canada 1991; IPCS 1994; US EPA 1993; Buffin & Jewell 2001).

A wide range of trials carried out under conditions of "Good Agricultural Practice" have resulted in residues in many different fruits, vegetables, grains and animal fodder crops (WHO & FAO 2005), so it can be assumed that residues in food are highly likely. Despite the failure to include glyphosate in routine residue monitoring, it has been found in grains, strawberries, lettuce, and carrots (Buffin & Jewell 2001; EFSA 2009). It has also been found in a number of cereal-based foods in the UK: bread, wheat flour, wheat, barley, bran, oats, breakfast cereals, cereal bars, and polenta (Harris & Gaston 2004).

There are also residue concerns with crops that have been genetically modified to be tolerant of glyphosate. When glyphosate tolerant soy was

permitted to be marketed in Australia and New Zealand, the Maximum Residue Level had to be increased 100 fold in order to accommodate the increased residues expected from direct application of glyphosate to the soybean crops (ANZFA 2000; FSANZ 2009). In Europe the MRL was increased 200 fold, from 0.1 mg/kg to 20 mg/kg (Dibb 2000).

Glyphosate is moderately persistent in water and not removed by normal drinking water processing (Agriculture Canada 1991).

Residues have occasionally been found in drinking water in the UK (Buffin & Jewell 2001).

Health Effects and Poisonings

There have been many cases of intentional ingestion of glyphosate-containing products, which have led to comprehensive descriptions of acute symptoms. Involuntary occupational or bystander exposure has also resulted in a long list of both acute and chronic effects.

Some authors have attributed the symptoms to the surfactant POEA rather than to glyphosate (Sawada et al 1988).

Acute effects observed in humans

Intentional ingestion

Symptoms reported following ingestion of glyphosate formulations include:

- corrosive effects on the gastrointestinal system with sore throat, mouth ulcers, difficulty swallowing, abdominal pain, massive gastrointestinal fluid loss, gastrointestinal haemorrhage, gastric and duodenal ulcers, nausea, vomiting, diarrhoea;
- kidney and liver impairment, renal failure, with decreased urine and severe hypoxia (inadequate oxygen in body), pancreatitis;
- respiratory distress, nasal, bronchial and lung congestion, bronchial constriction, swelling of the lungs, pleuritic chest pain, pneumonia, lung dysfunction;
- metabolic acidosis, elevated potassium in the blood (hyperkalaemia);
- pulmonary oedema, arrhythmias, low blood pressure, slowed heart rate (bradycardia), red blood cell destruction, leucocytosis (raised white cell count), abnormal electrocardiograms, hypotensive shock, cardiogenic shock;
- impaired consciousness, and death (US EPA 1980; Sawada et al 1988; Talbot et al 1991; IPCS 1994; Cox 1995a; Lin et al 1999; Bradberry et al 2004; Stella & Ryan 2004; Sampogna & Cunard 2007; Hsiao et al 2008).

One woman in Taiwan developed painful swelling and rhabdomyolosys (breakdown of muscle tissue) in her arm after injecting herself with a glyphosate formulation in a suicide attempt (Weng et al 2008).

A number of intentional ingestions of glyphosate formulations have been fatal: recently a 57 year old woman in Taiwan suffered metabolic acidosis, respiratory failure, shock, and finally death, after drinking nian-nian-chun, a Chinese formulation containing 41% glyphosate and 15% POEA (Chang & Chang 2009). Severe poisoning following ingestion of lethal amounts involves respiratory and kidney failure, cardiac arrest, coma, seizures, and death (IPCS 1994; Cox 1995a). Of 80 cases of ingestion in China between 1980 and 1989, 7 died (Talbot et al 1991); of 56 cases reported in Japan between 1984 and 1986, 9 died (Sawada et al 1988). In the latter report, fatality occurred after ingestion of only 206 ml (about ¾ of a cup). Of 2,186 cases in Taiwan between 1986 and 2007, 146 people died including one from injection of the herbicide (Chen et al 2009).

Death occurs much more rapidly with ingestion of glyphosate-trimesium. One accidental ingestion, of a mouthful of glyphosate-trimesium resulted in the death of a 6-year-old boy within minutes. A 34 year-old woman who died after ingesting 150 ml of the trimesium suffered erosion of the gastrointestinal mucus membranes, pulmonary oedema, cerebral oedema, and dilated right atrium and ventricle of the heart (Sorensen & Gregersen 1999).

Occupational and bystander exposure

A wide-range of symptoms have also been observed following occupational and bystander exposure:

- irritation, swelling, tingling, itching or burning of the skin, photo-contact dermatitis, recurrent eczema, blisters, rashes;
- numb face, swelling of the eye and lid, face, and joints;
- conjunctivitis, painful eyes, corneal injury, burning eyes, blurred vision, weeping eyes;
- oral and nasal discomfort, unpleasant taste, tingling and irritation of throat, sore throat;
- difficulty breathing, cough, coughing of blood, inflammation of lungs;
- nausea, vomiting, headache, fever, diarrhoea, debilitation;

- rapid heartbeat, palpitations, raised blood pressure, dizziness, chest pains (IPCS 1994; Cox 1998; Gallardo 2001; Bradberry et al 2004).

One agricultural worker was hospitalised with severe inflammation of the lungs, shortness of breath, irritative cough, dizziness, sore throat, and coughing of blood following exposure to Roundup: he had been cleaning and repairing tractor mounted spray equipment which contained residues of the herbicide (Pushnoy et al 1998).

One person developed acute dermatitis after the herbicide soaked through the seams of a shoe (Horiuchi et al 2008). Another person, a 78 year old woman, received extensive chemical burns on her feet, legs and back from contaminated clothing. She had first knelt on ground that had recently been sprayed with a glyphosate herbicide, and then put on clothing that had also lain for some time on the sprayed ground. After several hours she developed burning, blistering rashes, with extensive erosions and necrotic skin falling off in sheets. It took 4 weeks to recover (Amerio et al 2004).

A recent occupational exposure, in which the glyphosate was reputedly applied correctly, resulted in the applicator suffering severe dysphonia (loss of voice), with decreased vocal fold mobility suggesting damage to the laryngeal nerve (Ptok 2009).

Exposure to glyphosate was associated with both atopy (immune responses to allergens) and with atopic asthma (asthma resulting from exposure to allergens) in women, in the US's Agricultural Health Study involving 25,814 farm women (Hoppin et al 2008). The same study also found that rhinitis ('runny nose') is associated with use of both glyphosate and 2,4-D (Slager et al 2009).

Jamison et al (1986) reported increased respiratory problems in people handling flax that had been retted with glyphosate before harvest, as opposed to those handling flax that had not been so treated. They concluded that the acute bronchoconstrictor response to flax dust is increased by the glyphosate, causing increased shortness of breath, wheezing and coughing.

Ho & Ching (2003) reported "widespread disturbances of many body systems . . . after exposures at normal use levels. These include balance disorder, vertigo, reduced cognitive capacity, seizures, impaired vision, smell, hearing and taste, headaches, drops in blood pressure, body-wide twitches and tics, muscle paralysis, peripheral neuropathy, loss of gross and fine motor skills, excessive sweating and severe fatigue".

Dr Ricky Gorringe of New Zealand estimated, based on cases presenting to his clinic, that probably 1 in 20 New Zealanders are sensitive to Roundup. The most commonly occurring symptoms are unnatural fatigue, a band-like headache, a strange "spaced-out feeling with loss of confidence", a skin rash, and an otherwise unexplainable sudden increase in blood pressure (Watts 1994). The exposure route thought to give rise to these problems is largely that of micro-droplet inhalation.

Long-term effects observed in humans

Cancer

A significant number of epidemiological studies have suggested possible links between exposure to glyphosate herbicides and several kinds of cancer, most commonly non-Hodgkin's lymphoma (NHL), including hairy cell leukaemia (a rare type of NHL affecting circulating B-cell lymphocytes), and multiple myeloma.

- The first report of an association between glyphosate and NHL showed an increased risk of hairy cell leukaemia for people exposed to glyphosate (Nordstrom et al 1998).

- This was followed by a population-based case-control study in Sweden identifying an increased risk (odds ratio 2.3) of NHL. However this was based on only 4 exposed cases and 3 controls. The low number of cases was reflective of the relatively low usage of glyphosate prior to the time period of diagnosis, with use dramatically increasing since (Hardell & Eriksson 1999).

- A pooled analysis of these two studies yielded an even higher odds ratio, of 3.04, for increased risk of NHL associated with exposure to glyphosate (Hardell et al 2002).

- A further study, carried out in Sweden between December 1, 1999, and April 30, 2002, "considerably strengthened" the association between NHL and exposure to glyphosate (Eriksson et al 2008). The odds ratio was 2.02, increasing to 2.36 for exposure on >10 days (29 cases, 18 controls), demonstrating "a tendency to dose-response".

- A study of men, conducted across a large region of Canada, found an elevated risk of NHL associated with glyphosate use more frequent than 2 days/year (odds ratio 2.12, based on 23 cases and 36 controls) (McDuffie et al 2001).

- De Roos et al (2003) pooled data from three 1980 USA population-based case-control studies of NHL in Nebraska, Iowa and Minnesota, and Kansas. Their logistical regression analysis showed an association between exposure to glyphosate and NHL in men (odds ratio 2.1, based on 36 cases and 61 controls).

- In 2005, De Roos et al evaluated associations between glyphosate exposure and cancer incidence in a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina, USA. Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes (including NHL). However there was an association with incidence of multiple myeloma (odds ratio 2.6, 32 cases).

- In 2007, Paz-y-Miño et al found a significantly higher degree of DNA damage amongst 24 people exposed to aerial spraying of Roundup-Ultra (43.9% glyphosate + POEA + Cosmo-Flux 411 F) in northern Ecuador than in 21 non-exposed controls. The exposed group lived < 3 km from the Ecuador-Colombia border area where the aerial spraying occurred continuously during 3 days between December 2000 and March 2001, sporadic aerial spraying continuing for three weeks following the continuous spraying. The individuals had all presented symptoms of toxicity after several exposures (see section on 'Poisonings'). Half of the group had received spraying directly over their houses and half were living within 200 m to 3 km from the sprayed areas. The application rate was 23.4 l/ha of Roundup-Ultra (equivalent to 10.3 l/ha of glyphosate), more than 20 times the US maximum recommended application rate.

- In a study carried out by Doctors Mueckay and Maldonado, 22 women from the border region of Ecuador and Colombia, who had shown symptoms of poisoning, were found to have damaged DNA. All of the women studied showed the genetic damage, in about 36% of cells tested; and the level of damage was 500 times greater than in women living in the Amazon region 80 km away (Anon 2003; 2003b; Mueckay & Maldonado 2003).

- The latest available study (Bolognesi et al 2009) also found a relationship between exposure to aerial glyphosate spraying in Colombia and DNA damage, although the authors dismissed it as small, transient and "not biologically relevant". The frequency of binucleated cells with micronuclei (BNMN) was compared before, 2 days after, and 4 months after aerial application. The study involved 137 women and their spouses from 5 areas of Colombia: Santa Marta where organic coffee is grown and there is no exposure to glyphosate or other pesticides; Boyaca where unidentified pesticides are used; Putumayo and Narino where glyphosate is aerial sprayed for coca eradication; and Valle del Cauca where it is aerial sprayed for sugar cane "maturation". The base line testing showed that the BNMN levels in people from areas where pesticides are used were 2.5 times higher than those from the organic area. There was significant increase in BNMN in all exposed areas 2 days after aerial spraying, especially amongst those who reported direct contact with the spray. In Putumayo, that level increased again at 4 months after spraying, but it decreased in Narino. There was a slight decrease in Valle del Cauca but it was not statistically significant. Despite the authors attempts to dismiss the results because they were not consistent, this study provides further evidence that exposure to glyphosate may cause DNA damage.

The results of these studies fail to confirm the US EPA's classification of glyphosate as non-carcinogenic, and in fact suggest the opposite. Taken together with the studies reported in the Toxicology section, in which glyphosate, Roundup, and the metabolite AMPA caused a variety of genotoxic effects in human lymphocytes (Vigfusson & Vyse 1980; Bolognesi et al 1997; Lioi et al 1998a; Mañas et al 2009b), which indicate biological plausibility, there is very good reason to suspect that glyphosate-containing herbicides may well cause non-Hodgkin's lymphoma, and possibly other cancers.

Reproductive

A Canadian epidemiological study, the Ontario Farm Family Health Study which involved 1,898 couples and 3,984 pregnancies, found an association between exposure to glyphosate-

based herbicides, and spontaneous abortions (miscarriages) and pre-term deliveries. Pre-conception exposure of the father to glyphosate was associated with increased risk of pre-term delivery (odds ratio 2.4) and to a lesser extent of spontaneous abortion (odds ratio 1.5) (Savitz et al 1997). Use of glyphosate by the mother in the three months prior to conception was associated with an increased risk of late (12th to 19th weeks) abortions (odds ratio 1.7). However the risk was 3 times higher for older women (>34 years) than for women of the same age who had not been exposed to glyphosate (odds ratio 3.2) (Arbuckle et al 2001).

A positive association was found between decreased fecundity, as measured by time to pregnancy, and exposure of both spouses to a variety of pesticides including glyphosate (Curtis et al 1999), but a recent study in Colombia in which exposure to glyphosate was poorly characterised provided confused results and no clear link (Sanin et al 2009).

Neurological

A study of children born to pesticide applicators in Minnesota, USA, found a significant correlation between exposure to glyphosate-base herbicides and neurodevelopment effects, and in particular ADD/ADHD (Attention Deficit Hyperactivity Disorder). Forty three percent of the children who had parent-reported ADD/ADHD had parental exposure to glyphosate-containing herbicides (Garry et al 2002).

Accidental exposure, both dermal and inhalation, to a glyphosate herbicide has been linked to a case of parkinsonism. A 54 year old man developed skin lesions 6 hours after he accidentally sprayed himself, then one month later developed a “symmetrical parkinsonian syndrome”. Magnetic resonance imaging revealed effects, 2 years later, in the globus pallidus and substantia nigra regions of the brain, which are associated with Parkinson’s disease (Barbosa et al 2001).

Other

One man developed severe autoimmune blistering of skin and mucous membranes after exposure to the fumes of burning glyphosate (Fisher et al 2008).

Another woman developed severe skin problems when her backpack sprayer leaked. She had sprayed Touchdown Premium (36% ammonium salt of glyphosate) diluted to 1.6%, 2 hrs/day for 3 consecutive days. She developed redness on her arms, which became eczematous on the second day. Five days later reddish lesions appeared on her arms, as well as ‘target-like’ lesions with lymph-filled vesicles on her abdomen, armpits and groin (Heras-Mendaza et al 2008).

Poisoning incidences

Latin America

Many of the observations of adverse effects from exposure to glyphosate have come from Latin America, where populations have been repeatedly exposed to the herbicide from aerial spraying campaigns to eradicate coca in Colombia and along its border with Ecuador since 1997 (Solomon et al 2009), or for weed control in GM soybean fields in Argentina.

Colombia

Symptoms observed after direct exposures from aerial spraying included red eyes, dizziness, vomiting, diarrhoea, abdominal pain, gastrointestinal infections, itchy skin, skin rashes and infections (particularly prevalent in children), respiratory infections, headaches, and fever. One baby was observed to have blood in its urine and kidney problems 3 months after the spraying (Oldham & Massey 2002; pers com, Elsa Nivia, RAPAL, Colombia, November 2006).

In February 2001, the Health Department in Putumayo published a preliminary report on health effects in the municipalities of Orito, Valle del Guamuez, and San Miguel, which had been sprayed between December 22, 2000 and February 2, 2001. Three local hospitals reported “increased visits due to skin problems such as dermatitis, impetigo, and abscesses, as well as abdominal pain, diarrhoea, gastrointestinal infections, acute respiratory infection, and conjunctivitis following spraying in the rural areas surrounding their respective municipalities” (Oldham & Massey 2002).

CBS News reported in 2002 that “a Colombian health department worker . . . Nancy Sanchez, also says illnesses like fever, diarrhea and allergies were up 100 percent in the spraying areas and that 2,300 families have complained of sicknesses” (Kroft 2002).

In the town of Aponte, department of Nariño, a physician reported that “aerial spraying on indigenous people’s lands had caused an epidemic of rash, fever, diarrhea and eye infections” (Oldham & Massey 2002).

By July 2002, of the 800 complaints about the aerial spraying presented to the personero of La Hormiga, Putumayo, 73% included claims of impact on health, according to the Colombian Comptroller General's office (LAWG undated).

The human health problems have been accompanied by reports of large-scale destruction of legitimate food crops such as bananas, beans, and corn, as well as fish kills and sickness and death of livestock, contaminated water supplies, and severe environmental impacts in sensitive tropical ecosystems. A police investigation in the area of Valle del Guamuez (population 4,289), in the Province of Putumayo found that, of the 17,912 acres sprayed by February 21, 2001, < 12% was dedicated to coca cultivation. Crop and animal losses in the 59 settlements affected included:

- 2,263 acres of bananas, 1,030 acres of yucca, 1,032 acres of corn, 7,064 acres of pasture, 1,665 acres of other crops (coffee, peanuts, fruit trees, timber, and vegetables),
- 1,112 acres of forest,
- 38,357 domesticated chickens and ducks, 719 horses, 2,767 cattle, 6,635 guinea pigs, 128,980 fish (from aquaculture), and 919 other animals (pigs, cats, dogs).

A similar review for La Hormiga municipality, also in Putumayo, reported the destruction of 20,239 acres of food crops and adverse effects in 171,643 farm animals including livestock, poultry, and farmed fish (Oldham & Massey 2002).

Ecuador

A number of acute symptoms, as well as DNA damage, have been reported from people exposed to aerial spraying of Roundup-Ultra near the Ecuador-Colombia border area between December 2000 and March 2001. Shortly after the spraying began 44 people from one community reported stomach and skin problems (Gallardo 2001). Symptoms included intestinal pain, vomiting, diarrhoea, fever, heart palpitations, headaches, dizziness, numbness, insomnia, depression, debilitation, burning eyes and skin, blurred vision, weeping eyes difficulty in breathing, dry cough, and skin rashes or blisters (Gallardo 2001; Paz-y-Miño et al 2007). According to Paz-y-Miño et al (2007), the "Ecuadorian government data confirms the existence of health problems . . . in the spraying zone".

In October 2000, the health centre in Mataje, Esmeraldas, a community of 154, reported treating 44 residents and another 29 people from surrounding areas for skin and eye irritation, vomiting, and diarrhoea following the spraying (Oldham & Massey 2002).

In June 2001 the Ecuadorian press reported that the Marco Vinicio Iza hospital, in Sucumbios Province, which borders the Colombian province of Putumayo, was treating 10 to 15 patients a day for skin, respiratory, and other problems that local doctors attributed to the spraying (Oldham & Massey 2002).

Also in June 2001 the PAN Ecuador group, Acción Ecológica, undertook a clinical survey of 142 people from 6 communities within 10 km of the border zone. 100% of people within 5 km of the spraying were suffering acute poisoning symptoms, on average 6 symptoms. Those 8-10 km away were suffering an average of 4 symptoms. Schools in 2 farming cooperatives near the border had to close after 83 pupils became ill. Three months after the spraying, 33% of residents near the border, and 10% of those 5-6 km, were still suffering chronic poisoning symptoms, mainly dermatitis, fever, migraine and conjunctivitis (Gallardo 2001).

In addition to the human health impacts there have also been reports of deaths of domestic animals and fish in hatcheries (Leahy 2007). The survey by Acción Ecológica found that 80% of poultry in the 0-2 km zone died, as did numerous cattle, pigs, horses, dogs and goats. Calves were aborted. Animal deaths occurred up to 10 km away. The entire coffee crop was lost, rice yields dropped by 90%, and production of coca, plantain, sugarcane, cassava and fruit was badly affected (Gallardo 2001). More than 6,500 complaints had been filed, by 2007, about damage to legal crops (Lubick 2007).

After aerial spraying between August 5 and 25, 2001, 242 families (<10% of the population) surveyed in the Cimitarra River Valley in Santander had lost a total of 1,350 acres of food crops including corn, yucca, bananas, rice and yam. 600 acres of fruit trees and pasture suffered adverse effects. The deaths of a number of domestic animals, including cattle, mules, and chickens, were attributed to the loss of food and the contamination of water supplies, as secondary impacts of the spraying (Oldham & Massey 2002).

The government of Ecuador has asked Colombia to observe a "security strip" (no aerial spraying) of 10 km from their joint border (Sicard et al 2005).

Argentina
In Argentina numerous health effects have been linked to exposures to glyphosate resulting from the aerial spraying of GM soybean fields, over the last 5 years. These include cancers, birth defects, lupus, kidney disease, and respiratory and skin ailments (Valente 2009). Clinical studies have identified high rates of cancer, birth defects and neonatal mortality. In the small town of Ituzaingó in Cordoba which borders soybean farms, there was reported to be 300 cases of cancer in a population of 5,000, by 2009. At 6% of the population, this rate is 41 times the national average of 0.145% (Trigona 2009).

Paraguay
In 2003, 11 year-old Silvino Talavera died after direct exposure to pesticides used on soybean fields. His mother and siblings were hospitalised for nearly 3 months. In all, 25 people suffered varying degrees of poisoning. In 2004 a court convicted two men of culpable homicide caused by the irresponsible and criminal use of agrichemicals sprayed on soybean, specifically glyphosate. Three family members had glyphosate residues in their bodies (Williamson 2004).

Other countries
Italy
In 2005 glyphosate was the single largest cause of unintentional acute pesticide-related illness in Italy, responsible for 56 out of 625 cases (Settimi et al 2007).

USA
The State of California registered 202 cases of glyphosate-related illness on their website, for the years 2000-2007. Of these, only 10 were from ingestion, the rest being unintentional occupational or bystander exposure; 94 were caused by non-agricultural uses (Cal EPA 2009).

Environmental Effects

Glyphosate is still regarded by its supporters as safe for the environment, including scientists such as Duke & Powles (2008a) who described it as “very toxicologically and environmentally safe”, and as “environmentally benign” despite a wealth of information showing that it is far from benign, and may in fact be causing significant environmental harm.

Aquatic effects

Because glyphosate has high water solubility, and both it and its metabolite AMPA are increasingly found in the aquatic environment, effects on aquatic organisms are of growing concern (Contardo-Jara et al 2009).

Roundup and glyphosate are regarded as being of greater toxicity to fish than to mammals, yet they are widely applied to aquatic ecosystems for weed control. The US EPA (1993) concluded that “minimal risk is expected to aquatic organisms from technical glyphosate”.

Aquatic effects of pesticides are usually described in terms of acute toxicity to fish and invertebrates such as shrimps and the water flea *Daphnia*. But the healthy functioning of aquatic ecosystems depends on much more than these species. It depends on a wide variety of organisms including microorganisms, algae, and amphibia, effects on which are seldom if ever measured for registration purposes. The significant detrimental impact of glyphosate/Roundup on these less-regarded species is of far greater ecological importance that the singular measure of acute toxicity to fish.

Additionally, aquatic ecosystems are often exposed to pulses of Roundup, and such regular exposures may have a cumulative effect that is only expressed after several generations (Mann & Bidwell 1999). Most tests miss this effect, but one reported here clearly shows a 3rd generational effect on molluscs that was not apparent in the first 2 generations (Tate et al 1997).

Aquatic communities
The structure and composition of natural aquatic communities, the diversity of species, and the balance and interactions between them are of profound importance for ecosystem functioning right through all the trophic levels (Pérez et al 2007); and Roundup has been shown to have profound impacts on such communities. The effects on microorganisms, algae and amphibia vary considerably between species, raising concerns about how contamination of freshwater environments with glyphosate can tip the ecological balance, possibly giving rise to harmful algal blooms (Pérez et al 2007) and reducing species richness (Relyea 2005a).

In an aquatic mesocosm study published in 2005, Rick Relyea of the University of Pittsburgh showed that Roundup reduced species richness by 22%. Two species of tadpoles were completely eliminated and a third one nearly so, whilst wood frog survival was only reduced by 2%, resulting in an over all 70% decline in species richness of tadpoles. Predator (insect and salamander) biomass was reduced, but

algal biomass increased by 40%. The copepod (small crustacean) *Eurytemora affinis* was almost completely eliminated (Relyea 2005a).

In a second mesocosm study, Pérez et al (2007) found that Roundup affected the structure of phytoplankton and periphyton assemblages. Periphyton is the complex mixture of algae, cyanobacteria, microbes, and detritus attached to submerged surfaces in aquatic ecosystems. Total nano- and micro-plankton decreased, but picocyanobacteria increased by a factor of about 40. Diatoms were reduced. Amongst the periphyton there was an increased proportion of dead to living individuals, and increased cyanobacteria, leading the authors to warn that Roundup use may lead to algal (cyanobacteria) blooms, with consequent adverse effect on higher trophic levels.

A study carried out on a marine microbial community showed effects on microbial diversity and community composition after a 7 day exposure at levels as low as 1 *u*g/l, concentrations described as "typical of those already observed in polluted coastal areas" (Stachowski-Haberkorn et al 2008).

In a study on river microbial communities, Pesce et al (2009) found that glyphosate affected the composition of the algal community in summer but not in spring, reducing reproduction in the species *Asterionella*, *Cyclotella*, and *Oocystis*. This highlights the importance of seasonally dependent ecosystem characteristics in determining effects.

Microorganisms

Microorganisms underpin the entire aquatic food chain and, as well as the 2 mesocosm studies described above, a number of other studies have demonstrated the effects of Roundup or glyphosate.

Glyphosate was described by the IPCS (1994) as being slightly toxic to aquatic microorganisms, but formulations of it can be highly toxic. It can affect growth, greening processes, aromatic amino acid synthesis, and photosynthesis of blue-green algae (IPCS 1994).

More recent studies have shown that planktonic microorganisms are highly sensitive to glyphosate at environmentally relevant concentrations (Stachowski-Haberkorn et al 2008).

Such concentrations also caused significant shifts in bacterial community composition in freshwater lake sediment in Sweden (Widenfalk et al 2008).

Glyphosate was highly toxic, at "expected environmental concentrations", to freshwater diatoms (*Nitzschia* sp., *Cyclotella meneghiana*) and cyanobacteria (*Aphanizomenon flosaquae*), but not toxic to other cyanobacteria, algae or duckweed, in a Canadian study of aquatic organisms (Peterson et al 1994).

Aquatic invertebrates

LC_{50} = the concentration of glyphosate in water that kills 50% of test animals.

TL50 = the median lethal time, or the average time interval during which 50% of a given population dies.

Glyphosate was described by IPCS (1994) as being "slightly to very slightly toxic" to invertebrates, but formulations of glyphosate may be "moderately toxic". Roundup was described as highly toxic to crustaceans.

48 hr LC_{50} (mg/l):

	glyphosate	formulations
• *Daphnia*	780	5.3-930
• *Chironomus*	55	44-5,600

The US EPA (1993) described glyphosate as "practically non-toxic to grass shrimps and fiddler crab" and "slightly toxic to Atlantic Oyster":

	species	test	glyphosate
•	Fiddler crab	48 hr LC_{50}	555-1,570 mg/l
•	Grass shrimp	48 hr LC_{50}	207-381 mg/l
•	Atlantic oyster	48 hr TL_{50}	>10 mg/l

Parasitic freshwater horsehair worms (*Chordodes nobili)* were adversely affected by Roundup "at glyphosate concentrations lower than those expected to be found in freshwater environments and those specified in the [Argentinean] legislation". It decreased the infective capacity of larvae exposed, or derived from eggs that had been exposed, to > 0.1 mg/l of glyphosate (Achiorno et al 2008).

The sediment-dwelling freshwater blackworm *Lumbriculus variegatus* was exposed for 4 days to both glyphosate and to the Roundup Ultra formulation. Both, but particularly the formulation, caused oxidative stress. A low level of bioaccumulation was also found to occur, with a bioaccumulation factor for glyphosate varying

between 1.4 and 5.9 for exposure to the Roundup Ultra formulation (higher than for exposure to glyphosate alone). The accumulated amount increased with increasing concentration in the surrounding medium (Contardo-Jara et al 2009).

Molluscs

Glyphosate, Roundup, and especially POEA are all toxic to the freshwater mussel *Lampsilis siliquoidea*, regarded as being representative of 300 species native to North America, one of the "most imperilled faunal groups in the world". The mussel is one of the most sensitive of aquatic species to glyphosate-based herbicides (Bringolf et al 2007).

Long-term exposure to sublethal concentrations of glyphosate affected reproduction and development of the freshwater snail *Pseudosuccinea columella* (Tate et al 1997). It had a delayed effect on growth and development, egg-laying capacity, and hatching, not in the first or second generations, but in the third generation. The number of egg masses increased but they contained a greater number of abnormal or deformed embryos.

Sea Urchins

In 2005 Marc et al showed that glyphosate inhibits RNA transcription in sea urchin embryos, at a concentration 25 times below the level that is recommended for commercial spray application. Transcription inhibition was dose-dependent and caused a 50% adverse effect at a concentration of 1 mM equivalent of glyphosate in a Roundup formulation, resulting in delayed hatching of embryos.

Roundup caused DNA damage in sea urchin embryos (Bellé et al 2007).

Amphibians

Amphibians may be particularly susceptible to the effects of glyphosate herbicides because their preferred breeding sites are often shallow ephemeral pools that, by virtue of the small amount of water, can contain high concentrations of herbicides (Mann et al 2009).

The acute toxicity of Roundup and other formulations of glyphosate-containing POEA to larval amphibia vary with species, pH, and developmental stage; and the estimates for LC_{50} range from 0.4 to 11.6 mg glyphosate/l (Relyea & Jones 2009).

As reported earlier Relyea (2005a), when examining the impact of pesticides on the biodiversity of aquatic communities containing algae and 25 species of animals, found that Roundup (at 3.8 mg glyphosate/l) completely eliminated two species of tadpoles (leopard frogs and gray tree frogs), and nearly exterminated a 3rd species (wood frogs), resulting in a 70% decline in the species richness of tadpoles.

Relyea (2005b) also exposed tadpoles in an outdoor mesocosm to Roundup at a concentration (3.7 mg glyphosate/l) representing those expected when aquatic habitats are sprayed for weeds. Within 3 weeks it had killed 98% of tadpoles. In laboratory studies on juvenile frogs (post metamorphosis), it killed 68-86% within one day.

In another study he found that the addition of predator stress made Roundup twice as lethal, at least for one species, the wood frog (*Rana sylvatica*), something that is likely to occur frequently in the wild (Relyea 2005c).

Williams & Semlitsch (2009) found that exposure to Roundup WeatherMax at 0.57 mg/kg glyphosate acid equivalents resulted in 80% mortality of western chorus frog tadpoles.

Symptoms of acute toxicity of the formulated product Glyphos and adjuvant Cosmo Flux, used in Colombia, include slow swimming and remaining on the bottom with no movement at lower concentrations; and uncontrolled rapid swimming and remaining in a vertical position at higher levels (Bernal et al 2009).

In a number of studies, exposure to sublethal concentrations of POEA or glyphosate/POEA formulations has caused delayed development, accelerated development, reduced size at metamorphosis, developmental malformations of the tail, mouth, eye and head, and histological indications of intersex (Mann et al 2009). Lajmanovich et al (2003) found that glyphosate formulations caused craniofacial and mouth deformities, eye abnormalities and bent, curved tails in tadpoles of the species *Scinax nasicus*. Howe et al (2004) found that when tadpoles of a common North American amphibian, the northern leopard frog (*Rana pipiens*), are chronically exposed to environmentally relevant concentrations of POEA or glyphosate/POEA formulations, they developed decreased snout-vent length at metamorphosis and increased time to metamorphosis, tail damage, and gonadal abnormalities. The authors concluded that these effects may be caused by disruption of

hormone signalling involving the thyroid hormone receptor.

Concentrations of only 1 mg/l of Roundup for 48 hours caused the generation of reactive oxygen species and oxidative stress in bullfrog tadpoles (*Rana catesbeiana*) (Costa et al 2008). Roundup also caused DNA damage in bullfrog tadpoles at concentrations of 6.75 and 27 mg/l, but not at 1.69 mg/l (Clements et al 1997).

One study has shown that gray treefrogs avoid laying their eggs in water containing residues of Roundup at concentrations "expected to be found in the field" (Takahashi 2007).

Reptiles

Roundup caused dose-dependent DNA damage and micronucleus induction in the erythrocytes of newborn broad-snouted caiman (*Caiman latirostris*) after exposure *in ovo* to concentrations of Roundup of 500 *u*g/egg or higher (Poletta et al 2009).

Fish

Acute toxicity

A wide variety of acute toxicities have been reported for glyphosate and Roundup. Toxicity varies with species and age of the fish, their nutritional status (more toxic to hungry fish), and the temperature, pH and hardness of water (toxicity increases with temperature and pH) (Cox 1995b). Young fish are particularly vulnerable when water temperatures increase in spring and summer (Folmar et al 1979).

FAO (2000) described glyphosate as moderately to slightly toxic, on the basis of the following values for 96 hr LC_{50}:

- bluegill sunfish 5.8-34 mg/l
- rainbow trout 8.2-26 mg/l
- channel catfish 39 mg/l
- coho salmon 22 mg/l
- chinook salmon 20 mg/l
- pink salmon 14-33 mg/l

The 96 hr LC_{50} values reported by IPCS (1994) show the significantly increased toxicity of some formulations, particularly Roundup:

	glyphosate	formulations
• rainbow trout	10-197	3.2->1,000 mg/l
• bluegill sunfish	120-140	4.5->1,000 mg/l
• coho salmon	27-174	13-33 mg/l

Servizi et al (1987) showed that the acute toxicity of POEA to fish was more than 30 times that of glyphosate itself, and provided comparative toxicities for POEA (LC_{50}):

	Roundup	POEA
• rainbow trout fry	25.5	3.2 mg/l
• coho salmon fry	42.0	3.5 mg/l
• sockeye fry	28.8	2.6 mg/l

Sublethal acute effects of Roundup include loss of mobility, complete loss of equilibrium, darkened pigmentation, rapid respiration (IPCS 1994), and erratic swimming (Cox 1998)—these effects can increase risk from predators, as well as affecting feeding, migration and reproduction (Cox 1998).

Glyphosate is neurotoxic to the olfactory system in fish (Tierney et al 2006) and exposure to Roundup alters behaviour, in particular provoking an avoidance response at > 10 mg/l, but eliminating preference behaviour at only 100 *u*g/l (Tierney et al 2007). Impairment of olfaction is an ecologically important effect as it is critical for return migration, alarm response, feeding, and kin recognition (Tierney et al 2007).

Acute exposure of jundia fish to sublethal concentrations of glyphosate lowered their cortisol levels, and decreased their capacity to adequately cope with stress and to maintain homeostasis (Cericato et al 2008).

Fish breeding operations have been reported to be completely destroyed by aerial spraying of glyphosate formulations in Colombia (Sicard et al 2005).

Systemic effects

Szarek et al (2000) found that exposure to Roundup at concentrations of 40- to 20-fold lower than those generally used caused damage to liver cells in carp (the appearance of myelin-like structures, swelling of mitochondria and disappearance of internal membrane of mitochondria), and concluded that Roundup was harmful to carp when used in applied concentrations. Higher, sublethal, doses of Roundup modified liver enzymatic activity in Nile tilapia (Jiraungkoorskul et al 2003). In carp, sublethal concentrations of glyphosate increased the activity of the enzymes alkaline phosphatase in liver and heart, glutamic-oxaloacetic transaminase in liver and kidneys, and glutamic-pyruvic transaminase in kidney; and caused morphological changes in gill and liver tissue (Neskovic et al 1996).

Other studies have found that Roundup affects energy metabolism, free radical processes, and

acetylcholinesterase activity in fish (Rendón-von Osten et al 2005; Glusczak et al 2006, 2007; Langiano & Martinez 2008).

Chronic effects
Roundup has caused DNA damage and/or micronucleus induction in the neotropical fish *Prochilodus lineatus* (Cavalcante et al 2008), the fish *Tilapia rendalli* (Grisolia 2002), goldfish (*Carassius auratus*) (Cavaş & Könen 2007), and European eel (*Anguilla anguilla*) (Guilherme et al 2009). It has also caused oxidative stress in goldfish (Lushchak et al 2009).

Glyphosate adversely affected immune responses in *Tilapia nilotica* (el-Gendy et al 1998).

Terrestrial ecotoxicity

Glyphosate and/or Roundup can have very significant adverse effects on the agroecosystem, principally through effects on soil microorganisms and plant health.

A number of species of birds, mammals and beneficial insects suffer population loses through habitat and/or food supply destruction resulting from the use of glyphosate (Cox 1995b; IPCS 1994). There are also direct lethal and sublethal effects, which can lead to individual deaths and changes in community and ecosystem dynamics.

Soil microorganisms
Numerous studies have demonstrated a wide range of effects of glyphosate on soil microorganisms—some positive, others adverse, depending on the species. Actual effects following glyphosate use depend on a number of factors including soil type, environmental conditions and interspecies interactions (Guiseppe et al 2006; Lupwayi et al 2009). Repeated applications appear to have a greater impact on soil microbes than single applications (Lancaster et al 2009).

Carlisle & Trevors (1988) reported a study that showed 50 mg/kg glyphosate inhibited growth of 59% of randomly selected soil bacteria, fungi, actinomycetes and yeast; and that of the 9 herbicides tested, glyphosate was the 2nd most toxic.

Results can be inconsistent—for example, a study of 2 Brazilian soils found that glyphosate increased the number of fungi and actinomycete bacteria, and decreased the number of other bacteria (Araujo et al 2003). However other studies have reported that actinomycetes are more sensitive to glyphosate than other bacteria (Grossbard 1985). In fact the effect on soil bacteria varies between species—for example 5 *Pseudomonas* species were not inhibited by glyphosate, but a 6th species, *Pseduomonas fluorescens*, was (Kremer & Means 2009).

Increased microbial activity in soils has been reported (e.g. Lupwayi et al 2009), but generally this appears to result from an increase in the number of microorganisms capable of metabolising glyphosate and using its phosphate ions as a nutrient (Lancaster et al 2009).

The concern therefore is not that glyphosate will diminish microbial activity, but that it will alter microbial community dynamics in ways that are harmful to plants and to ecological balance. In commenting on their study, which showed that pre-sowing application of a mixture of glyphosate and 2,4-D to a canola crop significantly decreased the diversity of species, Lupwayi et al (2009) concluded "such shifts in the structure of soil microbial communities can lead to successions that could have long-term effects on soil food webs and soil biological processes". For example, glyphosate has been shown to inhibit a number of saprophytic fungi that decompose dead plant material and hence are important for soil fertility (Grossbard 1985).

There are also many studies showing that glyphosate increases the severity of soil-borne fungal pathogens and the resulting disease in plants: these are addressed in the following section on Plant diseases.

Plant diseases
The authors of a recent review of glyphosate and plant diseases (Johal & Huber 2009) concluded that "extensive use of glyphosate in agriculture is a significant factor in the increased severity or 're-emergence' of diseases once considered efficiently managed".

There are a number of ways in which glyphosate increases disease severity in plants: by increasing populations of pathogens in the soil, by immobilizing specific plant nutrients involved in disease resistance, by reducing vigour and growth of plants as a result of the accumulation of glyphosate in the plant, by altering physiological efficiency, and by modification of the soil microflora in ways that affect the availability of nutrients important to plants' disease resistance (Johal & Huber 2009).

Pathogens

Glyphosate can alter the balance between disease-causing and beneficial fungi in favour of the former: a number of studies have shown that it stimulates the growth of pathogenic fungi such as *Fusarium, Pythium, Phytophthora, Rhizoctonia*, and *Sclerotinia*, but inhibits beneficial fungi. For example:

- At low concentrations glyphosate stimulated the growth of *Fusarium solani* and *Fusarium oxysporum* (Krzysko-Lupicka & Sudol 2008). Long-term exposure led to a fungal community dominated by *Fusarium* species.
- Glyphosate application to soil containing maize or peanut crop residues increased growth and sporulation of *Fusarium* and *Pythium*, in comparison with fallowed fields lacking crop residues, whilst the populations of the beneficial fungi *Trichoderma* and *Gliocladium* remained constant (Meriles et al 2006).
- Application of glyphosate in greenhouse studies resulted in increased disease severity caused by *Fusarium oxysporum* and *Rhizoctonia solani* in GM sugar beet (Larson et al 2006).
- Other studies have also shown increases in *Pythium* and *Phytopthora* (Kawate et al 1997; Descalzo et al 1998).
- Exposure of GM soybean to glyphosate increased the severity of Sclerotinia stem rot (*Sclerotinia sclerotiorum* (Lib.) de Bary) in some but not all cultivars (Nelson et al 2002).
- Sublethal doses of glyphosate inhibited resistance in beans to *Colletotrichum lindemuthianum*, in tomato to *Fusarium* spp, and in apple trees to root rot (Levesque & Rahe 1992).
- Exposure of GM soybean to glyphosate increased sudden death syndrome caused by *Fusarium solani* (Sanogo et al 2000).
- Pre-planting use of glyphosate reduced resistance of barley to *Rhizoctonia* root rot and lowered yields (Smiley et al 1992).
- Glyphosate injected into the sapwood around the root collar of lodgepole pine trees increased the growth and spread of the blue stain fungus *Ophiostoma clavigerum*. The fungus is symbiotic with the mountain pine beetle, *Dendroctonus ponderosae*, and the authors concluded that glyphosate enhances brood development of the pest via enhancement of the fungus (Bergvinson & Borden 1992).

There has been a resurgence of *Fusarium* wilt in Roundup Ready cotton crops in Australia and "previous high levels of wilt resistance appear to be less effective under glyphosate management programs" (Johal & Huber 2009).

Fernandez et al (2009) have established an association between glyphosate use and cereal diseases, caused by *Fusarium avenaceum* and *Fusarium graminearum*, in wheat and barley grown in the Canadian Prairies under minimum-till systems that are heavily dependent on glyphosate. *Fusarium graminearum* produces a mycotoxin that can kill humans and animals.

In the US states of Washington, Idaho, and Oregon production of peas, lentils and wheat in rotation has been in slow decline as nitrogen fixation (for the peas and lentils) has declined and *Fusarium* diseases increased, commensurate with the extensive use of glyphosate in no-till programmes (Johal & Huber 2009).

Summary of glyphosate predisposing crops to disease-causing pathogens (Johal & Huber 2009)

Plant	Disease	Pathogen
apple	canker	*Botryosphaeria*
banana	Panama disease	*Fusarium*
barley	root rot	*Magnaporthe*
bean	anthracnose	*Colletotrichum*
	damping off	*Pythium*
	root rot	*Fusarium*
	hypocotyl rot	*Phytopthora*
canola	crown rot	*Fusarium*
	wilt	*Fusarium*
citrus	chlorosis	*Xylella*
	crown rot	*Phytopthora*
cotton	damping off	*Pythium*
	bunchy top	*Mn deficiency*
	wilt	*Fusarium*
grape	black goo	*Phaemoniella*
melon	root rot	*Monosporascus*
soybean	root rot	*Corynespora*
	target spot	*Corynespora*
	sudden death	*Fusarium*
	root rot	*Phytopthora*
	cyst nematode	*Heterodera*
	white mould	*Sclerotinia*

sugar beet	yellows	*Fusarium*
	root rot	*Rhizoctonia*
sugar-cane	decline	*Marasmius*
tomato	crown rot	*Fusarium*
	wilt	*Fusarium*
various	canker	*Phytopthora*
weeds	(used as a bio-control)	*Myrothecium*
wheat	bare patch	*Rhizoctonia*
	glume blotch	*Septoria*
	root rot	*Fusarium*
	head scab	*Fusarium*
	take-all	*Gaeumannomyces*

Micronutrient deficiency

Very low levels of glyphosate in the soil can greatly hinder the availability and uptake of the micronutrients manganese (Mn), iron, copper and zinc (Zn); and also impede their translocation within the plant. These nutrients are critical for plants' disease resistance mechanisms (Johal & Huber 2009).

Glyphosate binds Mn, so that Mn deficiency is now observed where once there was sufficient amounts of the micronutrient. Additionally, the glyphosate resistance gene in GM corn and soybean reduces the plant's uptake and use of Mn. There is now a "gradual recognition" of increased disease severity along with the Mn deficiency. *Corynespora* root rot, once considered minor, may now become economically damaging in Roundup Ready soybean because of the Mn effect, according to Johal & Huber (2009). Cereal take-all is another disease that is a Mn deficiency response to glyphosate, as are a wide range of diseases caused by the bacteria *Xylella fastidosa* (Pierce's disease of grapevine, plum scorch, almond scorch, citrus variegated chlorosis, coffee blight, citrus blight, alfalfa dwarf, pecan decline, etc). These diseases, which involve loss of vigour, slow decline, and reduced productivity, can be controlled by the elimination of glyphosate allowing the Mn and Zn micronutrient levels to be restored to sufficiency (Johal & Huber 2009).

Metabolic interference

Glyphosate reduced the production of lignin in asparagus and flax; and phenolic compounds in beans, soybean, the roots of tomato seedlings and the bulbs of the sedge *Cyperus esculentus* (Levesque & Rahe 1992). Both of these effects may reduce disease resistance in the plant (Johal & Huber 2009).

Nitrogen metabolism

Glyphosate modifies nitrogen metabolism resulting in changes, similar to high-temperature changes, that lead to *Fusarium* head scab in cereals, so that the disease is now prevalent in cooler areas where it was rarely observed before extensive use of glyphosate (Johal & Huber 2009). Climate change is likely to further exacerbate this problem.

Other effects on plants

Glyphosate can have inhibitory effects on desirable plants after it has been used on weeds. It can be transferred from weeds to non-target plants through the roots: when weeds in orchards were sprayed, glyphosate was released from dying weeds and taken up by the neighbouring citrus trees (Yamada et al 2009). In another study glyphosate used to kill ryegrass strongly impaired the growth and micronutrient status of sunflowers planted after the ryegrass (Tesfamariam et al 2009).

Nutrient deficiency

There are a number of ways in which glyphosate can cause nutrient deficiencies in plants; for example it inhibits ectomycorrhizal fungi which help plants absorb nutrients and water (Estok et al 1989; Levesque & Rahe 1992; IPCS 1994).

As reported in the previous section, glyphosate can decrease uptake of micronutrients resulting in deficiency symptoms (Yamada et al 2009). In a greenhouse experiment that simulated glyphosate drift, Cakmak et al (2009) demonstrated that glyphosate significantly reduced the seed concentration of calcium, magnesium, iron and manganese in soybean, most likely because glyphosate binds these minerals in poorly soluble complexes. In a similar experiment on sunflowers Eker et al (2006) found that simulated drift caused substantial decreases in leaf concentration of iron and manganese, and lesser decreases in zinc and copper. These effects may have implications for the nutritional quality of soy and other food crops subjected to low levels of glyphosate through drift or soil residues.

As well as binding some minerals, glyphosate also interferes with the root enzymes involved in mineral uptake from the soil—for example the activity of ferric reductase which is involved in iron uptake is reduced by low levels of glyphosate, and Ozturk et al (2008) linked this with the iron

deficiency that is "increasingly being observed in cropping systems with frequent glyphosate applications". The iron-deficient soybeans also pose animal and human nutritional concerns, as human iron deficiency is widespread.

Nitrogen cycle

Glyphosate is toxic to the nitrogen-fixing bacteria in legume root nodules that make nitrogen available to legumes (Zablotowicz & Reddy 2007). A number of studies have reported that the herbicide curtailed nodulation in soybean and inhibited growth of the bacteria, reduced nodule biomass and leghemoglobin (an oxygen carrying protein), and reduced nitrogen fixation and/or assimilation in the plant (Grossbard 1985; King et al 2001; de Maria et al 2006; Zablotowicz & Reddy 2007; Bellaloui et al 2008). Soybeans are most sensitive to these effects during early stages of growth (Bellaloui et al 2006), and under conditions of water stress (King et al 2001; Zablotowicz & Reddy 2007).

In laboratory studies, glyphosate also inhibited *Rhizobium* root nodulation and nitrogen-fixation in sub-clover, the inhibition being higher in sandy soils (Eberbach & Douglas 1983, 1989; Martensson 1992). Up to 70% reduction in nitrogen-fixing nodules occurred in clover planted 120 days after the glyphosate application at a concentration corresponding to typical application rates (Eberbach & Douglas 1983).

Glyphosate treatment of soil collected from a tea plantation in India reduced the population of nitrogen-fixing bacteria (Bezbaruah et al 1995).

Glyphosate has other effects on the soil's nitrogen cycle: in a Canadian study, application of glyphosate to a grass field resulted in a 20-30% increase in dinitrification up to 49 days after application, and hence contributed to nitrous oxide emissions (which contribute to ozone destruction) and nitrogen loss from the soil (Tenuta & Beauchamp 1995).

Compositional changes

Bellaloui et al (2008) found that glyphosate application to GM soybean at a rate of 3.36 kg/ha caused the beans to have a 10% increase in protein content, an increase in oleic acid, and a decrease in linoleic acids, suggesting effects on carbon and nitrogen metabolism. In a subsequent study they also found that glyphosate significnalty reduces iron content in the beans (Bellaloui et al 2009).

Glyphosate decreased chlorophyll content in GM soybean plants (Pline et al 1999), in sunflower leaves and shoot tips (Eker et al 2006), and in the freshwater green algae *Chlorella pyrenoidosa* it reduced chlorophyll and carotenoids increasingly with higher temperatures (Hernando et al 1989).

Other effects

GM soybean was more susceptible to infection by soybean cyst nematode than the normal soybean after exposure to glyphosate (Giesler et al 2002).

Roundup damaged the cytoskeleton of the microtubules of pollen from tobacco plants, potentially reducing pollen fertility (Ovidi et al 2001).

Glyphosate reduced the RNA content of petunia flowers and changed their shape (Shimada & Kimura 2007); and it caused oxidative stress in rice leaves (Ahsan et al 2008).

Earthworms

Earthworms are considered to be sentinels of soil heath and integrity (Verrell & Buskirk 2004), so any adverse effects on these organisms are of considerable concern.

According to the IPCS (1994), glyphosate is of low toxicity to earthworms:

- NOEC = 158 mg/kg

Exposure to higher concentrations can result in thin, slack and lethargic worms with a dark skin (IPCS 1994).

However Springett & Gray (1992) found that Roundup applied to the soil in repeated doses had a substantial adverse effect on the growth rate of the earthworm *Aporrectodea caliginosa* at all rates of application. The rates used ranged from 0.7 to 2.8 g ai/ha, substantially less than recommended agricultural rates. According to the authors, the highest rate used was only 20% of the normal applied, yet at this rate no earthworms matured. They concluded: "the reproductive capacity and the total population in the soil could be expected to fall following repeated low doses of biocides."

Exposure of the earthworm *Eisennia fetida* to the glyphosate formulation 'Glycel 41% SL', at commercial application rates, caused a 50% reduction in weight but no significant reduction in numbers (Yasmin & D'Souza 2007).

Eisennia fetida was also found to avoid soil contaminated with the glyphosate formulation 'Ortho Groundclear Total Vegetation Killer' (5% glyphosate) at "nominal concentrations" of "low to negligible acute toxicity". They rapidly migrated to the surface of the soil, and the authors expressed concern such an effect may compromise survival (Verrell & Buskirk 2004).

Beneficial arthropods

Some studies have shown that glyphosate/ Roundup can have adverse effects on a number of beneficial organisms that are important to a properly functioning agroecosystem, including a number of predatory insects and parasitoids.

The following effects were observed in a recent study (Schneider et al 2009) on glyphosate ingestion by the predator insect *Crysoperla externa*, which is associated with soybean pests and has potential as a biological control:

- severely reduced fecundity and fertility;
- most eggs were abnormal, smaller, dehydrated and became black 2 days after being laid;
- shorter development from 3rd larval instar to pupae;
- longer adult pre-reproductive period;
- reduced adult longevity;
- adults developed tumours in the abdominal region at 20 days after emergence, more drastic in females than males.

Other reported effects of glyphosate:

- high doses caused 100% mortality of the predatory mite *Amblyseius fallacis*, which predates the spider mites *Panonychus ulmi* and *Tetranychus urticae* (Hislop & Prokopy 1981);
- decreased longevity in the detritus-eating springtail (*Onychiurus quadriocellatus)* and woodlouse (*Philoscia muscorum* and *Oniscus asellus*) (Eijsackers 1985);
- carabid beetles moved out of glyphosate treated areas in wheat field experiments and numbers did not return to normal until 29 days after application, consequently lowering potential rates of predation on lepidopteran pests (Brust 1990);
- the common green lacewing (*Chrysoperla carnea*) experienced 53% mortality in its larval stage when exposed to low levels of glyphosate (0.7 kg/ha); at 3.7 kg/ha there was a 20% effect on mortality (EC 2002);
- significantly reduced abundance of the small field spider *Lepthyphantes tenuis* when glyphosate was sprayed in controlled experiments (Haughton et al 2001);
- female carabid beetles in glyphosate treated headland plots in spring wheat fields in the UK contained less eggs (Asteraki et al 1992);
- 50% mortality of a parasitoid wasp, a lacewing and a ladybug, and 80% mortality of a predatory beetle after exposure to freshly dried Roundup (Hassan et al 1988);
- carabid beetles crawling over residues of Roundup Biaktiv moved at significantly lower speed (Michalková & Pekár 2009).

Conversely, with the foliar-feeding nematode *Nothanguinea phyllobia*, glyphosate was shown to prolong larval survival by 50%, thus potentially increasing incidence of this pest nematode (Robinson et al 1977).

Bees

Glyphosate was described by the IPCS (1994) as being slightly toxic to honeybees, and by FAO (2000) as non-toxic:

- Oral toxicity LD_{50} = >100 *u*g/bee
- Dermal toxicity LD_{50} = >100 *u*g/bee

Birds

Glyphosate is described by the IPCS (1994) as slightly toxic to birds, with an LD_{50} of >3851 mg/kg body weight (IPCS 1994).

Little information appears to be available about chronic effects on birds. However Roundup can cause endocrine disrupting effects in animals just as in humans. Exposure to Roundup caused disruption of the male genital system in mallard ducks: it altered the structure of the testis and epididymis, serum levels of testosterone and oestradiol, and the expression of androgen receptors in the testis (Oliveira et al 2007).

Other animals

Accidental ingestion of glyphosate formulations by 25 dogs in France between 1991 and 1994 caused vomiting, hypersalivation, diarrhoea, and prostration, but no deaths (Burgat et al 1998).

"Nausea, vomiting, staggering and hindleg weakness have been seen in dogs and cats that were exposed to fresh chemical on treated foliage" (HSDB 2006).

Many animal deaths have been recorded after aerial spraying of glyphosate in Colombia - refer section on Human poisonings.

Environmental Fate

Soil persistence and mobility

Glyphosate is regarded as being 'relatively persistent' in some soils, with a half-life varying from less than a week to 180 days, depending on the extent of soil binding and microbial breakdown (Carlisle & Trevors 1988; US EPA 1993; IPCS 1994; EC 2002). Residues were detected in soil in Alberta, Canada, 10 months after spraying (Humphries et al 2005); and in Sweden up to three years after application (IPCS 1994).

Because degradation is largely microbial, glyphosate breaks down much more quickly under aerobic than anaerobic conditions: (EC 2002)

- DT_{50} lab 20°C aerobic 4-180 days
- DT_{50} lab 20°C anaerobic 3-1699 days
- DT_{50} field aerobic 1-106 days

Microbial degradation results in the metabolite AMPA, which has a median half-life of 240 days, ranging up to 958 days in some soils (US EPA 1993).

Glyphosate is adsorbed (bound) onto soil particles. Soils containing higher levels of clay minerals, iron, and aluminium increase adsorption of both glyphosate and AMPA (Piccolo et al 1994; Gerritse 1996). Higher levels of organic matter decrease adsorption (Gerritse 1996). Cooler climates tend also to increase persistence (US EPA 1993), as does soil acidity (Albers et al 2009).

Although glyphosate is frequently reported to be strongly adsorbed onto soil particles, and therefore to be biologically inactivated and have low potential to leach (IPCS 1994), in fact this is not always the case. Agricultural soils to which phosphate fertilisers have been added can be high in unbound glyphosate because the soil sorption sites are occupied by the competing phosphate ions from the fertiliser. So unbound glyphosate remaining in the soil is available for root uptake, microbial metabolism, and leaching into groundwater (Kremer & Means 2009). The risk of leaching is greater in fertilised soils (Simonsen 2008). Conversely studies have shown that the presence of glyphosate in some soils can reduce retention and availability of phosphate (Caceres-Jensen et al 2009), hence reducing fertility.

Other reviews and studies have also concluded that glyphosate, and to a greater extent AMPA, leaches through soils (e.g. Landry et al 2005), especially after high rainfall (Vereecken 2005). The California Department of Pesticide Regulation (Fossen 2007) described glyphosate as a "potential leacher".

There is also evidence that glyphosate does not remain bound to soil particles, that adsorption is not permanent. Desorption can occur readily in some soils and the desorbed glyphosate becomes highly mobile in the environment. Piccolo et al (1994) and Piccolo & Celano (1994) showed:

- a high percentage of bound glyphosate can be returned to the soil solution: the least adsorbing soils desorbed up to 80% of the adsorbed herbicide, and the high adsorbing soils released 15-35%;
- desorption readily occurred in soil with a high clay mineral but low iron oxide content;
- desorbed glyphosate can leach to lower soil layers;
- glyphosate can adsorb onto water-soluble humic substances (soil components primarily responsible for the mobility of pesticides in soil) and be transported with humic substances to lower soil depths.

Albers et al (2009) found that glyphosate sorbed to humic substances is more easily desorbed than that sorbed to iron and aluminium oxides.

Simonsen et al (2008) demonstrated in laboratory studies that glyphosate that had aged in soils for 6.5 months, before seeds were sown, was subsequently taken up by plants.

The presence of *Bacillus thuringienis kurstaki* (Btk)[3] toxins increases the persistence of glyphosate in soils (Accinelli et al 2004), as does the addition of the herbicide diflufenican (Tejada 2009).

Persistence in water

Glyphosate is soluble in water, resistant to hydrolysis (US EPA 1993) and, although it does break down by photolysis and microbial degradation, it can be persistent for some time in the aquatic environment, with a half-life up to nearly 5 months, and still be present in the sediment of a pond after 1 year.

- Solubility = 10.5 g/l at 20°C (FAO 2000)

[3] Genes from Bkt, a natural soil bacterium, have been spliced into some GM crops so that the crop continually expresses the toxins to make them resistant to some pests, hence these crops are likely to cause increased levels of the toxin in soils.

Photolytic degradation (EC 2002):
- DT_{50} = 33 days at pH 5 and 77 days at pH 9

Biological degradation (EC 2002):
- DT_{50} water = 1-4 days
- DT_{50} whole system = 27-146 days

The aquatic half life of POEA has been estimated as 21-41 days (Mann et al 2009).

Glyphosate dissipates from water into sediment or suspended particles (IPCS 1994). It has been found to then dissipate from the sediment of a farm pond with a half-life of 120 days; and to be still present in pond sediment at 1 mg/kg one year later (US EPA 1993).

Distribution in water/sediment systems (EC 2002):
- after 1 day: 47-64% in water, 31-44% in sediment
- after 100 days: 3% in water, 29-44% in sediment

Residues in surface waters

Glyphosate has been found in surface waters in many countries, including Canada, China, France, Netherlands, Norway, UK, and USA (Frank 1990; IPCS 1994; Buffin & Jewell 2001; Zhang et al 2002; Wan et al 2006; Kolpin et al 2006; Struger et al 2008; Botta et al 2009).

A study in southern Ontario, Canada found residues of glyphosate in a wide range of creeks, brooks, lakes, rivers, and drains, with the maximum detected level of 40.8 *u*g/l (Struger et al 2008). A previous study found it in "most of the wetlands and streams sampled" in Alberta (Humphries et al 2005).

A study of mid-western USA streams found glyphosate in 36% and AMPA in 69% of samples, with maximum levels of 8.7 *u*g/l glyphosate and 3.6 *u*g/l AMPA (Battaglin et al 2005).[4] Glyphosate has also been found in forest streams in Oregon and Washington, and in streams near Puget Sound (Cox 1998).

Glyphosate and AMPA were both found in vernal pools (pools that dry up in hot weather but reappear in wet weather, and are often critical for amphibians) in the US, with highest levels of glyphosate (328 *u*g/l) found in a national park (Battaglin et al 2009).

Analysis of water from urban streams in Washington (USA) over the period 1998-2003 found glyphosate in all samples (Frans 2004).

In another study of urban contribution to residues in US streams, AMPA was found in 67.5% and glyphosate in 17.5% of streams and with maximum concentrations of AMPA of 3.9 *u*g/l and glyphosate of 2.2 *u*g/l. There was a 2-fold increase in detections below urban wastewater treatment plants, indicating urban use is making significant contributions to stream contamination (Kolpin et al 2006).

This is supported by a recent study in urban Paris which found levels in Ogre river water frequently exceeded the European standard for drinking water of 0.1 *u*g/l, with levels as high as 90 *u*g/l found after rainfall (60% of Paris drinking water comes from surface waters). The origin is believed to be use of glyphosate on roadsides and railways sides (Botta et al 2009). Similarly glyphosate was found in sewage sludge in the same area at levels of 0.1-3 mg/kg (Ghanem et al 2007).

One study detected glyphosate in the runoff from no-till corn 4 months after application (Edwards et al 1980).

Groundwater

Glyphosate has been found in groundwater and wells in a number of countries, including Canada, Denmark, the Netherlands, and USA (IPCS 1994; US EPA 1992; Cox 1998).

In 2001/2002 38 out of 193 private water plants supplying households in Denmark were found to contain glyphosate and AMPA. Of these 15 still had residues in 2005, with 10 exceeding the EU standard of 0.1 *u*g/l. The 15 plants extracted water from wells in shallow groundwater layers (Brusch 2006).

In 2002 the European Commission (EC 2002) warned that member states "must pay particular attention to the protection of the groundwater in vulnerable areas, in particular with respect to non-crop uses".

Marine sediments and seawater

Glyphosate was detected in the waters of the Mareenes-Oleron Bay (France, Atlantic Coast), over an 11-day period in late spring 2004, at a

[4] AMPA residues can also originate from the breakdown of detergents.

peak concentration of 1.2 *u*g/l (Stachowski-Haberkorn et al 2008).

Bioconcentration

Bioconcentration is the accumulation of substances in an organism through uptake from water. The octanol-water partition coefficient (K_{ow}) is used to determine a chemical's ability to bioaccumulate.

Octanol/water partition coefficient (FAO 2000):
- log K_{ow} = < -3.2 at 25°C
- equivalent K_{ow} = < 6 × 10-4

The IPCS (2004) reported that bioconcentration factors for glyphosate were low in laboratory tests and there was no evidence of bioaccumulation, but residues of the metabolite had been found in carp 90 days after application.

Bioconcentration factors (BCF) for fish have been measured as 0.2 to 0.63, suggesting that bioconcentration in aquatic organisms is low (HSDB 2006).

Atmospheric transport and deposition

A Canadian study has identified glyphosate in particles in the air and has proposed that atmospheric transport of glyphosate is in association with particulate matter (dust) not vapour (Humphries et al 2005).

Volatility

The European Commission (EC 2002) concluded there would be no significant volatilisation from plant surfaces or soil:
- Vapour pressure = 1.3 x 10^{-5} Pa at 25^0C

Deposition

Interchange between air and water, which affects uptake into the atmosphere and redeposition in rain or snow, is described by Henry's Law constant (H)—the higher the value, the higher the deposition.

Henry's law constant for glyphosate (EC 2002):
- 2.1 x 10^{-7} Pa/m^3/mol

Glyphosate was one of the most frequently detected pesticides in rainwater in Belgium in 2001. It was found in 10% of rain samples at concentrations up to 6.2 *u*g/l, with AMPA found in 13% at a maximum concentration of 1.2 *u*g/l (Quaghebeur et al 2004). It was also measured in rain at Alberta, Canada, at all sites and throughout the "growing season", at a maximum concentration of 1.51 *u*g/m^2/day (Humphries et al 2005).

Herbicide Resistance and Weeds

Weed resistance to glyphosate was first recorded in 1996, in Australia, in the species *Lolium rigidum* (rigid ryegrass). Now, 13 years later, it is recorded in 16 different species and in 14 different countries (WeedScience.com 2009). There are at least 44 biotypes of these weeds, the majority of which have arisen in glyphosate-resistant crops (Dinelli et al 2008).

Resistance to glyphosate initially evolved very slowly: there were no reported cases until 20 years after the herbicide's introduction. However the upsurge in repeated applications of glyphosate in no-till systems and GM crops has greatly increased the risk of resistance developing (Dewar 2009). Ten of the 14 resistant species are recorded in USA, Argentina and Brazil, where glyphosate tolerant crops are widely grown, and are largely associated with Roundup Ready soybean, and to a lesser extent maize and cotton. The first glyphosate resistant weed associated with a GM crop was horseweed, *Coryza canadensis*, which appeared in the US just 3 years after the introduction of Roundup Ready soybean and it is now widespread across mid-west, southern and east coast USA (Dewar 2009).

Weeds	Countries
Amaranthus palmeri (Palmer amaranth/pigweed)	USA
Amaranthus rudis (Common waterhemp)	USA
Ambrosia artemisiifolia (Common ragweed)	USA
Ambrosia trifida (Giant ragweed)	USA
Conyza bonariensis (Hairy fleabane)	Brazil, Colombia, South Africa, Spain, USA
Conyza canadensis (Horseweed)	Brazil, China, Czech Republic, Spain, USA
Digitaria insularis (Sourgrass)	Brazil , Paraguay
Echinochloa colona (Junglerice)	Australia
Eleusine indica (Goosegrass)	Colombia , Malaysia
Euphorbia heterophylla (Wild pointsettia)	Brazil
Lolium multiforum (Italian ryegrass)	Argentina , Brazil, Chile, Spain, USA

Lolium rigidum (Rigid ryegrass)	Australia, France, South Africa, Spain, USA
Parthenium hysterophorus (Ragweed parthenium)	Colombia
Plantago lanceolata (Buckthorn plantain)	South Africa
Sorghum halepense (Johnsongrass)	Argentina, USA
Urochloa panicoides (Liverseedgrass)	Australia
Source: WeedScience.com 2009	

The mechanisms involved in the development of this resistance are not well understood, but they appear to involve gradual changes within the exposed weed populations, in some cases involving herbicide sequestration by the weed in tissues, limited herbicide translocation within it, and slow metabolism (Johnson et al 2009).

However there is another type of resistance—involving the spreading of the tolerance genes engineered into the Roundup Ready plants to wild relatives. This is known as gene flow, and it reduces the weed's susceptibility to glyphosate. Monitoring of GM sugar beet production in France lead to the discovery of resistant weeds that were descended from hybridisation of the GM sugar beet and weed beet, at up to 112 m distance from the nearest GM plant (Darmency et al 2007). Gene flow has also been found to occur from glyphosate-tolerant canola, corn, soybean, and creeping bentgrass. GE canola has been found growing as weeds along railways and roads in Canada. The glyphosate-tolerance genes in creeping bentgrass have been found in non-GM creeping bentgrass as far as 21 km distant from where the GM version was being grown under regulation (as it is not yet commercially released) (Mallory-Smith & Zapiola 2008).

Constant use of glyphosate in cropping systems has affected the dynamics of weed populations, causing a species shift away from those that are sensitive to glyphosate such as perennial grass and perennial broadleaf weeds, to weeds that are regarded as more difficult to control with herbicides, such as annual broadleaf weeds (Johnson et al 2009). It has also resulted in an increase in weed species richness in some crops, for example in a US corn-soybean rotation, in comparison with tillage and/or other herbicide regimes. Whilst these are not issues of resistance, they are important effects of glyphosate on weed dynamics, and they are reducing the utility of the Roundup Ready cropping systems (Johnson et al 2009).

Resistance to glyphosate of just 4 weeds—common ragweed, giant ragweed, common waterhemp and Palmer amaranth—is likely to have a significant effect on corn and soybean production in the US corn belt according to Johnson et al (2009). The same effects on cropping can be expected in other countries that are following the US in adopting GM herbicide-tolerant crops.

Some scientists, and even Monsanto, are now recommending that growers use other herbicides as well as glyphosate to reduce the development of glyphosate resistance in weeds within glyphosate-tolerant crops. Herbicides recommended include alachlor, atrazine, 2,4-D, diuron, flumioxazin, fomesafen, metolachlor, mesotrione, MSMA, and pendimethalin. In fact, a Monsanto suggestion for weed management in corn, cotton and soybean involves using glyphosate in only 2 out of 4 herbicidal treatments (Gustafson 2008). Fluometuron, prometryn, and trifluralin have also been suggested in Australia (Werth et al 2008). In Latin America glyphosate is now reported to be commonly mixed with other herbicides including atrazine, paraquat, and metsulfuron (Semino 2008).

Alternatives to Glyphosate

Alternative herbicides

There are many other synthetic chemical herbicides on the market, but these also have a range of adverse health and environmental effects, such as endocrine disruption, cancer, neurological damage, reproductive toxicity, groundwater contamination, persistence, etc. Hence their use is NOT recommended as replacements for glyphosate.

There are some herbicides derived from natural plant extracts that can kill or suppress weeds, such as extracts from pine oil and coconut oil. But care must be taken to ensure that formulations do not include toxic surfactants, solvents or other inert or adjuvant ingredients. Some formulations are permitted in certain circumstances in organic growing systems.

Generally, however, even a natural herbicide should be regarded as the choice of last resort,

with the primary focus being placed on alternative weed management practices that prevent the need for a spray.

Alternative weed management

Alternative weed management focuses on sustainable ecological solutions that minimise the incursion and build up of weeds. It takes a holistic approach to crop management that recognises weeds as an integral part of the whole agroecosystem, forming a complex with beneficial insects, weeds, and crops. The self-regulatory mechanisms of a highly biodiverse farming system help keep both weed and pest species in balance. Although weeds are generally regarded by the modern agricultural institution as reducing crop productivity and encouraging pests and diseases, there are many instances where the reverse is true. Weeds can play a vital role in suppressing pest and disease populations, improving soils and increasing yields.

So-called weeds can provide valuable ground cover, protecting the soil from sun and rain damage and erosion. Balanced weed populations can provide favourable microclimates that assist crop growth. Weed roots can help improve soil biological activity and structure. They can be useful green manures. Weeds can also produce chemicals that are beneficial to crop plants—for example corncockle produces the chemical agrostemmin, which can increase the yield and gluten content of wheat (Lampkin 1990).

Weeds can attract insect pests away from crops and/or provide habitat for beneficial insects that control pest species, for example for ladybirds that control aphids (Lampkin 1990); or the use of Napier grass in East African maize and sorghum systems: the grass produces an odour which attracts stem borer and a sticky substance which kills the larvae (Ho & Ching 2003).

Indian farmer Poorak Kheti, in Mohanpur, Uttah Pradesh uses the weeds baru (*Sorghum halepense*), doob (*Cynodon dactylon*), tipatuiya and motha (*Cyperus rotundus*) to improve soil fertility and the yields of his sugar cane (Sciallaba & Hattam 2002).

Weeds can also be very useful as prized herbal remedies or valuable additions to the diet because of their nutritive quality. Plants that are called weeds by some are in fact highly valued plants for others—for example the Napier grass mentioned above as a weed is highly prized as a source of food and fodder by some African communities and can be a lifeline for them.

Weeds are excellent indicators of problems with soil structure and fertility. Weed species can be read to indicate problems with pH, poor drainage, compaction, low friability of soils and nutrient deficiency (Lampkin 1990). Spraying the weeds with glyphosate or any other herbicide will not fix the problem, but solving the soil health problem will control the weed as well as increase productivity and resistance to pests and diseases.

Elements of alternative weed management can include:

- designing a farm ecosystem that encourages biodiversity, providing habitats for beneficial insects, and utilising weeds as an element of useful biodiversity whilst minimising the need for intervention to control them;
- reading weeds to identify soil problems and then making the necessary improvements to soil health;
- timely and appropriate cultivation prior to sowing the crop, to either bury weed seeds or encourage their germination before crop sowing, although mechanical disturbance of the soil should be minimised in order to protect the soil structure;
- sowing of green manures between crops helps prevent weed seed germination; then turning in the green manure and weeds before they flower provides added soil benefits;
- increasing competitiveness of the crop through appropriate nutrient use and improving soil health;
- controlling the spread of weed seeds through good sanitation practices, such as cleaning machinery, cleaning seeds for saving, careful use of animal manures, good composting practices, and avoiding letting weeds go to seed;
- selection of optimum planting dates with respect to crop choice, lunar cycles and weather patterns;
- appropriate mechanical methods and cultural practices such as hand and mechanical weeders, mulches, smothering methods, thermal weed control, solarisation, livestock grazing, rotations, use of under-sowed species;
- flame weeders can be used pre-emergence, post-emergence, and even as pre-harvest defoliants for crops such as potatoes and onions;
- introducing ducks into rice growing systems to eat weed seeds and seedlings;

- introducing insect species that provide biological control of weeds. (Lampkin 1990; Ho 1999; BIO-GRO 2001)

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Pesticide Action Network Asia and the Pacific (PAN AP) is one of five regional centres of PAN, a global network working to eliminate the human and environmental harm caused by pesticides, and to promote biodiversity-based ecological agriculture.

"Our vision is a society that is truly democratic, equal, just, culturally diverse, and based on food sovereignty, gender justice and environmental sustainability". **Thus PAN AP asserts people's food sovereignty based on the right to food for all, founded on the right to land and productive resources and the right of communities to decide on our own food and agriculture policies. We are committed to protect the safety and health of people and the environment from pesticide use, and genetic engineering in food and agriculture. We strive to protect and promote the rights, equality and dignity of women. We will promote and protect biodiversity based ecological agriculture. Our goal is to strengthen people's movements to eliminate hunger and achieve food sovereignty. We endeavour to achieve these goals by empowering people within effective networks at the Asia and the Pacific, and global levels.**

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