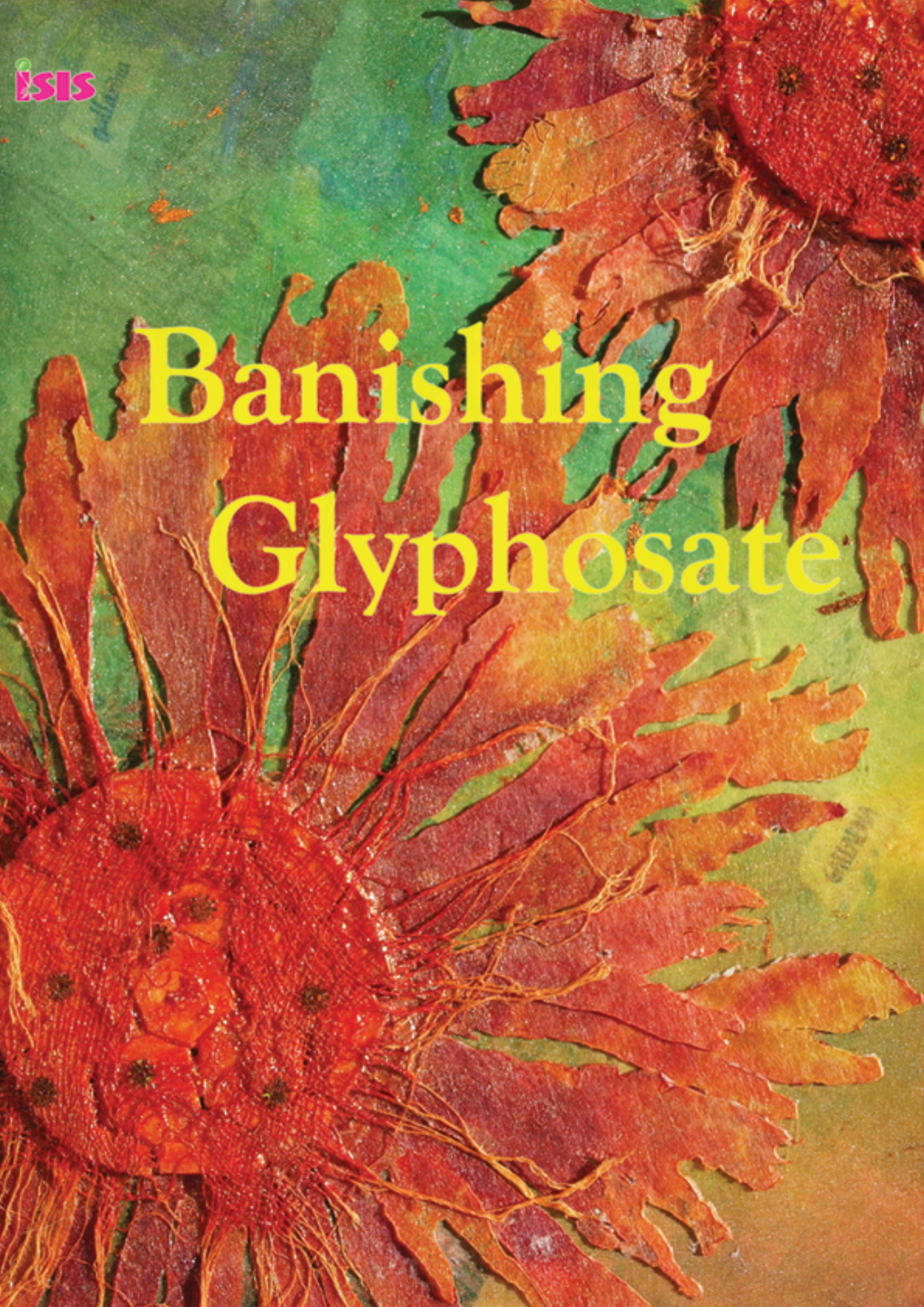
ISIS
Banishing
Glyphosate

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Preface

Glyphosate was released as an herbicide in 1974, and rapidly became the world's most popular herbicide especially since the introduction of genetically modified (GM) glyphosate-tolerant crops in the 1990s. Currently, 85 % of GM crops are herbicide-tolerant, with glyphosate-tolerant crops making up the vast majority of those planted. In the US for example which is the largest producer of GM crops, 93 % of soybean and 85 % of maize crops are glyphosate-tolerant (see Chapter 5).

A total of 137 glyphosate-tolerant varieties have been approved by May 2015 (see Supplement online Table 1 Approved glyphosate tolerant crops). There are 19 varieties of cotton, 115 of soybean and 81 of maize; and in addition, 1 wheat, 2 sugar beet, 4 potato, 3 Polish canola, 8 Argentine canola, 1 creeping bentgrass and 3 alfalfa. 80 % of these crops are stacked, containing additional traits such as tolerance to glufosinate and 2,4-D herbicides and/or pesticidal properties. Of the glyphosate-tolerant crops generated, over 99 % of those grown belong to only four species - soybean, maize, cotton and canola.

According to the new yearly report from industry funded International Service for the Acquisition of Agri-Biotech Applications (ISAAA) [1], "18 million farmers in 28 countries planted more than 181 million hectares [of GM crops] in 2014, up from 175 million in 27 countries in 2013." This has spurred huge sales of glyphosate, giving it a market value of US$5.4 billion in 2012 with a total demand of 718 000 tonnes [2]. Globally it is a key ingredient in more than 700 products [3] and is also used to control weed in gardens, along roadsides in commercial and residential areas, and on millions of hectares of farmland. Its presence is pervasive, in the air, in the soil, in our food and drinking water (see Chapter 1).

Underlying its success has been the repeated claim that the chemical is benign for human health, that its killing mechanism for plants works via an enzyme that does not exist in animals and is therefore safe for both human and animals. This claim goes counter to evidence that existed right from the start. Studies revealed both carcinogenicity and teratogenicity as far back as the 1980s, but were buried by industry with the support of regulatory bodies such as the US Environmental Protection Agency and the European Food Safety Authority (see Chapter 5 and [4] EU Regulators and Monsanto Exposed for Hiding Glyphosate Toxicity, *SiS* 51).

Meanwhile, overwhelming evidence of glyphosate toxicity across the globe has come to light. Everywhere, people are seeing steep rises in cancers, birth defects and other serious illnesses as glyphosate use increases. The World Health Organisation's recent re-assessment of glyphosate as a 'probable carcinogen' vindicates the evidence witnessed by communities, researchers, doctors and campaigners for many years.

Despite rising glyphosate use and GM crop cultivation, recent data show that global GM crop adoption rates are falling, covering only 3.5 % of arable land. The markets of high-adoption rate countries are becoming saturated, while few additional countries have been cultivating GM crops, indicating that nations and farmers are turning the backs on a failing technology [5]. With the rise of weeds evolving resistance to glyphosate, US Farmers reported a decline in the effectiveness of glyphosate on almost 44 % of acres planted with soybeans in 2012. More than 47 % of those acres are in the Corn Belt, which contains the majority of soybean acreage in the United States, followed by the Northern Plains (23 %), Delta (11 %), Lake States (10 %), and Appalachia (9 %). The failure of GM crops could also have a major impact on the future of glyphosate use [6].

With its increasing lack of efficacy on top of the rising awareness of its toxicity, people across the globe are taking action to rid glyphosate from their farms, their food and their land, air, and water. Lawsuits are being filed against Monsanto both in the US for false claims of safety, and in China for hiding the toxicology documents used for registering the chemical in the country. China is the world's largest producer of glyphosate and the largest importer of GM soybeans [7] (How Grain Self-Sufficiency, Massive Soybean Imports & Glyphosate Exports Led China to Devastate People & Planet, *SiS* 67); and feelings are running high against both. A recent petition has even gone so far as to call for the complete overhaul of the Ministry of Agriculture, whose Agricultural GMO Safety Evaluation is deemed inadequate for ensuring that "GMOs developed abroad or within China are safe". It goes on to claim that there has been collusion between them and Monsanto, resulting in the submission of "fake samples", the carrying out of "false tests" as well as the falsification of "safety conclusions" (see [8] China's Ministry of Agriculture Accused of Colluding with Monsanto, *SiS* 67). The ultimate rejection of glyphosate and GM crops by the Chinese people could be a turning point not just for China but the world. Meanwhile in Argentina, a federal judge has accepted an unprecedented class action lawsuit demanding a ban on GM foods and their associated pesticides [9]. Defendants of this case include not only all the major GM crop and chemical corporations, but the Argentine national government and the Federal Council for the environment. Claiming that GMOs contribute to the trend towards monoculture, direct seeding with consequent reduction of rural labour, concentration of profit in few producers and impacts of health of rural populations and environment, the lawsuit demands the passing of a biosafety law, labelling of GM crops, and the remediation of environmental damage such as the soil in addition to the bans.

The WHO declaration may well be the final nail in the coffin for Monsanto's flagship product, as it has intensified campaigns to ban the chemical. Several countries are already implementing bans of the chemical just 2 months after their assessment was published [10] (Fallout from WHO Classification of Glyphosate as Probable Carcinogen, *SiS* 67). Sri Lanka, suffering from an epidemic of fatal kidney disease, is the first to declare a complete and immediate ban. Earlier, Bermuda has banned glyphosate imports with immediate effect. And Colombia will no longer use it for its large aerial campaigns to destroy illegal coca plantations, a US-led war on drugs that is displacing Colombian citizens and compromising their land and water supplies. The Ecology Minister of France has ordered garden centres to stop selling it [11] and even private companies are taking the chemical off their shelves [12,13,14]. At a scientific UK parliament briefing on the 15th July, the Soil Association called for a ban of wheat pre-season spraying destined for bread after tests conclude that UK glyphosate use has risen by 400 % in the last 20 years [15]. Also attending was a member of the glyphosate researcher from WHO's IARC who reiterated the findings stating that glyphosate is "definitely genotoxic". Healthcare workers and campaigners are demanding action from governments that have so far supported the use of glyphosate, with Argentina seeing a recent statement backed by 30 000 healthcare professionals to ban its use completely, in line with the WHO assessment that vindicates all their work documenting rising rates of cancers and other illnesses linked to

widespread GM soy cultivation. Their message seems to be getting through, with the Argentinian town of Lago Puelo now taking action to ban the marketing and use of glyphosate [16]. The Brazilian National Institute of Cancer José Alencar Gomes da Silva (INCA), a body of the Ministry of Health is similarly calling for a sustained reduction of pesticide use following the IARC declaration. Their report [17] states that glyphosate as well as diazonin and malathion, also declared probable carcinogens in the same assessment, are all widely used in Brazil as a result of GM crop cultivation. They urge for a sustained gradual reduction in pesticide use and a move to agroecological methods that support societal and environmental health, farmers' rights and social justice and economic efficiency.

In the US, state officials are following the advice of the IARC. California's Office of Environmental Health Hazard Assessment intends to list glyphosate as "carcinogenic", which may well be the first step in restricting its use in the US [18].

The EU is yet to make the final decision, expected later this year, on whether it will re-approve glyphosate. The approval process by the EU commission thus far relying on a summary of data provided by a consortium of chemical companies including Monsanto that form the Glyphosate Task Force, it is time that we make sure that the EU does not continue to corrupt the approval process and instead take into account the WHO assessment as well as the many other independent studies that were omitted from the assessment by the task force (see Chapter 11).

This report summarises the converging pattern of glyphosate toxicities from farm to clinic to the laboratory that leaves us in no doubt glyphosate must be banished (a combination of ban and vanish) as a matter of urgency. A global ban is in order; the momentum to do so is already gathering pace. But we must start as individuals, in our family and home, our local communities. Above all, we must take this opportunity to stop poisoning people and planet with agrochemicals and shift comprehensively to sustainable, organic, non-GM agriculture that can truly guarantee food security under climate change (see [19] Food Futures Now *Organic *Sustainable *Fossil Fuel Free, ISIS Special Report) .

All chapters in this report (except Chapter 5 by Dr Mae-Wan Ho and Prof Peter Saunders, and Chapter 9 by Professor Emeritus of plant pathology Dr Don Huber) are selected from articles published by ISIS online and in print between 2013 and 2015. Chapter 1 is updated and substantially enlarged from [20] A Roundup of Roundup Reveals Converging Pattern of Toxicity from Farm to Clinic (*SiS* 65) incorporating Chapter 1 of [21] Ban GMOS Now (ISIS special report). Chapter 2 is from [22] Marked Deterioration of Public Health Parallels Increase in GM Crops and Glyphosate Use, US Government Data Show (*SiS* 65). Chapter 3 is updated from [23] Devastating Impacts of Glyphosate Use with GMO Seeds in Argentina (*SiS* 66). Chapter 4 is from [24] Glyphosate/ Roundup & Human Male Infertility (*SiS* 62). Chapter 6 is updated from [25] Sri Lanka Partially Bans Glyphosate for Deadly Kidney Disease Epidemic (*SiS* 62). Chapter 7 is from [26] Changing from GMO to Non-GMO Natural Soy, Experiences from Denmark (*SiS* 64). Chapter 8 is updated from [27] USDA scientist reveals All (*SiS* 53). Chapter 10 is from [28] How Roundup Poisoned my Nature Reserve (*SiS* 64). Chapter 11 is from [29] Scandal of Glyphosate Re-assessment in Europe (*SiS* 63). Chapter 12 is from [30] Glyphosate 'Probably Carcinogenic to Humans' Latest WHO Assessment (*SiS* 66).

We thank all our co-authors who have contributed to separate chapters of this report, adding invaluable personal perspectives and especially first hand personal experiences of glyphosate toxicities.

Eva Sirinathsinghji *and* ***Mae-Wan Ho***
September 2015

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Converging Pattern of Toxicity from Farm to Clinic to Laboratory Studies

Why we need to ban glyphosate from our own communities as most governments fail to protect citizens

Dr Eva Sirinathsinghji

What is glyphosate?

Glyphosate, perhaps surprisingly for a chemical so ubiquitously associated with our food, was not first used as an agricultural chemical but instead first patented as a metal chelator in 1964 by Stauffer Chemical company (US 3160632 A) [1] and used as an industrial pipe cleaner. It was later patented by Monsanto as an herbicidal agent in 1974 (US3799758 A) [2] based on its ability to block the shikimate pathway involved in the production of aromatic amino acids in both plants and bacteria. It has become the most popular herbicide in the world especially since glyphosate tolerant genetically modified (GM) crops were commercialized in the mid-1990s, together with the assumption (perpetrated by Monsanto) that the herbicide is safe for health and the environment. In 2010, it was also patented by Monsanto as an antibiotic agent. Moreover, it is being increasingly used as a pre-harvest desiccant for drying seeds, a process that results in contamination of non-GM grains, one of the main exposure routes in the EU where GM crops are not commonly grown. Thus, an estimated 70 % of UK oil seed rape (canola) and 50-60 % of EU sunflowers are sprayed with glyphosate [3], resulting in products of major food brands in the UK testing positive for glyphosate residues in a 2014 analysis by GM Freeze, with glyphosate the most commonly detected of all chemicals [4].

All of glyphosate's chemical properties already mentioned have implications for the health of both people and planet. Scientific research has additionally implicated glyphosate as an endocrine disruptor and a DNA mutagen; and it affects over 291 different enzymes in the body [5]. It is increasingly linked with a wide variety of illnesses, the sharp rises in illnesses occurring in parallel with glyphosate application across various GM cultivating regions of the world.

The most convincing evidence of glyphosate toxicity is the consistent pattern of diseases associated with glyphosate that has emerged from the farm to the clinic and from scientific studies to citizen testimonials.

Glyphosate widespread in the environment and in our bodies

Glyphosate's popularity is due in large measure to its concomitant use with the most widely planted type of GM crops, those tolerant to glyphosate-herbicides. Monsanto commercialised the first Roundup-ready crop in 1996 (Roundup being the commercial formulation containing 'adjuvants' that make it much more toxic than the active ingredient glyphosate alone, see later). In countries such as Argentina where large swaths of the country have been dubbed soy deserts, GM soybean cultivation has resulted in

an 858 % rise in glyphosate use (see Chapter 3). Similarly, the US has seen even greater rises of 2 500 % from 1987 to 2007 [6].

This widespread and massive application of glyphosate herbicides has resulted in almost ubiquitous contamination of the environment. A 2014 study on US water systems across 38 states found glyphosate and its principle metabolite AMPA (aminomethylphosphonic acid) not only in rivers, lakes and streams, but also rain, soil and sediment, ditches and drains and groundwater (see [6]). Some 70 % of rain samples tested positive for glyphosate. Similarly in Europe, (in Catalonia, a large region of Spain) it was found that all 11 groundwater sites were positive for glyphosate despite it being a region free from glyphosate-tolerant crop cultivation; 41 % of samples were above detection limits [7]. ***The detection in groundwater goes against one of the claims on glyphosate safety that its propensity to bind to soil and sediment means it will not leach into our fresh water supplies***. In Argentina, new data of rain sample measurements averaged an extreme 6.5 µg/L and reaching as high as 67 µg/L (67 ppb) across four regions from October 2012 to April 2014 [8] and new watershed data finds glyphosate contamination outside of agricultural plots and both glyphosate and AMPA detection in soil sediment, stream water and soils [9]. The high proportion of glyphosate in proportion to its metabolite, its detection 10 months after application as well as its presence as deep as 35cm below the soil surface again indicates the persistent presence of glyphosate in the environment and its potential to contaminate groundwater supplies. The levels in Argentinian rainwater are far higher than those seen in US rain samples where the average and maximum concentrations were 0.11 µg/L and 2.5 µg/L respectively [6].

Tap water and rivers also test positive for glyphosate with UK samples coming up (30 parts per trillion (ppt) and 190 ppt respectively) at concentrations within range of those found to be toxic in lab studies (see Chapter 10). Urban areas also get sprayed, prompting London citizens to organise banning campaigns of glyphosate spraying in public areas including child-friendly zones [10]. Even oceans are not spared from glyphosate poisoning, with run-offs into the sea persisting for up to 267 days in sea water obtained from the Great Barrier Reef and tested in the lab [11].

Due to the official 'safe' status of glyphosate, data on how much we are being exposed have been scarce, forcing citizen activists and civil society organizations to find out for themselves. Friends of the Earth Europe commissioned an analysis of 182 volunteers across 18 EU countries and found detectable levels in 44 % of urine samples [12] with concentrations ranging from 0.16 µg/L average in Switzerland, to 1.82ug/L in Latvia. Of the UK citizens tested, 7 out of 10 were positive. In the US, urine samples show concentrations 8 times those in Europe [13]. The analysis, commissioned by Moms Across America, also tested 10 mother's breast milk, which came up positive for glyphosate with levels ranging from 76 µg/L to 166 µg/L (76-166 ppb) (see [13]). These levels are 760 to 1600 times higher than the European Drinking Water Directive allows for individual pesticides, and raise obvious concerns as they fall within the range of concentrations at which developmental toxicity has been observed in animal studies (see below). This analysis is the first of only two fully independent studies on breast milk to date, as no government or public health body has found it necessary to carry out any study on bioaccumulation in internal organs and tissues or in breast milk fed to infants. The second was performed in Germany where far fewer GM crops are consumed, and the Green Party found glyphosate levels ranging from 0.210-0.432 µg/L; higher than EU drinking water limits of 0.1 µg/L [14]. In an attempt to suppress growing concern over these findings, a press release from Washington State University claims to have found 41 samples of glyphosate-free breast milk from an agricultural region of Idaho, though methods are yet to be published [15]. The press release takes aim at Moms Across America's results which were conducted by a fully accredited laboratory, stating them to be "flat out wrong". Sustainable Pulse who collaborated with Moms Across America for the study, have however exposed the study as little more than propaganda, highlighting the clear ties between the researchers and Monsanto and industry [16].

Detection of glyphosate in the tissues contradicts one of the assumption-based arguments used by industry and regulators that due to glyphosate's high water solubility, it is rapidly excreted from the body and therefore risks of harm are negligible

Recent independent scientific studies have backed up the work of activists and civil society organisations. Awad Shehata and colleagues in Germany looked at glyphosate levels in the urine of both chronically ill and healthy people, and found significantly higher levels in ill people in samples taken from 102 and 199 healthy and chronically ill people respectively [17]. Those who ate predominantly organic food had lower levels, along with livestock that were fed conventional versus genetically modified feed. The study also looked at levels in cow tissues as well as urine. ***Detection of glyphosate in the tissues contradicts one of the assumption-based arguments used by industry and regulators that due to glyphosate's high water solubility, it is rapidly excreted from the body and therefore risks of harm are negligible***. In such a case, the levels of glyphosate in urine would be expected to be much greater than levels found in the tissues. However, urine levels in cows averaged 27-42 µg/ml (27-42 parts per million (ppm)), while the level in tissues (intestine, liver, spleen, kidney and muscle) averaged between 14-20 µg/ml, which is within range of urine levels. Though they did not compare glyphosate levels in urine and internal organs of the same cow, the average levels across all cow samples dispute the assumptions taken by regulators that glyphosate does not remain in the body at levels that can cause harm.

With the expected EU re-approval of glyphosate by the end of 2015, the German Federal Institute for Risk Assessment which was responsible for the renewal reassessment report submitted to the European Food and Safety Authority (EFSA) in 2014 (see later), published a paper strongly dismissing the findings of glyphosate detection in urine as a potential health concern [18]. They argue that the levels of glyphosate are below the allowed daily intake (ADI) and therefore unlikely to present a public health concern. No safety assessments to date have assessed low dose exposure but instead extrapolated from their high dose experiments what a safe exposure level is. We know that many chemicals, including endocrine disruptors however, can actually be more toxic at lower concentrations; and most crucially, the only two studies that tested low doses indeed showed toxicity in both rats and *in vitro* cancer cell lines (see later).

In summary, glyphosate is almost ubiquitous in our environment and in people and livestock; it has even been discovered in hospital feeding tubes for child cancer patients in the US [19]. The impacts are described below.

Box 1

Evidence of glyphosate as an endocrine disruptor

The endocrine system consists of various glands that release hormones into the bloodstream, acting as chemical messengers affecting many functions including metabolism, growth and development, tissue function, behaviour and mood. Disruption of the endocrine system does not commonly result in cell death, or acute toxicity. Instead, endocrine disruption can have serious health effects through interference in cell signalling and physiology, resulting in a range of developmental impacts including sexual and other cell differentiation, bone metabolism, liver metabolism, reproduction, pregnancy, behaviour, and hormone-dependent diseases such as breast or prostate cancer. Endocrine disruption may well underlie many of the reproductive, teratogenic, and carcinogenic effects of glyphosate. The synthesis of sex hormones is disrupted by glyphosate and Roundup® in both males and females. Mouse and rat testicular Leydig cells (testosterone producing cells) have reduced testosterone levels as well as increased levels of aromatase, an enzyme complex that converts testosterone into oestrogen [47,33]. Human placental cells, on the other hand, showed decreased aromatase expression [113]. All these imbalances were observed with concentrations well below agricultural dilutions, and effects were more pronounced with commercial formulations containing adjuvants. Abnormal expression of testosterone and/or oestrogen receptors as well as oestrogen regulated genes has been documented in human liver cells exposed to both glyphosate alone or four commercial formulations, and breast cancer cells exposed to glyphosate [114, 115]. Other hormones were shown to be dysregulated in the presence of glyphosate, including increased expression and serum concentration of luteinising hormone and increased expression of follicle-stimulating hormone. These are both gonadotropin hormones secreted by the pituitary glands that regulate growth, sexual development and reproduction [33]. Rats exposed to Roundup and/or Roundup-tolerant maize over two years exhibited a range of endocrine disruption effects that, typically, differ between the sexes [55]. Thus mammary tumours were rife in exposed females while liver pathologies predominated in exposed males. Similarly, pathology of the pituitary was more significantly increased in exposed females; and big kidney and skin tumours were confined to males.

A birth defect epidemic in people and animals

Argentina is one of the biggest cultivators of GM soybeans and the country has witnessed a sharp increase in serious illnesses since cultivation began. Concerned doctors and health practitioners founded the Network of Physicians of Crop Sprayed Towns and met in 2010. They presented data showing increased incidence of birth defects, spontaneous abortions, infertility, still births, cancers, Down's syndrome, mental disability, immune and endocrine disorders, as well as acute effects such as increased convulsions in epileptic patients at time of fumigation, respiratory and dermatological problems (see Chapter 3) and [20] Pesticide Illnesses and GM Soybeans, *SiS* 53) [21].

The Network, together with a large citizen movement, is pushing for a complete ban on aerial spraying of agrochemicals plus a ban of its use within a kilometre of residential areas. They documented a 2-5 times increase in birth defects in sprayed towns compared to before spraying began. Common defects include neural tube defects, which are replicated in laboratory studies on glyphosate (see later).

A 2013 report from the Centre of Congenital defects claims that nationally, the number of cases has not gone up, but a closer scrutiny gives a different picture. Data gathered during a 6 month period from the hospital Maternidad Provincial in Córdoba showed that despite recording a low level of birth defects of 36 out of a total of 2140 births (1.68 %), 22 of those came from mothers living in crop-sprayed towns, which accounts for 61 % of all the birth defects (see Chapter 3).

The US has seen a surge in neural tube birth defects (anencephaly) in the Yakima River, Washington State. The source remains a mystery to officials who have ruled out common causes such as low folic acid and lifestyle choices. Rates have reached 8 cases per 10 000 births from 2010-2013 compared to a national average of 3 cases per 10 000 births. Glyphosate has emerged as a prime suspect as the state of Washington use herbicides, most often glyphosate, to kill noxious weeds in both land and water. An estimated 146 pesticides were applied in the area in the year 2000, and studies are now needed to confirm whether or not glyphosate, either alone or in combination with other chemicals is responsible for neural tube defects in the area [22]. Reproductive problems such as miscarriages and infertility have also risen in Argentina (see Chapter 4). Physicians of sprayed towns have recorded as many as 23 % of women suffering from miscarriage in the last 5 years [21].

The latest victims of Argentina's chemical agricultural system, of which GM cultivation is an extreme example, could very well have been spared if the evidence of the teratogenic properties of glyphosate produced by industry since the 1980s had not been dismissed [23]. Monsanto's own toxicology tests submitted to the EU commission showed evidence of teratogenicity (see [24] EU Regulators and Monsanto Exposed for Hiding Glyphosate Toxicity, *SiS* 51). The submitted test reports describe rats and rabbits with skeletal abnormalities including the development of a 13th rib in offspring, as well as cardiac abnormalities. Scientific studies such as that of the late Professor Andrés Carrasco reporting neural tube birth defects in frog and chick embryos exposed to agricultural concentrations of glyphosate [25] have validated both Monsanto's findings and clinical observations (see also [26] Lab Study Establishes Glyphosate Link to Birth Defects, *SiS* 48). Probing into the mechanisms underlying the defects, Carrasco discovered that glyphosate disrupted retinoic acid activity, a well-known regulator of developmental processes.

Epidemiological studies have linked increased incidence of birth defects (spina bifida, circulatory/respiratory anomalies, tracheo-esophogeal defects, gastrointestinal defects, urogenital defects, cleft lip, adactyly, clubfoot, musculoskeletal anomalies, Down's syndrome and other birth defects) and reproductive toxicity in those who live near agrochemical-sprayed fields [27-29] while other lab studies are accumulating evidence of birth defects and reproductive toxicity in a range of animals from rats to catfish [30-33]. A host of Chinese studies align with this data. Short summaries in English are available (see [34] China's Ministry of Agriculture Accused of Colluding with Monsanto, *SiS* 67).

Evidence from the farm follows the same pattern. Ib Borup Pedersen recently documented personal experiences on his pig farm, where removing GM soybean feed from the diet resulted in pronounced improvement in the health of his pigs, reducing medicine use by a third and increasing his profits (see Chapter 7). Profits were also increased due to his sows living longer and giving birth to more piglets. After researching glyphosate and GMOs Ib investigated further and collaborated with scientists in

Germany who analysed 38 of his 1-day old deformed piglets, finding glyphosate in various organs of the pigs. Pigs suffered defects ranging from severe to mild, including spinal, cranial defects and others affecting limbs, gender, internal organs, tongue and more. Many appear to be neural tube defects as seen in the clinic and laboratory.

WHO declares it a 'probable carcinogen' as cancers skyrocket in South America

In March 2015 the oncology arm of the World Health Organisation, the International Agency for Research on Cancer (IARC) employed 17 experts from 11 countries to assess the carcinogenicity of organophosphate pesticides, declaring glyphosate a 'probable carcinogen' (category 2A) [35] (see Chapter 5 & 12). The working group were chosen for their expertise as well as their *absence of real or apparent conflicts of interest*. Their assessment was based on the latest scientific evidence from published peer-reviewed papers and government reports that are publically available. This highly significant report has caused a predictably aggressive response from Monsanto, who admitted to being outraged by the report, ironically accusing the group of "cherry picking" papers while they themselves have participated in the glyphosate task force that was responsible for the re-approval of glyphosate in the EU in 2014, discounting any research that was exposing harm of glyphosate, relying heavily on industry data as well as industry funded data, excluding those that showed harm (see below for details). In an attempt to silence and censor evidence that may harm their profits, Monsanto are seeking a retraction of the paper in yet another attempt to control science for their own ends in a desperate attempt to protect their hallmark product (see [36] Elsevier Climb Down over Séralini Retraction but IARC Retraction Next for Monsanto, *SiS* 66).

Neighbourhood resident organisations such as the association of Mothers of Ituzaingo, (from Argentina), in collaboration with the Network of Sprayed Towns have been mapping cancer incidence in their towns for many years to draw attention to the epidemic they are facing. It is has reached the point where now, 30 % of all deaths in these regions are from cancers, affecting both adults and children. Cities such as Hernando have seen a 258 % rise in cases between 2001-2002 and 2010-2012 [6].

Rises in cancer rates can be explained by glyphosate's role in cancer-causing mechanisms including DNA damage and endocrine disruption. Endocrine disruption may well also underlie some of the reproductive and teratogenic effects of glyphosate described above. Lab studies show glyphosate damages DNA in lab animals as well as in people who were exposed to the chemical in Argentina [37-39]. The latest study analysed genetic damage in children living near GM glyphosate-tolerant crop fields. Looking for the frequency of micronuclei which is an established method for assessing genetic damage, they found that those who lived within 500 meters of spraying areas have over 66 % more cells with micronuclei than those living more than 3000 meters away [40]. It also disrupts cell cycle regulation that can lead to increased cell division and cancer development [41, 42]. The glyphosate metabolite AMPA was also shown in a 2014 study to induce DNA damage in fish at concentration ranges previously documented in streams and surface water in N. America [43]. Glyphosate's carcinogenic potential has been documented since the 1980s (see Chapter 5).

One argument for the safety of GM food and their associated pesticides is that the US has been consuming them for years without ill effect. However, in the absence of labelling GM foods, it is illegitimate to make such a claim. On the contrary, there has been a drastic deterioration of public health in the US since GM crops were introduced

Distinct from DNA damaging properties, glyphosate also mimics oestrogen at very low levels and promotes the growth of hormone-dependent breast cancer cell lines [44]. Actually glyphosate is becoming well recognised as an endocrine disruptor (see box 1) and alters the expression of multiple hormones including testosterone, luteinising hormone, follicle-stimulating hormone, and the aromatase enzyme complexes that convert testosterone to oestrogen [30, 45, 45, 47].

Epidemiological studies corroborate lab studies and reports from local citizens in Argentina and the US [48-50]. The Ministry of Health of Córdoba in Argentina reported in June 2014 the doubling of cancer cases in high agrochemical use areas compared to the national average [51]. Consistently, a new meta-analysis found association between glyphosate and cancers following occupational exposure [52]. The study looked at all epidemiological papers on non-Hodgkin lymphoma (NHL) incidence that had been published in English since 1980 that reported agricultural, occupational exposure to specific pesticides. A total of 44 papers were analysed, covering 80 active ingredients and 21 pesticide chemicals, finding the strongest associations between pesticides and specific subtypes of NHL, including an association between glyphosate and B lymphoma. They also found that phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and the active ingredient lindane, an organochlorine insecticide, were positively associated with NHL.

The most comprehensive GMO feeding study to date carried out by Gilles-Eric Séralini and his team, looked at the effects glyphosate and glyphosate tolerant maize NK603 on rats during their life-time (2 years). It showed increased incidence of tumours (including cancers), other illnesses, as well as reduced life-span and altered hormone status [53]. The 2012 publication was aggressively attacked by industry and its supporters and unilaterally and illicitly retracted a year after publication following the appointment of an ex-Monsanto employee as an editor for the journal (see [54] Retracting Séralini Study Violates Science and Ethics, *SiS* 61). It has subsequently been republished elsewhere [54] after massive public protest (see [56] Open Letter on Retraction and Pledge to Boycott, *SiS* 61).

Fatal kidney disease epidemic across continents foreseen by lab studies

Kidney disease has reached epidemic levels in regions that heavily use glyphosate such as farmers in Sri Lanka and sugar cane workers in Central America. Kidney problems have been highlighted by scientific studies, including Séralini's rat feeding study where kidney tumours were observed [55]. A meta-analysis of feeding studies conducted by Séralini's lab revealed kidney pathol-

Box 2

Evidence of neurotoxicity

The most obvious indications of neurotoxicity come from the development of Parkinsonism following acute exposures. Two published cases include a 54 year old man in Brazil was diagnosed with Parkinsonism following accidental spraying; he developed skin lesions six hours after being exposed to spraying, and a month later he developed Parkinson's disease symptoms [116]. The other case involved a woman in Serbia who ingested 500 millilitres of glyphosate solution and developed Parkinsonism along with lesions of the brain's white matter and pons (part of brain stem), and altered mental status. The woman suffered additional non-neurological symptoms (see acute toxicity section) and eventually died [117]. Consistently, increased oxidative stress, mitochondrial dysfunction and loss of cell death markers were found in the substantia nigra (the brain region most affected in Parkinson's disease) of rats exposed chronically to glyphosate at sub-lethal levels [118, 119]. Oxidative stress represents an imbalance between the production of reactive oxygen species (ROS), also known as free radicals, and the body's ability to detoxify these reactive intermediates or repair the damage caused by them. ROS are a natural by-product of oxygen metabolism such as mitochondrial respiration, and have important roles in signalling and metabolism. Excess amounts however, can have damaging effects on many components of the cell including lipids in cellular membranes, DNA and proteins. Excess ROS has been implicated in the aetiology of a wide array of diseases including Alzheimer's disease, Parkinson's disease (PD), atherosclerosis, heart failure, myocardial infarction and cancer (see [120] Cancer a Redox Disease, *SiS* 54). Indeed Parkinson's symptoms such as hypoactivity are mimicked in rats repeatedly exposed to glyphosate, accompanied by reduced dopamine levels, as well as binding of dopamine receptors in the substantia nigra and nucleus accubens brain regions [121]. Activation of the tightly regulated apoptotic and autophagic cell death pathways is also implicated in neurodegenerative diseases and has been observed in rat neuronal cell lines exposed to glyphosate in a dose-dependent manner [122]. Other mechanisms of neurotoxicity include the inhibition of acetylcholine esterase (AChE), an enzyme that metabolises the excitatory neurotransmitter acetylcholine. AChE inhibitors such as organophosphate pesticides are potent nerve agents. Symptoms of AChE inhibition include miosis (closing of the eyes), sweating, lacrimation, gastrointestinal symptoms, respiratory difficulties, dyspnea, bradycardia, cyanosis, vomiting, diarrhoea, personality changes, aggressive events, psychotic episodes, disturbances and deficits in memory and attention, as well as coma and death. Further, increased risk of neurodevelopmental, cognitive and behavioural problems such as Attention-Deficit Hyperactive disorder (ADHD), deficits in short-term memory, mental and emotional problems have been associated with exposure to glyphosate-based herbicides in children and the new-born [123]. Although glyphosate is an organophosphate, it is not an organophosphate ester but a phosphanoglycine, and therefore not been assumed to inhibit AChE. New studies suggest otherwise. Catfish and another fish species, *C. decemmaculatus*, showed AChE inhibition at environmentally relevant concentrations of Roundup® and glyphosate respectively [124, 125]. Furthermore, these effects were seen following acute exposure of up to 96 hours. A tentative association between glyphosate and ADHD in children has been made in an epidemiological study [126]. Further studies need to be done by independent scientists as original neurotoxicology data presented by Monsanto was ruled invalid by the EPA [127].

ogy in animals fed Roundup Ready soybeans, while *in vitro* studies have shown that glyphosate had cytotoxic effects on human embryonic kidney cell lines [57,58] (see [59] GM Feed Toxic, Meta-Analysis Confirms, *SiS* 52, [60] Death by multiple poisoning, glyphosate and Roundup, *SiS* 42). Abnormal kidney and liver transcriptome and histopathological profiles have also been found in rats fed low doses of 0.1ppb Roundup (50 ng/L glyphosate equivalent) for 2 years [61].

In Sri Lanka, chronic kidney disease of unknown aetiology (CKDu) has afflicted the agricultural population in recent years. A study published in 2014 first linked glyphosate-based herbicides to the epidemic. It appears that hard water in the agricultural regions leads to heavy metal toxicity in the kidneys via glyphosate's metal chelating activity, and is responsible for the 400 000 cases of the disease and 20 000 fatalities [62] (see Chapter 6). The government temporarily banned glyphosate from hard water areas, but this decision was reversed due to a lack of agricultural workers to take over the manual weeding required without the application of glyphosate. New research is validating the 2014 study, finding CDKu to be positively associated with spraying glyphosate (5.12 fold increased risk), drinking from wells (2.52 fold increased risk) and even worse, from abandoned wells (4.69 fold increased risk); being male (4.69 fold increase risk versus women). Men are more likely to be farmers and therefore exposed more than women. Testing the abandoned wells, they also discovered that all had very high water hardness with significantly higher levels of certain trace metals (Ca, Mg, Ba, Sr, Fe, Ti, V and Sr) as well as significantly higher levels of glyphosate than in-use wells [63]. The latest publication finds urine samples of CKDu patients to have significantly higher levels of heavy metals and glyphosate compared to control healthy groups from both endemic areas as well as low prevalence areas of Colombo city [64]. Following the election of the new President, a former farmer and health minister, Maithripala Sirisena, the country has now reinstated a full ban with immediate effect following the WHO declaration, making the country the first to enact an outright ban [65].

Similar health problems are widely affecting communities in Central America with one in four sugar cane workers reporting kidney disease in some areas [66, 67]. The El Salvador government had to call for international help after the epidemic began overwhelming the health systems. The El Salvadorian government has since approved legislation to ban glyphosate herbicides, though this is yet to be enforced.

Digestive illnesses widespread

Digestive illnesses plagued the pig farm in Denmark (mentioned earlier) while they were being fed GM soy. When GM produce and glyphosate were removed from their diet, the pigs no longer suffered chronic diarrhoea, which was so severe that 30 % of new born piglets were dying as a result (see Chapter 7). Chronic botulism, caused by the *Clostridium botulinum* bacteria, has also been on the rise in livestock in Germany, the US, and UK since the 1990s [68]. The latest study shows that glyphosate results in dysbiosis of the cow gut, with a reduction of beneficial bacteria in the rumen of cows accompanied by a rise in *C. botulinum* microbes [69].

The digestive illnesses in livestock mirrors a growing health problem in the West, particularly in the US where food intolerances, allergies, celiac disease, bowel diseases, infections and other problems continue to become more common. Nancy Swanson and colleagues showed a clear correlation between spikes in both inflammatory bowel

disease and intestinal infection with glyphosate in the US [70]. Deaths from intestinal infections have risen from less than 0.25 deaths per 100 000 in 1979 to over 80 deaths per 100 000 in 2010. Inflammatory bowel disease has risen from around 3 diagnosed cases per 100 000 in 1990 to almost 90 per 100 000 in 2010. Moms across America's testimonials reflect the evidence from the farm and science studies, with children who come off GM and glyphosate covered foods reducing the severity of allergy symptoms as well as other problems such as regular vomiting [71]. With glyphosate's antibiotic properties, it had already been previously shown to cause disruption of the gut bacteria in poultry, swine and cows [72-74]. *Salmonella* and *Clostridium* are highly resistant to glyphosate, whereas *Enterococcus*, *Bifidobacteria*, and *Lactobacillus* are especially susceptible. Perturbation in the balance of these microbial species is associated with digestive disorders such as celiac disease. Similarly, chronic botulism in cows is rectified in livestock by feeding fermented and pro-biotic foods along with charcoal and humic acids. These both bind to the toxins produced by the bacterial pathogen. This treatment also reduces the urinary content of glyphosate, suggesting its binding as an underlying mechanism in the recovery of the infection (see [74]). The latest work reveals that it undermines the effectiveness of antibiotics against pathogens including *Salmonella* and *E.coli* by increasing resistance in these pathogens [75]. Gut dysbiosis is thought to influence susceptibility to many diseases including colitis, Crohn's disease and celiac disease, irritable bowel syndrome as well as more systemic diseases such as obesity, autism, cancer and diabetes. It is becoming increasingly clear that the relationship between the gut microbiome and health is highly complex. Therefore, regular consumption of a known antimicrobial agent is a public health concern.

Another way in which glyphosate may exert toxicity via the gut microbiome is through inhibiting the shikimate pathway in bacteria. We depend on the gut bacteria as well as plants to supply us with the essential aromatic amino acids, tryptophan, tyrosine, and phenylalanine. Glyphosate is therefore expected to lead to deficiencies in aromatic amino acids as well as other bioactive molecules that require the shikimate pathway metabolites as precursors, including serotonin, dopamine, thyroid hormone, folate, coenzyme Q10, vitamin K and E (reviewed in [76]).

Autistic people are well known to have disturbed intestinal function and dysbiosis of the gut. Autism rates are also spiking in parallel with glyphosate use in the US [70] and glyphosate's interference with the gut microbiome through various mechanisms including serotonin depletion as well as induction of gut dysbiosis have been linked as contributing factors [76]. Anecdotal evidence from mothers have documented improved autism symptoms in their children after giving them a glyphosate- and GM-free diet. For details on the mechanisms linking glyphosate and manganese deficiency to disease please read Seneff and Samsel (2015) [76].

Box 3

Evidence of glyphosate effects on crop and plant health

Glyphosate use has been associated with the increased incidence and/or severity of many plant diseases and the overall deterioration of plant functions such as water and nutrient uptake (see Chapter 8 and 9, [128] Glyphosate Tolerant Crops Bring Death and Disease, *SiS* 47) [86, 99, 100].

As mentioned above, glyphosate's mechanism of action is the systemic chelation of metals, including manganese, magnesium, iron, nickel, zinc and calcium, many of which are important micronutrients. They act as co-factors for numerous plant enzymes including those involved in the plants' immune system [129]. While non-transgenic varieties are killed by glyphosate, glyphosate-tolerant crops do not die; but their physiology can be compromised. Manganese is a co-factor for 25 known enzymes involved in processes including photosynthesis, chlorophyll synthesis and nitrate assimilation, and enzymes of the shikimate pathway to which EPSPS belongs. The shikimate pathway is responsible for plant responses to stress and the synthesis of defence molecules against pathogens, such as amino acids, lignins, hormones, phytoalexins, flavenoids and phenols. The virulence mechanism of some pathogens, including *Gaeumannomyces* and *Magnaporthe* (which lead to 'take-all' and root rot respectively) involves the oxidisation of manganese at the site of infection, compromising the plant's defence against the pathogen. Glyphosate-tolerant crops were found to have reduced mineral content, confirming glyphosates' metal chelating activity [130-133]. Changes in physiology including reduced water uptake [130] and photosynthetic parameters (chlorophyll a degradation and chlorosis) were documented *in vivo* with glyphosate-tolerant soybeans even at recommended spraying concentrations [134].

Various plant diseases have reached epidemic proportions in the US, including Goss' wilt, sudden death syndrome and *Fusarium* fungal colonisation resulting in root rot and *Fusarium* wilt. Not only does glyphosate affect disease susceptibility, there is also evidence of increased disease severity. Examples include 'take all', *Corynespora* root rot in soybean, *Fusarium* spp diseases, including those caused by *Fusarium* species that are ordinarily non-pathogenic. Head-scab caused by *Fusarium* spp of cereals increases following glyphosate application, and is now prevalent also in cooler climates when previously it was limited to warmer climates. Nine plant pathogens have been suggested to increase in severity as a result of glyphosate treatment of crops, while some 40 diseases are known to be increased in weed control programmes with glyphosate and the list is growing, affecting a wide range of species: apples, bananas, barley, bean, canola, citrus, cotton, grape, melon, soybean, sugar beet, sugarcane, tomato and wheat [135].

USDA scientist Professor Emeritus Don Huber presented detailed evidence to the UK Parliament that glyphosate-tolerant crops are less healthy and yield less. They have a compromised immune system and require extra water, which are major problems as climate change is likely to increase infectious diseases and exacerbate water scarcity (Chapter 8). With regard to non-GM crops, pre-application of glyphosate has been shown to damage wheat varieties. This effect was exacerbated by additional factors including long-term non-tillage farming, which increases the glyphosate residues in the soil and high weed densities; and the application of phosphorus fertilizers that actually remobilise glyphosate in the soil. Weed density increases glyphosate toxicity through accumulation in the roots of weeds [136].

As with animal species, endocrine dysfunction has been suggested in plants exposed to glyphosate, potentially affecting plant health as well as crop yields. Inhibition of auxins involved in plant growth and development, and reduced methionine levels have been observed; methionine is a principle substrate for fruit, flower opening and shedding of leaves [137]. Various aquatic species including microalgae, protozoa and crustaceans are susceptible to glyphosate, but more so to the surfactant POEA [138] in Roundup formulations, in common with human cells.

Health of American citizens deteriorating

One argument for the safety of GM food and their associated pesticides is that the US has been consuming them for years without ill effect. However, in the absence of labelling GM foods, it is illegitimate to make such a claim. On the contrary, there has been a drastic deterioration of public health in the US since GM crops were introduced. A 2014 publication by Swanson and colleagues plots the rise of 20 chronic diseases using available US government data, all correlating closely with increasing glyphosate application to corn and soy crops, especially over the past several years. The diseases included cancers, Parkinson's (see Box 2), autism, obesity, diabetes, heart disease, digestive disease and kidney failure [77]. Correlation does not prove causation, but such strong association certainly cannot be dismissed, especially in combination with the plethora of other evidence from laboratory studies, and the experiences of doctors in their clinics and farmers in the fields. (For a detailed analysis of the study please see Chapter 2).

Though heart disease had not been studied as extensively as cancers and birth defects in relation to glyphosate, the above study implicates its role in cardiac dysfunction. This is corroborated by the new finding that glyphosate formulations cause abnormal heart rhythms (arrhythmia) by interfering with the electrical activity of heart cells in rabbits [78]. Further validation of the first study comes from new analyses of Centre for Disease Control (CDC) discharge data (1998-2010) [79], which show stark rises in rates of many diseases including lymph disorders; skin disorders; new-born blood, lung, genitourinary and heart disorders; congenital eye and heart disorders; as well as metabolic disorders. The incidence rates correlate tightly with the rise in glyphosate use in the US. Use of other common pesticides were also tracked (2,4-D and dicamba), which has been declining in recent years, suggesting that these pesticides maybe be at least partly responsible for disease rates in earlier years of the analysis, while glyphosate could be responsible for the rises in more recent years. Similar deteriorations in health is occurring in US wildlife (Montana State), where many conditions such as thyroid and congenital defects have been rising in the last 20 years.

A new study published in 2015 finds a correlation between glyphosate use and pineal gland pathology. The pineal gland is located in the brain and is known to regulate circadian rhythm through melatonin secretion. Glyphosate is hypothesised to disrupt melatonin metabolism, as well as pineal gland function through aluminium-induced hypoxia that results from the metal chelating properties of glyphosate. In this way, glyphosate use tightly correlates with the rises in sleep disorders as well as other disorders with symptoms of sleep dysfunction such as autism and dementia [80].

It is becoming clear that glyphosate has multiple toxicities that link it to many diseases through its metal chelating, antibiotic, endocrine disrupting, and genotoxic properties. Glyphosate also has the ability to block cytochrome P450 (CYP) enzyme activity, a class of enzymes involved in detoxifying xenobiotics amongst other things. Glyphosate therefore not only is a toxin in its own right, but enhances the toxicity of other chemicals by preventing the CYP enzymes from detoxifying the body [81].

Americans are definitely getting sicker in numerous ways highly correlated with adopting GM crops and rise in glyphosate use (Chapter 2) and, as shown by all the testimonials from Moms across America, peoples' health improves after removing GMOs and glyphosate residues from their foods by buying organic [71].

Environmental toxicity a concern for biodiversity, agriculture and sustainability

The spread of glyphosate-resistant weeds is increasingly compromising the effectiveness of the herbicide. There are now a reported 32 species of resistant weeds, up from 23 a year ago as recorded by the Weed Science organisation in the US [82]. In Brazil, an aggressive spread of weeds prompted a former DuPont agronomist to acknowledge the difficulties faced by farmers cultivating glyphosate-tolerant GM crops both in Brazil and Argentina [83]. Monsanto now recommends an 'integrated weed management' strategy that includes tilling the soil (of previously no-till land) and using multiple herbicides. The main selling points of Monsanto's Roundup Ready (RR) GM crop system was to reduce environmental damage through no-tillage agriculture and glyphosate use – a supposedly 'safe' herbicide compared to older chemicals. Not only is glyphosate toxic to health and the environment, but a cocktail of even more lethal herbicides have to be deployed to deal with glyphosate-resistant weeds, and an end to no till agriculture, resulting in further soil erosion. In short, we have an ecological and agronomic disaster.

Glyphosate toxicity to wildlife is well-documented. Many species, including aquatic organisms, reptiles, beneficial soil organisms including certain microbes and worms have been shown in scientific studies to be affected by glyphosate exposure (see [84] Ban GMOS Now, ISIS special report). This includes chronic and acute toxicity to the model aquatic organism *Daphnia magna* at below accepted thresholds for glyphosate presence in US freshwater [85]. A 2015 study also finds that glyphosate at concentrations below the permitted level for soybeans in the US causes increased mortality, reduced reproduction and delayed development in *Daphnia magna* [86]. Amphibians, the most endangered animals in the world, are so sensitive to glyphosate that 78 % of frogs died in one study on being exposed to Roundup herbicide [87]. Glyphosate has been shown to stimulate the growth of soil fungi, and to increase the pathogenicity of soil pathogens such as *Xylella fastidosa* while numerous beneficial soil organisms are decimated [88] (see [89] Scientists Reveal Glyphosate Poisons Crops and Soil, *SiS* 47). The latest study on soil organisms concluded that non-target organisms are at risk of local extinction after finding sub-lethal doses of glyphosate reduced fertility as well as survival of juvenile and adult *E. fetida* worms [90]. Monarch butterfly decline has been linked to glyphosate destruction of the milkweed in the US, the only food source for its larvae. Their migration from the US is at an all-time low and has been declining for the last 17 years (1994-5 to 2010-2011) (see [91] Glyphosate and Monarch Butterfly Decline, *SiS* 52) [92]. This decline has prompted a move to protect the butterflies under the Endangered Species Act by over 200 organisations and 40 scientists in November 2014 [93]. Even 52 members of US congress have written to the President over the issue, also recommending putting them on the endangered species list in order to give legal muscle to attempts to protect them from "widespread overuse of glyphosate" [94]. A new report on a Welsh nature reserve documents the decline in insects including beneficial pollinators such as bees as glyphosate levels increase (see Chapter 10). This is consistent with a 2015 study showing that sub-lethal doses of glyphosate impair honeybee navigation. These findings suggests that exposure to levels commonly found in agricultural settings impairs the cognitive capacities needed to retrieve and integrate spatial information for a successful return to the hive [95].

Not only are non-target organisms negatively affected, but also the target crops. Glyphosate's metal chelating properties reduce the micronutrients available to the plant, which it needs to maintain a fully-functioning immune system, thereby increasing its susceptibility to disease. This mechanism is thought to underlie the spread of over 40 crop diseases in glyphosate-tolerant GM

crops (see Chapter 8 and Box 3). Indeed, USDA senior scientist Don Huber states that glyphosate's ability to kill plants is through the destruction of their immune system. This was clearly demonstrated by his experiments showing that non-GM plants grown in a sterile soil do not die when sprayed with glyphosate as the pathogens are not there to take advantage of the compromised immune system (see Chapter 9).

A reduction in mineral nutrients has health impacts on those eating the crops such as abnormalities in calves that are caused by manganese deficiency, which are on the rise and may well result from glyphosate chelation [96]. Farm animals are further suffering from other illnesses (and birth defects) as described by the Danish pig farmer earlier. Similar problems have been reported in Germany, where cows are suffering from chronic infections such as botulism [67] and in the US, with for example, the veterinarian Art Dunham reports botulism in dairy cows, as well as reproductive problems, bloody bowels, rickets and viral diseases in hogs [97].

As a result of the problems faced by farmers, many are now moving away from GM and glyphosate-based systems. The US is seeing a growth in the non-GM seed market (see [98] Global Status of GMO and non-GMO crops, *SiS* 62). Agriculture experts such Howard Vlieger are helping 300-400 farmers in the US switch from GM to non-GM crops without glyphosate use due to its ill effects to soil, plants and animals [99]. Glyphosate-tolerant crops have also been shown to need more water and do worse in drought situations (see [100] GM Crops and Water – A recipe for Disaster *SiS* 56, and [101] GM Crops Destroyed by US Drought but non-GM Varieties Flourish, *SiS* 56). This is consistent with their health being compromised by glyphosate.

While GM crops are causing problems for farmers, non-GM crops are leading the way in providing drought- and salt-tolerant varieties, which makes sense when one considers that the majority of traits are highly complex, involving multiple genes and pathways and therefore too complicated to mimic with crude genetic engineering techniques (see [102] Genetic Modification Trails Conventional Breeding By Far, *SiS* 64).

Regulatory science corrupt, ban glyphosate locally

Glyphosate re-assessment by the EU commission was performed in 2014, not only re-approving glyphosate, but approving increased residue levels for food and feed, with the final decision expected in 2015. The reassessment was performed by industry, though Germany acted as the rapporteur state, submitting the renewal assessment report to the European Food Safety Authority (EFSA) (see Chapter 11). This report relied on summary assessments provided by the Glyphosate Task Force, which consists of Monsanto and other chemical companies such as Syngenta UK and Dow Italy. Assessments were made on glyphosate excluding commercial formulations most frequently used such as Roundup, and focused on studies showing less toxic results. The EU has recently also set up a consortium with the purported aims of providing "comprehensive reviews of the health, environmental and socio-economic impacts of GM plants – considering both risks and possible benefits" called the GRACE (GMO Risk Assessment and Communication of Evidence). They also claim that the work will lead to improve risk assessment standards, testing various trial methods. The project is rife with conflicts of interest; many members of the consortium work with institutions funded by industry and further, one of the member institutions is a lobby group advocating lower regulatory standards for GM plants, as revealed by a Testbiotech report [103]. It comes as no surprise that the results of a 90-day feeding trail with MON810 maize conducted by GRACE reported no ill effects [104].

It has been well-documented and previously explained in Ban GMOS Now [82], that adjuvants present in glyphosate formulation products such as POEA, as well as glyphosate metabolites like AMPA have their own toxicity and moreover, that glyphosate and the adjuvants together are far more toxic than glyphosate alone. A new 2014 study by Professor Séralini's group further confirms this, showing for the first time that glyphosate formulation products (as well as insecticide and fungicides) are far more toxic than glyphosate alone at concentrations well below agricultural dilutions [105]. Using human cell lines (HEK293, JEG3 and HepG2), they showed formulations to cause significant reductions in cell viability at concentrations 125 times less than glyphosate alone, challenging the relevance of the current acceptable daily intake (ADI). Séralini's group, in their latest review, have compiled the evidence of glyphosate formulations and their toxicity at levels below regulatory EU limits, clearly highlighting this concern, as well as other regulatory limitations such as the complete absence of testing at ADI levels [106]. Adding to this are new data showing that Roundup at 10 mg/kg bw/d (body weight per day) is sufficient to cause endocrine disruption in male rats. Though endocrine disruption is well documented with glyphosate, this is the first to explore adrenal gland steroidogenesis effects, with levels of circulating corticosterone being affected [107]. Again, these concentrations are well below the ADI set for glyphosate. With the work finding effects even at the lowest tested levels, it confirms that we do not yet know what the "safe" levels of exposure are, officially termed the NOAEL (no observed adverse effect level), from which ADIs are derived in regulatory risk assessments. Furthermore, no other effects were seen at the lowest dose, showing that such modes of toxicity are being missed in current risk assessments which do not include analysis of endocrine effects. It is also important to note that so far, no studies have yet been carried out on the effects of pesticide cocktail mixtures, a far more likely scenario in real life. It is no wonder that the EU commission is refusing to let independent experts gain access to the renewal assessment report by the German Federal Institute for Risk Assessment (BfR) [108].

To conclude

The evidence of glyphosate toxicity to both human and animal health and the ecosystem has built up to such an extent that some governments are taking action. As mentioned earlier, both El Salvador and Sri Lanka have led the way. Colombia, following the WHO report, has also decided to suspend its aerial spraying of cocoa fields in the US-led war on drugs. The Netherlands successfully banned its sale to private individuals [109]. Russia has banned the import and cultivation of all GM crops due to health and environmental concerns [110], while a section of the Chinese army has reportedly banned its consumption [111]. In Brazil a public prosecutor is also looking to suspend its use [112].

For those of us who are not being protected by our governments, it is time to start initiating our own campaigns, banning it first from our home, our community, our schools, local counties, regions.

2

Marked Deterioration of Public Health Parallels Increase in GM Crops & Glyphosate Use, US Government Data Show

The steep rise in incidence of 22 chronic diseases in the US correlates strongly with the increase in GM crops and the application of glyphosate-based herbicides

Prof Peter Saunders

Ample evidence of glyphosate toxicity already exists

Despite what the manufacturers say, there is ample evidence to show that glyphosate, the active ingredient of Monsanto's Roundup, Syngenta's Touchdown, Dow's Durango and many other herbicides, is highly toxic and a serious hazard to human and animal health. There is documentation of miscarriages, birth defects, carcinogenesis, endocrine disruption, DNA damage, neurotoxicity, and toxicity to liver and kidney at levels well below recommended agricultural use (See Chapters 1 and 5). Several countries, among them Denmark, The Netherlands, France, El Salvador and Sri Lanka have recognised the dangers imposed total or partial bans on the use of glyphosate (see Chapter 6).

Other countries, especially those with large chemical and biotech industries and/or a major commitment to industrial farming, take a totally different view. The US Environmental Protection Agency (EPA) recently increased the permitted tolerance levels for glyphosate residues in food. The European Food Safe Agency (EFSA) has recommended the re-approval of glyphosate for use in Europe with an increase in acceptable daily intake (ADI) from 0.3 to 0.5 mg per kg body weight. It is not surprising that EFSA reached this decision; the review was in fact carried out by a 'Glyphosate Task Force' (GTF) made up of a consortium of chemical companies including Monsanto, and based its conclusions largely on reports submitted by the manufacturers (see Chapter 11).

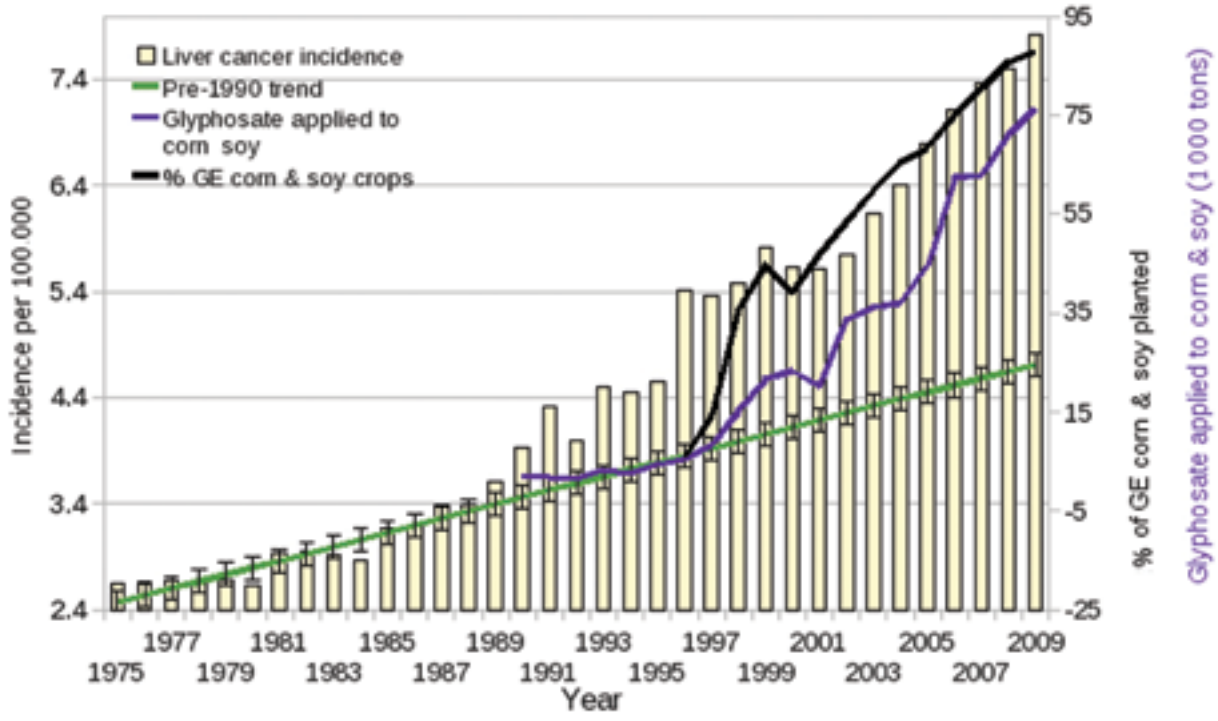
The industry does its best to keep evidence of glyphosate toxicity out of the public's view and the public record. The recent improper unilateral retraction of a published paper by Séralini and his group (see [1], [2] Support Séralini Team for New GMO and Pesticide Risk Research, [3] Retracting Séralini Study Violates Science and Ethics, *SiS* 61) is a case in point. It followed the appointment by the journal of a former Monsanto employee to a newly created editorial post. Unusually, it was done in the open. We know of other cases that were not made so public, and possibly many more that we have not even heard about.

That's not all. Confidential papers obtained from the US EPA by Moms Across America under the Freedom of Information Act contain studies carried out by industry showing that glyphosate is lethal to shrimps, fish, oysters and canaries after 96 hours, and at concentrations of <1 to hundreds of parts per million (ppm), to which humans are routinely exposed [4].

Millions of Americans are said to have been eating GM food with no ill effects

The argument that the industry relies on most heavily is that for fifteen or more years, millions of Americans have been eating GM food, or food that have been sprayed with glyphosate, or both, and they have not been harmed; and this surely proves

Figure 1 Incidence of liver cancer, % GE corn & soy, and glyphosate applied from 1975 to 2009



beyond doubt that neither GMOs nor glyphosate are hazardous to health [5]. This is obviously a totally unscientific statement; because there has been no GM labelling in the US, it is impossible to tell how much GM food anyone has eaten. Nevertheless, physicist and former scientific adviser to the US Navy Nancy Swanson realised that it is possible to examine the health status of the nation before and after the introduction of GM food and the sharp increase in glyphosate herbicides that went with it. What she and her colleagues found was devastating.

Over the past fifteen or twenty years there has been a large increase in the number of Americans suffering from a whole range of chronic diseases. This is the same period over which there has been a very large increase both in GM crops and in the use of glyphosate-based herbicides [6]. The team have made use of the best available government data from the Centres for Disease Control (CDC) for the incidence of diseases, and the Department of Agriculture (USDA) for GM crops grown and glyphosate herbicide used.

Because there are records for each year, it is possible to compare how both GMOs and glyphosate on the one hand and the various diseases on the other have changed over time. And the results are striking. Graph after graph showed the same parallel increases over time. On example is given in Figure 1 for liver and intrahepatic bile duct cancer.

Note that the increase in liver cancer incidence rises sharply above the long term trend that goes back to the 1970s. In other words, while liver cancer had been increasing for some time, the rate of increase accelerated at about the same time that GM crops appeared and glyphosate use rose more sharply. The incidence is now about double what it would be if it had continued to rise at the pre-1990 rate.

Table 1 shows the correlation coefficients between each of the conditions and the amount of glyphosate used, and % of GM maize and soya. None of the 44 correlation coefficients falls below 0.8 - the conventional minimum level for a correlation to be called 'strong' - and all but seven are greater than 0.9.

There is clearly a strong correlation between the conditions on the one hand and GMOs and glyphosate use on the other. This does not by itself prove there is a causal relationship, but it is certainly evidence in favour of one. When we add to it the evidence that glyphosate has led to birth defects in humans, that it has been found to harm laboratory rats, cattle on farms, and other animals as well, that it interferes with an important metabolic pathway in animals, that it adversely affects beneficial gut bacteria, that it acts as an endocrine disruptor, and more besides, the case against glyphosate becomes very strong indeed (see Chapter 1).

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Table 1 Pearson correlation coefficients between the incidence in the US of 22 chronic diseases since 1995 and (a) the amount of glyphosate applied to maize and soy (b) the percentage of maize and soy planted that was GM (from [6])

Condition	Glyphosate use	%GM
Hypertension	0.923	0.961
Stroke	0.925	0.983
Diabetes prevalence	0.971	0.983
Diabetes incidence	0.935	0.955
Obesity	0.962	0.962
Lipoprotein metabolism disorder	0.973	0.955
Alzheimer's	0.917	0.937
Senile dementia	0.994	0.918
Parkinson's	0.875	0.952
Multiple sclerosis	0.828	0.876
Autism	0.989	0.933
Inflammatory bowel disease	0.938	0.812
Intestinal infections	0.974	0.901
End stage renal disease	0.975	0.958
Acute kidney failure	0.978	0.967
Thyroid cancer	0.988	0.938
Liver cancer	0.960	0.911
Bladder cancer	0.981	0.945
Pancreatic cancer	0.918	0.841
Kidney cancer	0.973	0.940
Myeloid leukaemia	0.878	0.889

To conclude

There have been all too many examples in the past of substances where there was compelling evidence that they were dangerous to health or the environment or both and yet they continued to be produced and used because of pressure from the manufacturers and weak regulators and governments. These include tobacco, asbestos, lead, polychlorinated biphenyls (PCBs), benzene, and many more [7, 8]. If governments continue to rely on advice from the industry and ignore the growing body of evidence, glyphosate will be yet another example of serious harm that could have been avoided.

3

Devastating Impacts of Glyphosate & GMOs in Argentina

Widespread GM soybean cultivation and accompanying pesticide spraying is wreaking havoc on the health of millions

Dr Medardo Ávila-Vázquez

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Toxic Agriculture and crop-sprayed towns

Over the last 20 years, industrial agriculture in Argentina has expanded by almost 50 %, taking over regions intended for other productions, for family farming, and most of all, forests.

A ton of soy was priced at US$160 in 2001; in July 2012, it reached US$600. At an average yield of 3 to 4 tons (T) per hectare (ha) and production costs 200-250 US$/ha, the profit is enormous.

Of the 300 000 farmers nationwide, 80 000 are engaged in transgenic and chemical agriculture; of those, 20 000 account for 70 % of the production, and are basically corporations and agricultural conglomerates renting fields or trespassing on lands belonging to peasants and native peoples [1].

The prevailing monoculture agribusiness model comes in a technology package that includes direct sowing, transgenic seeds, and the application of pesticides. In order to sustain production, increasing amounts of agrochemicals are applied in an area where transgenic crops coexist with more than 12 million people.

We must recognize that the agrochemicals used are all poisonous: herbicides like glyphosate, 2,4-D ((2,4-Dichlorophenoxy) acetic acid) or Atrazine, are designed to kill plants, and endosulfan, chlorpyrifos, dimethoate, cypermethrin, imidacloprid, etc. are designed to kill insects and are the most widely used; they all have deleterious effects on human health and the environment. The use of these pesticides has been increasing exponentially since 1990: back then, 30 million litres* of poisons were used; during the 2012/2013 crop season more than 318 million litres were applied. On the same hectare where 2 or 3 litres of glyphosate were used per year, today 8 or 12 litres are used with 1.5 litres of 2,4-D in addition. In Santiago del Estero, Salta, and Chaco (north-western Argentina) up to 20 litres/ha/year of Round Up are used [2].

To grow 100 ha of GM soy today requires 14 working days for a single worker: one day for sowing, another for harvesting at the end, and the remaining 12 days in between for applying poisons over the same field.

Birth defects and increasing cancer

After 18 years of systematic sprayings, health teams in fumigated towns detect a change in the pattern of diseases in their populations: respiratory problems are much more common and are linked to the application of agricultural poisons, as is chronic dermatitis. Similarly, during fumigation, epileptic patients convulse much more frequently, and depression, immune and endocrine disorders are more frequent.

High rates of miscarriages are recorded (up to 23 % of women of reproductive age had at least one abortion in the past 5 years) and consultations for infertility in men and women have significantly increased. Herds of goats belonging to farmers and indigenous people in some areas record up to 100 % of abortions or premature deaths due to malformations linked to pesticide exposure. Increased thyroid disorders and diabetes are also detected in local people.

More and more children are born with defects in these areas, especially if the first months of pregnancy coincide with the time of spraying. Down's syndrome, spina bifida, myelomeningocele (neural tube defect), congenital heart disease, etc. are diagnosed more frequently in those areas; in some towns and during some years, at triple the normal rates, and directly linked to increased pesticide applications around the towns [3, 4] (see Figure 1). Neural tube defects are among the most common developmental birth defects observed, which is consistent with lab studies and farm observations (see Chapter 1).

Crop-sprayed towns also show a change in the causes of death. According to data from the civil records offices to which we had access, over 30 % of deaths are from cancer, while nationwide, the percentage is less than 20 %. Cancer death rates have clearly increased in those areas, and this is a new phenomenon detected by our colleagues since 2000 [3, 4, 5]. Significantly, the date coincides with the expansion in the use of glyphosate and other agrochemicals massively applied in those areas. In May 2014, the Ministry of Health of the Province of Córdoba published data from its cancer registry, confirming that in the most intensive agricultural areas, deaths due to cancer exceed by 100 % those in the city, and by 70 % the provincial average [6]. Our latest study on the small town of Monte Maíz, in the region of Córdoba exemplifies the exaggerated levels of illness afflicting the region, with rates of cancers, rheumatism, birth defects and other chronic diseases all significantly higher than national and international levels (see Table 2) [7]. Cancer rates in the town are three times the provincial and national average. The study was performed in collaboration with other groups from the National University of Córdoba and the National University of La Plata at the request of the local mayor due to his concern for the town's citizens. The Mayor subsequently implemented corrective and preventive measures, including banishing 22 agrochemical storage deposits containing nearly 600 000 litres of glyphosate that was being used in the area, prohibiting equipment used for pesticide applications into the town and prohibiting spraying around the inhabited area to protect the community. This study and the action taken by the Mayor drew a backlash from the University of Córdoba administration, which threatened sanctions against the work and my position at the University, likely on account of their ties with agribusiness [8]. The dean of the university reportedly signed a deal with Monsanto last year. The threats were later dropped due to tremendous support for our work from social, labour, student and political organisations as well as scientists.

We must recognize that the agrochemicals used are all poisonous: herbicides like glyphosate, 2,4-D (2,4-Dichlorophenoxy) acetic acid) or Atrazine, are designed to kill plants, and endosulfan, chlorpyrifos, dimethoate, cypermethrin, imidacloprid, etc. are designed to kill insects and are the most widely used; they all have deleterious effects on human health and the environment

The toxic agrochemicals affect everyone, but it is the poor people, the labourers, their wives and children, who are the least likely to be protected and to recover their health. Also, in the North of Córdoba and Santa Fe, most of the new ventures into toxic agriculture are owned by corporations and agricultural conglomerates that use air fumigation, delivering much higher doses of poison due to the climatic and biological conditions in the region; and mainly indigenous peoples and peasants suffer the consequences.

Scientific evidence

The clinical manifestations that physicians working in the crop-sprayed towns find in patients are consistent with the results of scientific research on the effects of various pesticides including glyphosate on experimental animals. Laboratory research by our scientists show how glyphosate acts on embryonic development to produce birth defects [9], and how this poison damages DNA molecules in the cell nucleus, promoting mutant cell lines that will cause cancer if they cannot be eliminated by the individual [10-12].

Also, a number of scientific papers worldwide show how exposure to toxic agrochemicals significantly increases the rate of birth defects, miscarriages, cancer, and hormonal disorders in people subjected to repeated sprayings [13-16].

The Systematic Reviews of Evidence-Based Medicine – representing the highest standard of critical analysis of scientific and medical information - supports the need to reduce exposure on the strength and consistency of the available evidence indicating that exposure to pesticides increases the risks to human health [17-19].

Despite all the complaints presented to the authorities, the use of toxic agrochemicals in our country is still continuously increasing. In 1990, according to data from the business chambers of toxic agrochemicals, 39 million litres of agrochemicals (herbicides, insecticides and fungicides) were used; in 2013, the same chamber reports that its business nearly reached u$s3000 million

The toxic agrochemicals affect everyone, but it is the poor people, the labourers, their wives and children, who are the least likely to be protected and to recover their health

with the sale of 318 million litres. Glyphosate is the most commonly used toxic agrochemical in Argentina, comprising 64 % of total sales, and 200 million litres of glyphosate were applied during the last crop season [2].

In usage studies conducted by agronomists from the Sociedad Rural Argentina (Rural Society, the main soy-business institution in the country) [20], in 2010 in the core area (main agricultural area), almost 10 litres of pesticides were applied per hectare per year, which in the study area is equivalent to 31 litres of agricultural poisons for each of the residents of the Department concerned (Gral. Lopez in Santa Fé). In Argentina, we estimate that 7 litres of pesticides are applied for each of the 40 million inhabitants per year, but in the productive areas of agribusiness, the toxic dose rises to between 30 to 45 litres per person per year, generating a cumulative load of chemical toxicity inevitably reflected in the hardest health indicators such as death rates.

Rethinking scientific postulations for bio-technology and safety

The model of agricultural production foisted on Argentina by international bio-technology companies has led to 858 % increase in the amount of pesticides used per year, resulting in a massive environmental and health impact in the region.

This 858 % increase in the use of toxic agrochemicals far exceeds the increase in cultivated areas. Between 1990 and 2010, the area growing cereals and oilseeds

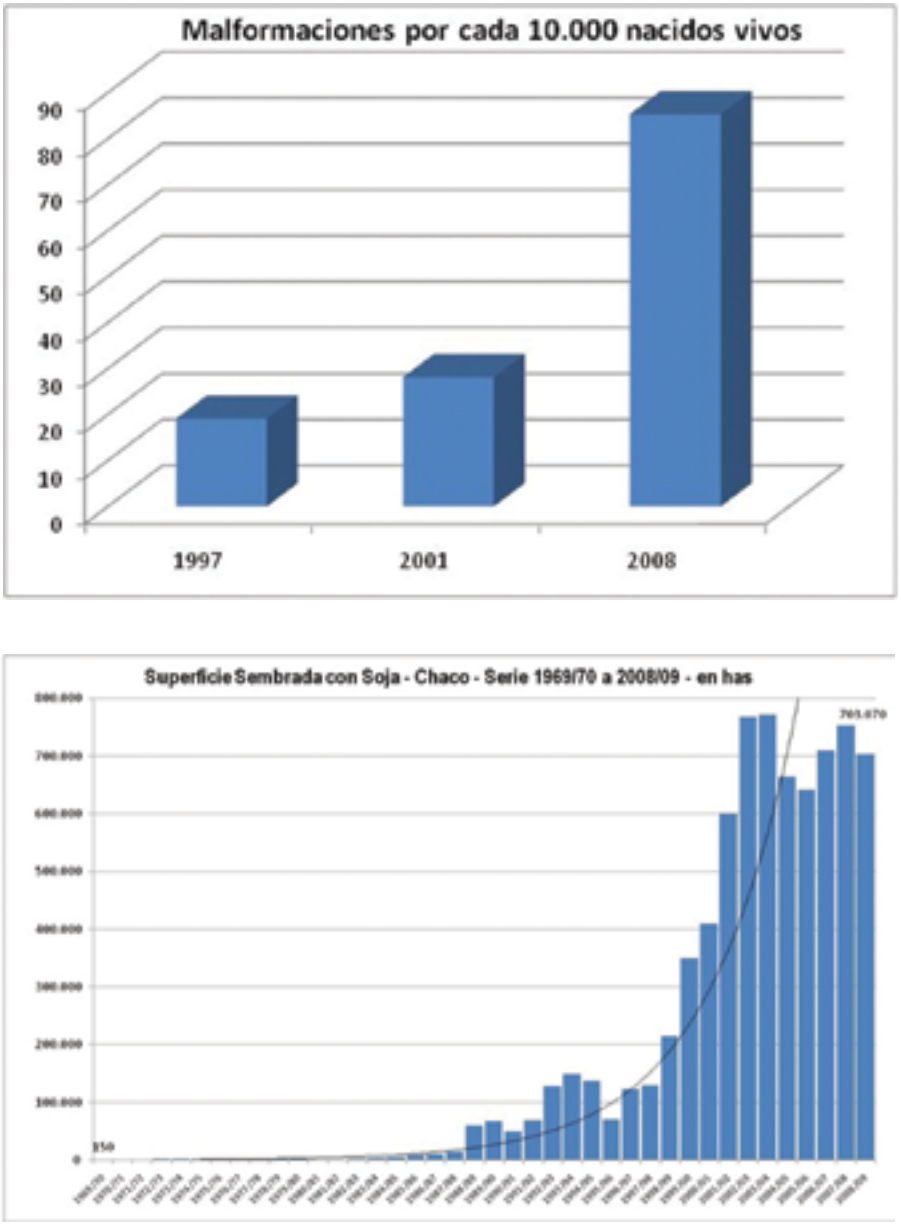


Figure 1 The rise in birth defects correlates with the rise in cultivation of GM glyphosate-tolerant soybeans in Chaco, Argentina. Birth defects per 10 000 live births from 1997-2008 have risen drastically (top), as has the hectares of land dedicated to GM soybean cultivation (bottom)

increased by 50 % from 20 million hectares to 30 million hectares, while the use on fruit and vegetable crops and regional crops such as vine, tobacco and sugar account for less than 15 % of total applied [2].

The premise that transgenic seeds use fewer toxic agrochemicals cannot be verified in Argentina. In 1996/7, the time when transgenic soybean began to be sown, 3 litres per ha per year of glyphosate were applied; currently the applied amount of glyphosate adds up to 12 litres per ha per year. This shows the failure of the toxic agricultural model to overcome the adaptation responses of nature, such as the emergence of resistance in plants and insects. The only recourse is to increase the poison applied, thereby selling more pesticides to farmers, and adding even more dangerous and toxic agrochemicals to the fumigating mixtures, or adding transgenic "events" so that plants secrete several Bt insecticidal toxins.

Another myth perpetrated by the biotech industry is that it increases crop yields. However, the number of independent scientific studies proving this a lie is accumulating. An increase in grain production (cereal and oilseed) is admitted, but these researches show that the increase in yields per hectare (ha) is related to the application of traditional agricultural techniques incorporated during the last 20 years, such as the increase in density of plants (less separation between plants in the furrow and between furrows), etc. [21, 22]. In Argentina the average yield in 1994 was 2.2 T per ha, and 3 T in 2010, an average increase of 30 % in crop yields [2], yet during this period we used 858 % more agricultural poisons.

Thus, the 858 % increase in the toxic agrochemicals is far in excess of the 50 % increase in cultivated areas, and the 30 % increase in crop yields per hectare.

The inefficiency of the biotechnology model is evident also in the environmental damage created by the massive clearing of the country; the increasing pollution that is observed along all surface watercourses in the region, such as the Suquia [23] and Paraná rivers in its entirety; in the levels of glyphosate collected in rainwater from soy-growing areas [24] exceeds by 10 times those detected in USA [25]; in the increasing rate of cancer, birth defects, miscarriages, mental disabilities, endocrine and immune disorders suffered by rural populations systematically exposed to increasing doses of toxic agrochemicals every year (see earlier); and in the growing load of pesticide residues in grains exported from Argentina, as has already been verified in Denmark and the Netherlands, where, as of 2015 the purchase of organic soybeans and corn to feed their livestock will be prioritized [26, 27].

Increasing pesticide residues in foods made with grains are a growing concern in Europe, and its danger has become evident especially after investigations by the French researcher Gilles-Eric Séralini [28]. Recently, glyphosate was detected in urine of students from the University of Berlin and other Europeans from 18 different countries, and was less high in those on organic diets;

Young Soy Plants in Argentina, photo Pedro Reyna, Flickr

Table 1 Summary of disease frequency in Monte Maíz, region of Córdoba, Argentina

Illness	Frequency of illness in Monte Maíz	Frequency of illness in reference control region
Lung disease (13-14 year olds)	39. 86 %	22 % (City of Córdoba)
Lung disease (7-8 year olds)	52.43 %	14 % (world)
Hyperthyroidism in ≥ 20 year olds	10. 9%	6 % (USA)
Rheumatoid arthritis	1 per 516 people	1 per 1123 people (USA)
Lupus	1 per 516 people	1 per 1123 people (USA)
Spontaneous abortions	9.98 %	3 % (Argentina)
Congenital malformations	2.93 %	1.9 %
Cancer incidence	707.64 per 100 000 people	259.4 per 100 000 people (City of Córdoba)
New cases of cancer per year	35	11 to 13.5 expected for Monte Maíz
Cancer prevalence in last 5 years	2122.89 per 100 000 people	883.82 per 100 000 (Argentina)
Cancer mortality	383.14 per 100 000 people (year 2014)	136.97 per 100 000 (City of Córdoba, year 2009)
% mortality due to cancer	33.9 – 38.7 %	18-20 % (City of Córdoba)

More and more children are born with defects in these areas, especially if the first months of pregnancy coincide with the time of spraying. Down's syndrome, spina bifida, myelomeningocele (neural tube defect), congenital heart disease, etc. are diagnosed more frequently in those areas; in some towns and during some years, at triple the normal rates, and directly linked to increased pesticide applications around the towns

in cattle and rabbits similar results were obtained: higher levels of glyphosate in urine and tissues from those fed GM fodder [29]. The export market to Europe is poised to shrink as consumers reject GMOs and glyphosate tainted food.

To overcome the problems caused by the resistance of weeds and insects, the biotech industry (Monsanto, Bayer, Dow, Dupont, etc.) is providing more of the same. New transgenic seeds are promoted, which are tolerant to glyphosate, glufosinate and 2,4-D [30]. Do we want yet higher levels of more and more dangerous herbicides in our food, when the existing burden on health is already intolerable?

Seeds are also promoted, which, in addition to tolerating several herbicides also produce several Bt toxins, such as Cry1A.105, Cry2Ab, Cry3Bb [31], offering, for now, protection against Lepidoptera and Coleoptera but damage many insects that are beneficial and useful for preserving ecological balance. The safety of these toxins to humans is open to question.

For 100 000 years our species was in contact with minimum amounts of these toxins, but now, thanks to biotechnology, we are exposed to massive amounts of these proteins. They have been found in human breast milk, in human blood and in the blood of the human umbilical cord, and we also know that they produce immune and allergic risks to people [32]. They may well turn out to be much more toxic when we start seeing the consequences of this new exposure within a few years.

Today we know that 40 % of the genes of the human genome are shared with plants and regulate our cellular activities as in the plants, we also know that 60 % of the genes of insects such as the fruit fly are in our genetic code [33]. In other words, we share with insects and plants many mechanisms of cellular metabolism. When we attack these mechanisms with a heavy arson of chemicals, to block or distort them, to kill plants or insects, we cannot ignore the fact that these toxic products can reach people, either through occupational exposure, residential exposure or by ingesting food or water contaminated with residues, and may well have adverse effects on them; we cannot presuppose that they are harmless.

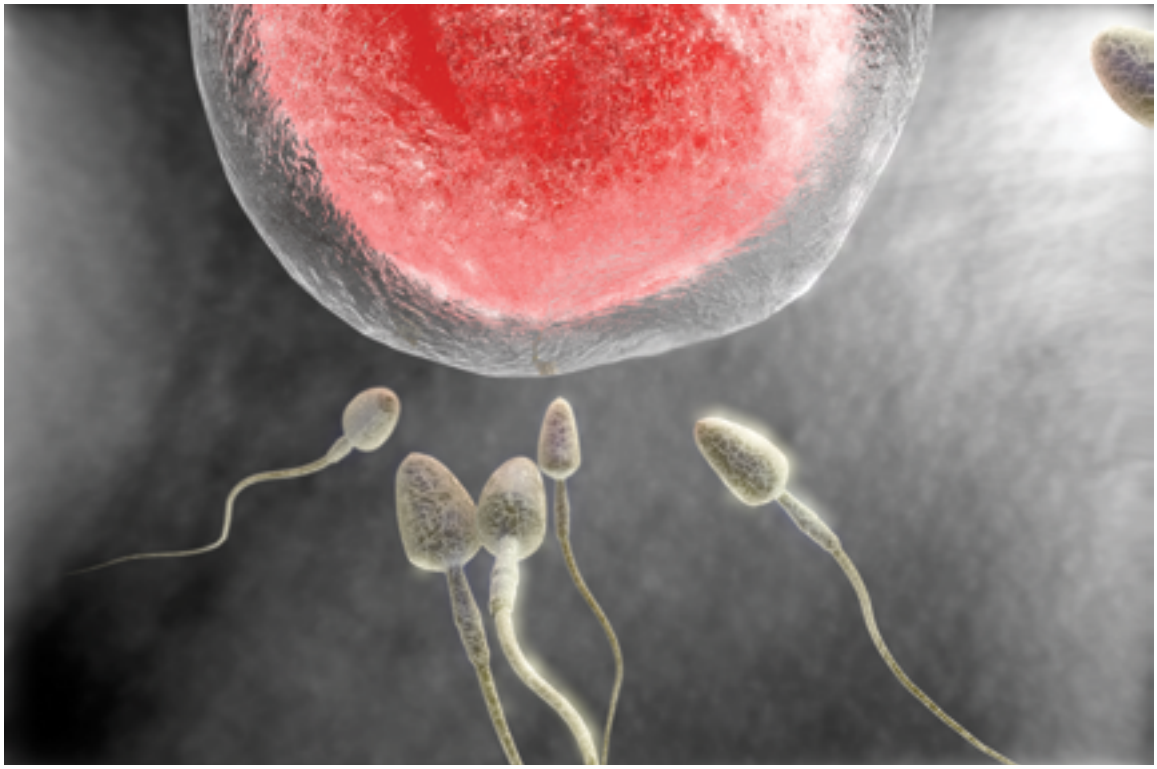
*Note added by the editor: The amount of glyphosate used is commonly measured as kg/L in Argentina, as quoted by The Chamber of Agricultural Health and Fertilizers (CASAFE). We understand that this might mean either kilograms or litres, and refer to all formulations of herbicides and insecticides. The specific gravity of Roundup® Original Max is 1.36, so in the case of Roundup, 1 litre = 1.36 kg.

4

Glyphosate/Roundup and Human Male Infertility

Steep decline in human male sperm count concomitant with rise in testicular germ cell cancer, congenital malformations of the male reproductive tract and drop in serum testosterone levels, all pointing towards increasing exposure to glyphosate/Roundup herbicides during the past decades, now corroborated by lab findings

Dr Mae-Wan Ho



"The infertility time bomb: are men facing extinction?"

The headline of a newspaper article published in 2010 [1] refers to findings from decades of research carried out by Niels Shakkebaek, a professor at University of Copenhagen. Male infertility has been rising sharply in industrialized countries worldwide, one in five healthy men between the ages of 18 and 25 produce abnormal sperm counts. The problems start in the womb, says Dr Gillian Lockwood, medical director of Midland Fertility Services in the UK. Testis development begins in the growing foetus. Factors blamed include too much beef in the diet rich in polycyclic aromatics, obesity during pregnancy, exposure to smoke, pesticides, traffic fumes, plastics and even soybeans.

Shakkebaek first highlighted the issue during a mini symposium at the European Medical Research Councils plenary meeting in Strasbourg in 2009. Semen quality has been declining in the past half century. In men without fertility problems, average sperm count dropped from 113 x 10^6 to 66 x 10^6/ml. About 20 % of young men in various European countries have sperm counts below the WHO (World Health Organization) reference level of 20 m/ml, and 40 % of have levels below 40 m/ml associated with prolonging the time to pregnancy [2]. Concomitantly, the demand for assisted reproductive technology (ART) is growing. In Denmark, more than 7 % of all children born in 2007 were conceived using ART.

There are geographical differences in semen quality. Finnish men have 35 % higher sperm counts than Danish men, while Scottish and French sperm counts are in between. Japanese sperm counts are as low as those of the Danes, and Singapore men have even lower sperm counts.

The trend in semen quality has implications for health in general, as men with poor semen quality seem to have increased mortality rates and shorter life expectancy. Infertility is also closely linked to several dysfunctions and abnormalities of male reproductive organs that have been rising concomitantly with infertility.

Infertility trend associated with testicular germ cell cancer, congenital malformations & low testosterone

Testicular germ cell cancer (TGC) is the commonest cancer in young men in many countries, associated with impaired semen quality and lower fertility rates even prior to cancer development. The incidence of TGC has been increasing over the past 40 to 50 years in the majority of industrialized countries coincidentally with the declining trend in semen quality. TGC is initiated during

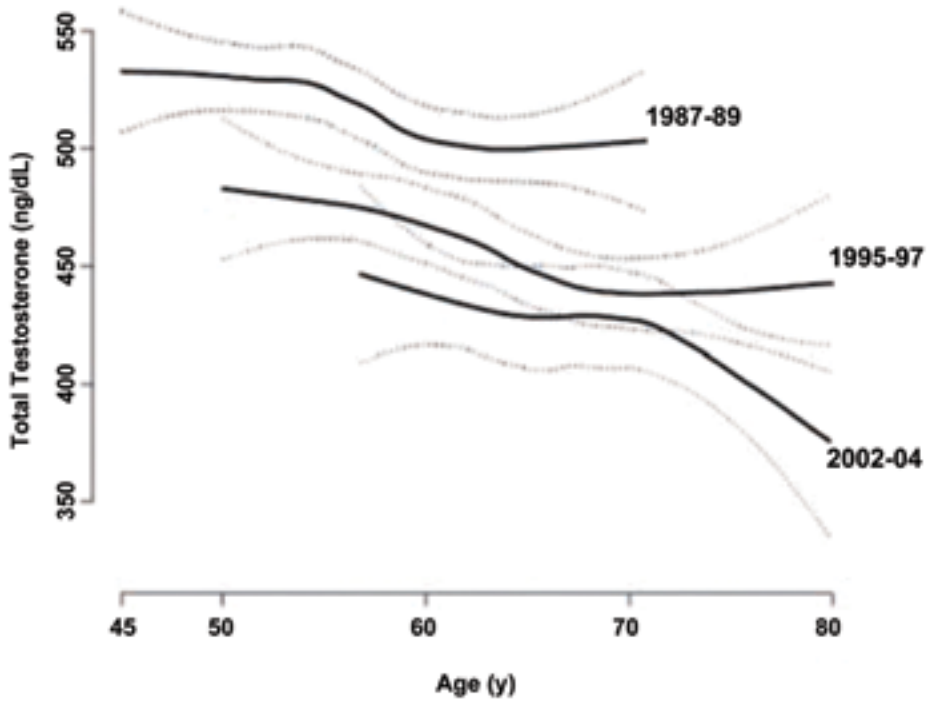


Figure 1 Age-independent decline in serum testosterone in America

foetal development. The regional differences in TGC incidence in Europe follow the same pattern as observed for semen quality.

Congenital malformations of the male reproductive tract – undescended testis and incomplete fusion of the urethral folds that form the penis – are among the most frequent congenital malformations in human males. These two abnormalities share common risk factors, both associated with reduced fertility; the first malformation is also associated with poor semen quality and considerably increased risk of TGC. Incidences of these malformations appear to have been increasing in the Western world over recent decades.

Testosterone, the male hormone, is the major driver of male reproductive development and function. Suppression of its levels within the adult testis shuts down spermatogenesis and induces infertility. Studies of men with idiopathic infertility – for which the cause is unknown - and low sperm counts often show evidence of abnormal Leydig cells, which produce testosterone in the testis.

In Europe, incidences of TGC and congenital reproductive tract malformations have been going up coincidentally with a downward trend in semen quality and testosterone levels (although there are only data for the latter in Denmark). These disorders share common risk factors and are risk factors for one another. Consequently, it has been proposed that the conditions collectively may represent a syndrome - a testicular dysgenesis syndrome (TDS) - caused by a common underlying causal factor, which is either a change in lifestyle or an environmental toxin, especially endocrine disrupting chemicals such as pesticides. Notably, the review published by the European Science Foundation (an official body that coordinates international research programmes in Europe) fails to mention glyphosate explicitly, even though its use has been rising most rapidly among pesticides in Europe and in the rest of the world since the 1980s to 1990s.

There is already evidence that glyphosate is an endocrine disrupting chemical, but the extent of the problem is far greater than it appears. Different glyphosate formulations vary in toxicity, mainly because some of them contain adjuvants that are either toxic by themselves, or else exert synergistic effects with glyphosate. It has long been known that Monsanto's formulation Roundup, the most widely used glyphosate herbicide, is far more damaging than glyphosate itself

Age-independent testosterone decline reflects rise in glyphosate use with GM crops

In America, there has been a substantial age-independent decline in testosterone that does not appear attributable to observed changes in explanatory factors including health status and lifestyle characteristics such as smoking and obesity. The estimated declines were larger than the cross sectional declines typically associated with age, as shown in Figure 1 [3].

The data are from randomly selected men living in greater Boston, Massachusetts in the United States, not connected with studies on infertility but with aging in general, as considerable loss of serum testosterone is thought to be a mark of male aging.

It is notable that the steep decline in testosterone levels began just after the introduction of genetically modified (GM) crops in 1994 with concomitant increase in glyphosate herbicides use on glyphosate tolerant GM crops. A comprehensive review article has blamed glyphosate for "most of the diseases and conditions associated with a Western diet" including infertility [4], although the precise mode of action, at least in the case of infertility, remains unclear.

Roundup more damaging than glyphosate

There is already evidence that glyphosate is an endocrine disrupting chemical (see later), but the extent of the problem is far greater than it appears. Different glyphosate formulations vary in toxicity, mainly because some of them contain adjuvants that are either toxic by themselves, or else exert synergistic effects with glyphosate. It has long been known that Monsanto's formulation Roundup,

the most widely used glyphosate herbicide, is far more damaging than glyphosate itself (reviewed in [5] Ban GMOs Now, ISIS special report).

Giles-Eric Séralini and colleagues at University of Caen in France clearly demonstrated that POEA (polyethoxylated tallowamine, a major adjuvant surfactant in Roundup) alone was by far the most cytotoxic for several human cell types, at concentrations a hundredth to ten-thousandth that of glyphosate itself and other formulations without POEA [6]. Another study from the same laboratory also showed that Roundup exposure damages testosterone producing Leydig cells from mature rat testis at concentrations a tenth of agricultural use and beginning 1 hour after exposure [7]. Within 24-48 h, the same formulation was toxic to other cells inducing cell death, in contrast to glyphosate alone, which is only toxic to Sertoli cells (feeder cells for germ cells). At 48 h, Roundup induces apoptosis (programmed cell death involving DNA fragmentation) in germ cells and in Sertoli/germ cells co-culture. At the very low, non-toxic concentration of 1 ppm, both Roundup and glyphosate decreased testosterone level by 35 %. These experiments expose a major inadequacy in the regulatory regime, which still regards POEA in Roundup as an inert adjuvant for which no risk assessment is required.

A recent laboratory experiment shows that Roundup has direct, acute impacts on the mammalian testis at levels of exposure orders of magnitude below recommended agricultural concentrations.

Acute Roundup exposure at very low concentrations kills cells in the immature testis

The Brazilian research team led by Ariane Zamoner at the Federal University of Santa Catarina in Florianópolis, and Federal University of Rio Grande do Sul in Porto Alegre, are well aware of the increased toxicity of Roundup compared with glyphosate, and were prompted to investigate the effects of Roundup by the high prevalence of reproductive dysfunction among agricultural workers occupationally exposed to the herbicide. They looked at concentrations of Roundup 2 to 3 orders of magnitude below the 10 000 to 20 000 ppm (10-20g/L) used in agriculture, which is quite realistic in terms of exposure levels for agricultural workers and members of the general public close to or within the spraying range [8].

The researchers found that brief exposure to Roundup at 36 ppm (0.036 g/L) for 30 minutes was sufficient to induce oxidative stress (a failure of energy metabolism, see later) and activate multiple stress-response pathways leading to cell death in the pre-puberty rat testis.

The team concluded [8]: "Altogether, the Ca^{2+}-mediated disturbances by glyphosate-Roundup in rat testis cells around 36 ppm, could contribute to the reproductive effects observed in male agricultural workers exposed to this pesticide at prepubertal age."

The key to understanding the action of Roundup on male infertility is the reactive oxygen species (ROS) generated in oxidative stress. Not only are ROS implicated in practically every chronic human disease including cancer, but also play an essential role in the pathogenesis of many reproductive processes

Detailed mechanisms of action identified

The team found that Roundup increases intracellular Ca^{2+} concentration by opening L-type -voltage-dependent Ca^{2+} channels – thereby allowing Ca^{2+} to enter the cells - as well as targeting the endoplasmic reticulum IP3 (inositol triphosphate) and ryanodine receptors (both Ca^{2+} release channels), leading to Ca^{2+} release and overload within the cells, setting off cell death. The mechanisms involved were inferred from experiments with specific inhibitors that cancelled out the effect of Roundup as well as Ca^{2+} influx; and confirmed by the increase in radioactive tracer $^{45}Ca^{2+}$ uptake by testis incubated with Roundup at 36 ppm. These events were prevented by the antioxidants Trolox and ascorbic acid, which counteract the reactive oxygen species (see below) responsible for the oxidative stress. Activated protein kinase C, phosphatidylinositol 3-kinase, and the mitogen-activated protein kinases such as ERK1/2 and p38MAPK all play a role in eliciting Ca^{2+} influx and cell death.

Roundup also decreases the levels of reduced glutathione (GSH, the tissue's own antioxidant) as consistent with oxidative stress, and increases the amounts of thiobarbituric acid reactive species (TBARS) and protein carbonyls, which are signs of oxidative damage from reactive oxygen species to lipids and proteins respectively. Exposure to Roundup stimulates the activities of a whole collection of enzymes supporting the down-regulation of GSH levels.

The research team looked at acute Roundup exposure of both whole immature Wistar rat testis and isolated Sertoli cells in culture; and the findings were very similar in the two systems.

Based on their experimental results, the team propose that Roundup toxicity is due to Ca^{2+} overload, resulting in cell signalling fault, a stress response and/or defence against depleted antioxidants, all contributing to the death of Sertoli cells, thereby impacting on male fertility.

The new findings are consistent with the well-known involvement of Ca^{2+} in cell death from oxidative stress. Oxidative stress causes Ca^{2+} influx into the cytoplasm from the extracellular environment and from the endoplasmic reticulum [9].

Rising Ca^{2+} concentration in the cytoplasm in turn causes Ca^{2+} influx into the mitochondria and nuclei. In the mitochondria, Ca^{2+} accelerates the disruption of normal oxidative metabolism leading to necrotic cell death. In nuclei, Ca^{2+} modulates gene transcription and nucleases that control apoptosis (programmed cell death that involves fragmentation of DNA).

There is already evidence that glyphosate may act as an endocrine disruptor for both males and females by altering aromatase activity, oestrogen regulated genes, and testosterone levels in rats [10]. But Roundup acts via different mechanisms. Roundup exposure during pregnancy and lactation at a level that did not induce maternal toxicity in Wistar rats nevertheless induced adverse reproductive effects in male offspring, including decreased daily sperm production during adulthood, increase in abnormal sperms, and low testosterone serum level at puberty. In exposed female offspring, only a delay in vaginal canal opening was observed [11].

Oxidative stress and endocrine disrupting effects specific to Roundup

The key to understanding the action of Roundup on male infertility is the reactive oxygen species (ROS) generated in oxidative stress (see [12, 13] The Body Does Burn Water and Living with Oxygen, *SiS* 43). Not only are ROS implicated in practically every chronic human disease including cancer [14] (Cancer a Redox Disease, *SiS* 54), but also play an essential role in the pathogenesis of many reproductive processes as detailed in a review published in 2003 [15]. In male-factor infertility, oxidative stress attacks the lipids of the sperm plasma membrane and the integrity of DNA in the sperm nucleus. In addition, ROS induce DNA damage, accelerate germ cell death and decrease sperm counts, thereby contributing to male infertility.

ROS is so closely linked to male infertility that infertile males generating high levels of ROS are 7 times less likely to initiate a pregnancy compared with those with low levels of ROS. A meta-analysis demonstrated that ROS levels were significantly correlated with the fertilization rate in couples undergoing *in vitro* fertilization [16].

Ashok Agarwal at the Centre for Advanced Research in Human Reproduction, Infertility and Sexual Function, Cleveland Ohio in the United States led a retrospective study on 132 male factor infertility (MFI) patients (failure to initiate pregnancy with fertile partner after one year of unprotected sex) consisting of 24 with all normal sperm parameters, 38 with all abnormal parameter and the rest with 1 or more abnormal parameters [17]. They found that the 34 normal healthy donors (controls) had significantly higher sperm concentrations, motility and morphology compared with all MFI patients. There was a significant association between MFI and ROS with odds ratio of 4.25, independently of sperm parameters and age. They concluded that high ROS is an independent marker of MFI, *irrespective of whether these patients have normal or abnormal semen parameters*. They proposed that ROS measurement should be included a part of idiopathic infertility evaluation, and treatment with antioxidants may be beneficial for such patents.

ROS are generated as intermediates in the central metabolic process whereby oxygen-breathing organisms obtain energy to fuel all their activities. The energy metabolism takes place in the mitochondria, the tiny membranous powerhouses within cells where fragments from the breakdown of glucose are oxidized ultimately into carbon dioxide and water. It involves a tightly coupled process of *oxidative phosphorylation* in which electrons and protons are extracted from the chemical fragments, with electrons transported *down* the electron transport chain and protons transported *up* the proton gradient, so that their energy can be tapped to make ATP (adenosine triphosphate, the universal energy intermediate of the body) (for a good summary of the entire process see Chapters 21 and 22 of [18] *Living Rainbow H2O*, ISIS publication). During this tightly coupled process, ROS are generated as partially oxidized intermediates [13]. Consequently, disturbances that uncouple oxidative phosphorylation lead to a failure of oxidation and release the partially oxidized and damaging ROS intermediates into the cell, resulting in oxidative stress.

It is very likely that the primary target of Roundup, especially its POEA surfactant, is the mitochondria, which plays a key role in the development of sperm cells and sperm motility [19]. In addition, male infertility could arise from ROS damages to mitochondrial DNA.

Francisco Peixoto at University of Trás-os-Montes, Real, in Portugal compared the effects of Roundup with glyphosate on isolated rat liver mitochondria [20] and found dramatic differences. Roundup collapses the transmembrane potential of the mitochondria and uncouples oxidative phosphorylation, depressing the rates of oxidation, with effects starting at 0.5 mM (7.5 ppm). These effects are most likely due to non-specific permeation of the mitochondrial membrane by Roundup or its adjuvant POEA. In addition, Roundup specifically inhibited succinate dehydrogenase, succinate cytochrome c reductase, and ATP synthase and ATPase, key enzymes in oxidative phosphorylation. Glyphosate, on the other hand, does not have any significant effects on the function of mitochondria up to the highest concentration used, 15 mM (253.5 ppm).

5

Glyphosate *is* Carcinogenic

The WHO expert panel reclassified glyphosate as 'probably carcinogenic' more than 40 years after it was brought to market, but the range of available evidence is sufficient to classify it definitely carcinogenic. Glyphosate's carcinogenic potential has been known to Monsanto and the US Environment Protection Agency from long term animal experiments since the early 1980s, but repeatedly dismissed. This has resulted in two decades of people and planet being poisoned by glyphosate herbicides on a misclassification of 'noncarcinogenic' that has allowed the manufacturer to claim it is 'safe' and perpetrating many other falsehoods to promote its ubiquitous and liberal use

Dr Mae Wan Ho and **Prof Peter T. Saunders**

Introduction

The International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), has released the results of its year-long assessment of five organophosphate insecticides and herbicides. In this, the 112th study into potentially carcinogenic agents, it has reclassified glyphosate in Group 2A 'probably carcinogenic to humans' [1, 2]. This category is used [1] "when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals." Previously, the US Environment Protection Agency (EPA), which last reviewed glyphosate in 1993, classified glyphosate in Group E 'noncarcinogenic' [3]. Similarly, a 2013 review by the German Institute for Risk Assessment (BfR) conducted on behalf of the European Union did not recommend a carcinogen classification of either 2A or 2B ('possibly carcinogenic'); though that review is mired in controversy, having been largely conducted by a consortium of chemical companies including Monsanto [4] (Scandal of Glyphosate Re-assessment in Europe, *SiS* 63). Monsanto has called on IARC to retract its assessment [5]. But Aaron Blair, scientist emeritus at the National Cancer Institute who chaired the 17 member Working Group of the IARC that carried out the assessment, robustly defended the decision, saying it is "appropriately based on current science" [6]. The IARC experts in the Working Group were selected for their expertise and most importantly, *the absence of real or apparent conflicts of interest*. Following the protocol required by the IARC, the Working Group considered only "reports that have been published or accepted for publication in the openly available scientific literature" as well as "data from governmental reports that are publicly available".

Notably, Blair told a journalist there were good grounds to declare that glyphosate definitely causes cancer [7]. But "the epidemiologic data was a little noisy." While several studies suggested a link, another study in the US of farmers in Iowa and North Carolina did not. There had been a similar inconsistency in epidemiological studies of benzene now universally acknowledged as a carcinogen, Blair added.

What Blair did not mention, for example, was that crucial evidence of carcinogenicity in animal experiments had existed at least since 1981 but successively dismissed as documented in EPA's own archives (see below). In the meantime, US government

data show steep rise in dozens of chronic diseases including cancers closely tracking the rapid increase in glyphosate use and the adoption of genetically modified (GM) crops, of which USA is the top producer by far [8]. In Argentina, the third producer of GM crops, where the use of pesticides including glyphosate has increased more than 8.5-fold since the introduction of GM crops 20 years ago, non-government organizations and doctors have been documenting rising incidences of cancers and birth defects among farmers and their families and others exposed to glyphosate spraying (see Chapter 3). Taking these and other additional findings into proper account would surely have been sufficient to classify glyphosate as a definite carcinogen.

Asked to comment on the IARC's reclassification, Fernando Manas, a member of the Genetics and Environmental Mutagenesis (GEMA) Group at the National University of Río Cuarto in Córdoba, Argentina, who has investigated the effect of agrochemicals for the past 9 years, confirmed the link between glyphosate and genetic damage, which leads to cancer and a higher risk of spontaneous abortions and birth defects in the new born, and said that the classification by IARC-WHO is a consequence of the growing scientific evidence generated by independent investigators. Furthermore, he pointed out that [9] ***this evidence, which has been deliberately ignored until now, means that "millions of gallons of herbicide with carcinogenic potential have been used according to regulations designed for a virtually harmless substance." For two decades, entire populations were "subjected" to chronic pesticide exposures "based on criteria developed by the same companies that produce and market" agrochemicals.***

Box 1
Explanations of terms used in epidemiology studies

Cohort study
A cohort is a group of people who share a common attribute or experience. A cohort study follows over a period of time such a group of people who do not have the disease and uses correlations to determine the absolute risk of contracting the disease (modified from [12])

Case-control study
A study that compares patients who have a disease (cases) with patients who do not have the disease from the same population (controls), and looks back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease (modified from [13])

Relative risk (RR)
Ratio of the probability of disease occurring in exposed group to the probability of disease occurring in a non-exposed control group, where probability in each group is defined as number of diseased/total number in group (modified from [14])

Odds ratio (OR)
The odds of disease occurring in exposed group to the odds of disease occurring in the non-exposed group, where the odds in each group is calculated as number of diseased/number of healthy (modified from [14])

95 % confidence interval (CI)
A confidence interval is the range within which the data indicate a parameter - such as the population mean - is to fall (see for example, [15]); most studies use 95 %, which correspond to significance at the 5 % level.

The IARC Monograph on glyphosate

The IARC Monograph Volume 112 detailing the deliberations on all five organophosphate pesticides is yet to be published in full, but the part dealing with glyphosate is available, running to 92 pages [10]. It concluded that there is

1. Limited evidence in humans for carcinogenicity of glyphosate in a positive association with non-Hodgkin lymphoma
2. Sufficient evidence in experimental animals for carcinogenicity of glyphosate.

The overall evaluation places glyphosate in Group 2A, probably carcinogenic to humans. In addition, the IARC Working Group noted other relevant data supporting the classification.

- There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans *in vitro* and studies in experimental animals.
- There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid (AMPA, a metabolite of glyphosate) can induce oxidative stress based on studies in experimental animals including aquatic species, and studies in human cells *in vitro*.

Genotoxicity and oxidative stress are both recognized as key characteristics of known human carcinogens.

The IARC report on glyphosate is comprehensive, dealing with many other aspects of its toxicity. In this review, we shall limit ourselves to the key aspects of the evidence relating to its carcinogenic potential, as outlined above, and to include relevant findings not covered by the IARC report.

Human carcinogenicity

The Working Group identified 7 reports from the Agricultural Health Study (AHS), a large prospective cohort study of farmers and pesticide applicators in North Carolina and Iowa - people most likely to be exposed to pesticides [11]. (For explanations of terms see Box 1). The AHS cohort, a pooled analysis of the case-control studies in the Midwest USA, and the cross-Canada study were considered key investigations on account of their relatively large size. Reports from two or more independent studies were available for non-Hodgkin lymphoma (NHL), multiple myeloma, Hodgkin lymphoma, glioma, and prostate cancer. For other cancer sites, only one study was available for evaluation.

Glyphosate exposure and NHL

Two large case-control studies of NHL from Canada and the USA, and two case-control studies from Sweden reported statistically significant increased risks of NHL with glyphosate exposure.

The Canadian multicentre population-based case-control study on specific pesticide exposure and NHL published in 2001 involved 517 cases and 1 506 controls among men of 6 Canadian provinces [16]. Odds ratios (ORs) of 1.26 (95 % CI 0.87-1.80; 51 exposed cases adjusted for age and province) and 1.20 (95 % CI 0.83-1.74, adjusted for age, province and high-risk exposures) were found for exposure to glyphosate. Participants with >2 days of exposure per year had an OR of 2.12 (95 % CI 1.20-3.73, 23 exposed cases) compared with those with < 2 days of exposure.

The population-based case-control study among men in 6 Canadian provinces between 1991 and 1994 also investigated association between lifetime use of pesticides and multiple myeloma (a subtype of NHL) [17]. Data from 342 cases of multiple myeloma and 1 357 controls were obtained for ever-use of pesticides, number of pesticides used, and days per year of pesticide use. The OR for ever use of glyphosate was 1.19 (95 % CI 0.76-1.87; 32 cases). When the analysis was done for level of exposure, no association was found for light users <2days per year of exposure; while the OR in heavier users (> 2 days of exposure per year) was 2.04 (95 % CI 0.98-4.23, 12 exposed cases).

The US study published in 2003 [18] used pooled data from three case-control studies of NHL conducted in the 1980s in Nebraska, Kansas, and in Iowa and Minnesota. The study population included 870 cases and 2 569 controls; another 650 cases and 1933 controls were included for the analysis of 47 pesticides to control for potential confounding by other pesticides. Based on 36 cases exposed, the OR for association between glyphosate exposure and NHL were 2.1 (95 % CI 1.1-1.4) in the logistic regression analysis and 1.6 (95 % CI 0.9-2.8) in the hierarchical regression analysis, where adjusted estimates were based on prior distributions for the pesticide effects, which provides more conservative estimates than logistic regression.

The incidence of 12 cancers – lung, melanoma, multiple myeloma, NHL, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate and leukaemia - was investigated among the 57 311 glyphosate-exposed pesticide applicators in the AHS study [19]. Glyphosate exposure was not associated with all cancers combined, or with most of the cancer subtypes studied. There was a suggested association with multiple myeloma (a subtype of NHL). The RR was 1.1 when adjusted for age (95 % CI 0.9-1.2, 32 cases), and 2.6 (95 CI 0.7-9.4) when adjusted for multiple confounders: age, smoking, other pesticides, alcohol consumption, family history of cancer and education). In the analysis of cumulative exposure days and intensity weighted exposure days, the RRs were around 2.0 in the highest third of the exposed subjects. The association between multiple myeloma and exposure to glyphosate only appear within the subgroup for which complete data were available on all the covariates, even without any adjustment. A re-analysis of these data [20] confirmed that the excess risk of multiple myeloma was present only in the subset with no missing information (22 cases in the restricted data set). The AHS sought information on the use of 50 pesticides [11] and it has been demonstrated that misclassification of pesticide exposure would bias relative risk estimates in the AHS towards the null and diminish the power of the study [21].

Successive studies in Sweden since 1998 reported association of NHL with glyphosate use, but the numbers were small (reviewed in [10, pp. 26-27]). A pooled analysis of two case-control studies one on NHL and another on hairy cell leukaemia (a subtype of NHL) based on 515 cases and 1141 controls published in 2002 [22] reported increased risk for exposure to glyphosate. The OR was 3.04 (95 % CI 1.08-8.52, 8 exposed cases) in the univariate and 1.85 (95 % CI 0.55-6.02) in a multivariate analysis that considered study, study area, and vital status. A population-based case-control study of exposure to pesticides as a risk factor for NHL published in 2008 included men and women aged 18-74 years living in Sweden from 1 December 1999 to 30 April 2002, giving a total of 910 cases and 1 016 controls matched for age and sex [23]. The OR for exposure to glyphosate was 2.02 (95 % CI 1.10-3.71) in a univariate analysis and 1.51 (95 % CI 0.77-2.94) in a multivariable analysis. When exposure for more than 10 days per year was considered, the OR was 2.36 (95 % CI 1.10-3.71). The association of glyphosate exposure with lymphoma subtypes was also found; for B-cell lymphoma, OR 1.87 (95 % CI 0.998-3.51) and subcategory of small lymphocytic lymphoma/ chronic lymphocytic leukaemia, OR 3.35 (95 % CI 1.42-7.89, not adjusted for other pesticides). (NHLs are a heterogeneous group of more than 20 B- and T-cell lymphomas affecting the immune system/lymphatic system and arising primarily in the lymph nodes [24].)

A hospital-based case-control study was conducted at 6 centres in France between 2000 and 2004 of cases with a diagnosis of lymphoid neoplasm aged 20-75 and controls recruited in the same hospital [25]. The analysis included 491 cases (244 cases of NHL, 87 cases of Hodgkin lymphoma, 104 lymphoproliferative syndrome, and 6 cases of multiple myeloma) and 456 age- and sex-matched controls. ORs associated with any exposure to glyphosate were 1.2 (95 % CI 0.6-2.1; 27 cases) for all lymphoid neoplasmas combined, 2.4 (95 % CI 0.8-7.3) for multiple myeloma, and 1.7 (95 % 0.6-5.0; 6 cases) for Hodgkin lymphoma, after adjusting for age, centre, and socioeconomic category.

A pooled analysis of case-control studies conducted in 6 European countries in 1998-2004 – Czech Republic, France, Germany, Ireland, Italy, and Spain - involved 2 348 cases of lymphoma and 2 462 controls [26]. Lymphoma overall and B-cell lymphoma were not associated with any class of the investigated pesticides, while the risk of chronic lymphocytic leukaemia was elevated among those ever exposed to inorganic and organic pesticides. The ORs for glyphosate exposure and B-cell lymphoma was 3.1 (95 % CI 0.6-17.1, 4 exposed cases and 2 exposed controls).

A systematic review and meta-analysis of NHL and occupational exposure to agricultural pesticides [27] for which 6 previous studies were included [16, 18, 19, 22, 23, 25] yielded a meta risk ratio of 1.5 (95 % CI 1.1-2.0). The Working Group noted that the most fully adjusted risk estimates from [22, 23] were not used. After considering the adjusted estimates of these two Swedish studies, the Working Group estimated a meta risk-ratio of 1.2 (95 % CI 1.03-1.65) (see [10, p.30]).

Glyphosate exposure and other cancer sites

A case-control analysis nested in the AHS examined associations between pesticide use and cancer of the pancreas included 93 incident cases (64 applicators, 29 spouses) and 82 503 cancer-free controls The OR for ever *versus* never exposure to glyphosate was 1.1 (95 % CI 0.6-7.55; 55 exposed cases), while the OR for the highest category of level of intensity-weighted lifetime days was 1.2 (95 % CI 0.6-2.6, 19 exposed cases) [28].

An investigation on the relationship between agricultural pesticide exposure and incidence of cancer of the colorectum in the AHS included 56 813 pesticide applicators with no prior history of cancer of the colorectum, and 305 incidents of cancer of the colorectum (colon 212, rectum, 93) diagnosed during the study period 1993-2002 [29]. Most of the 50 pesticides studied were not associated with risk of colorectal cancer. The relative risks with exposure to glyphosate were 1.2 (95 % CI 0.9-1.6), 1.0 (95 % CI 0.7-1.5) and 1.6 (95 % CI0.9-2.9) for cancers of the colorectum, colon, and rectum respectively.

A case-control study of 1 516 patients with prostate cancer in British Columbia, Canada, from 1983 to 1990 and 4 994 age-matched controls with cancers at all other cancer sites excluding lung and unknown primary site reported OR for glyphosate exposure 1.36 (95 % CI 0.83-2.25, 60 cases) [30].

No association with glyphosate exposure was found in the AHS for childhood cancer, breast cancer among farmers' wives,

prostate cancer, cutaneous melanoma (each represented by a single study, reviewed in [10]). No association was found for in case-control studies for glyphosate exposure and adenocarcinomas of the oesophagus and stomach (one study), glioma (three studies), or soft tissue sarcoma (one study) as reviewed in [10].

In summary, there is evidence that glyphosate exposure is associated with increased risk of non-Hodgkin's lymphoma from several large studies as well as smaller studies. In addition, single studies have found non-significantly increased RRs or ORs for glyphosate exposure and several cancer sites.

Increase in pesticide burden on health due to glyphosate use with glyphosate tolerant GM crops

Glyphosate contamination ubiquitous in the environment

Glyphosate herbicides have been marketed since the 1970s, but the steep rise in their use began with the commercial release of GM glyphosate-tolerant crops 30 years ago, and they rapidly become the world's top selling herbicides. Currently, 85 % of GM crops planted globally are herbicide-tolerant, with glyphosate-tolerant crops making up the vast majority of those planted [31]. In the USA, the largest producer of GM crops, 93 % of soybean, 85 % of cotton, and 85 % of maize crops are glyphosate-tolerant [32]. In recent years, the use of glyphosate herbicides has expanded to include weed control in residential and commercial areas and as desiccant to aid in harvesting a wide range of conventional non-GM crops [33]. The global glyphosate market demand in 2012 was 718 600 tonnes [34], with GM crops accounting for 45.2 % of the total demand, and glyphosate ~25 % of the global pesticide market [35]. In the USA alone, overall pesticide use increased by an estimated 183 million kilograms (404 million pounds) in the first 16 years of GM crops between 1996 and 2011 [36]; and glyphosate is estimated to account for ~40 % of all pesticide use (by weight of active ingredient) from figures provided by the US EPA in 2007 [37]. Glyphosate and glyphosate residues have contaminated the entire environment, air, soil, water, urban, suburban, and rural, representing an enormous increase in the pesticide burden on global health.

A compilation representing the largest and most comprehensive assessment of the environmental occurrence of glyphosate and AMPA in the US conducted to-date summarises the results of 3 732 water and sediment and 1 018 quality assurance samples collected between 2001 and 2010 from 38 states and the District of Columbia [38]. The results indicate that glyphosate and AMPA are detected frequently together, that they are mobile and occur widely in the environment. Overall, glyphosate was detected in 39.4 % of samples (median < 0.2, maximum 476 µg/L or kg in soil and sediment), and AMPA in 55.0 % (median 0.05, maximum 397 µg/L or kg in ditches and drains). Glyphosate and AMPA were detected frequently in soils and sediment (91.1 % and 93.3 % respectively), ditches and drains (70.9 % and 80.7 % respectively), precipitation (70.6 % and 71.8 % respectively), rivers (53.1 % and 89,3 % respectively) and streams (52.5 % and 55.0 % respectively, and less frequently in lakes, ponds, and wetlands (33.7 % and 29.8 % respectively), soil water (34.5 % and 65.5 % respectively, and groundwater (5.8 % and 14.3 % respectively).

Glyphosate builds up and leaches from soil

Glyphosate is a polar amphoteric compound that binds strongly to soils but is also very soluble in water. It has a soil half-life ranging from 2 to 215 days, and an aquatic half-life of 2 to 91 days. Glyphosate degrades in the environment primarily by microbial action to AMPA, which is also very water soluble, and degrades more slowly than glyphosate. AMPA has a soil half-life of 60-240 days and an aquatic half-life comparable to that of glyphosate. AMPA ultimately degrades to inorganic phosphate, ammonium and CO_2, adding phosphate pollution to aquatic systems (reviewed in [38]). Recent samplings in Argentina showed glyphosate levels in rain water averaging 6.5 µg/L and as high as 67 µg/L, more than 20 times the level in the USA. In Spain all 11 groundwater sites sampled were positive for glyphosate despite it being a region free from glyphosate-tolerant GM crop cultivation (reviewed in Chapter 1). Thus both glyphosate and its main metabolite AMPA are long-lasting in the environment, and leach easily into water; this is contrary to claims by the manufacturer, which has been repeatedly prosecuted for false advertising that Roundup is "biodegradable", "won't build up in the soil", "no leaching", and "less toxic to rats than table salt", "'practically non-toxic'" to mammals, birds and fish" [39, 40]

Glyphosate bioaccumulates

In the IARC report on glyphosate, it is stated that [10, p. 45]: "Overall, systemically absorbed glyphosate is not metabolized efficiently, and is mainly excreted unchanged in the urine." This has been shown to be false, as AMPA has been detected frequently in human urine, and glyphosate in human mother's milk and in animal tissues (reviewed in Chapter 1).

A study commissioned by Friends of the Earth Europe analysed 182 volunteers across 18 EU countries found that 80 (43.9 %) have glyphosate, with a mean of 0.21 µg/L and a maximum of 1.82 µg/L. AMPA was present in 65 (35.71 %), with a mean of 0.18 µg/L and a maximum of 2.63 µg/L. In the US, urine samples show concentrations 8 times those in Europe. The analysis, commissioned by Moms Across America, also tested 10 mothers' breast milk, which came up positive for glyphosate with levels ranging from 76 to 166 µg/L, higher than those in urine, and 760 to 1600 times higher than the European Drinking Water Directive allowed levels for individual pesticides, falling within the range of concentrations at which developmental toxicity has been observed in animal studies. A second study on breast milk commissioned by the Green Party was performed in Germany, where far fewer GM crops are consumed, and glyphosate levels ranged from 0.210-0.432 µg/L, well above the EU drinking water limit of 0.1 µg/L.

In a peer-reviewed study published in 2014 [41], not included in the IARC assessment, glyphosate was detected in human, cow, rabbit and hare urine as well as in tissues of cows. Samples were collected from Germany (except for urine from Danish cows) as follows: urine of cows from conventional farms in (N=343), urine from cows kept in GM free areas (N=32); organs from slaughtered cows from conventional husbandry: gut wall (N=32), liver (N=4), kidney (N=26), lung (N=23) and muscle (N=6); urine from Danish cows (N = 242); urine from 192 hares and 77 fattening rabbits; human urine from 99 on conventional diet and 41 on organic diet; and further human urine samples from 102 healthy subjects and 199 chronically ill subject. A two-way analysis of variance followed by unpaired Student's t-tests was used to identify significant differences between means. The results are presented in Figure 1 (unfortunately, the authors chose not to tabulate the numerical values). As can be seen, urine from German cows had on average significantly less glyphosate than urine from cows in Denmark ($p<0.0001$); cows kept in GM free regions had significantly lower concentration of glyphosate in their urine than cows kept on conventional farms ($p<0.001$); glyphosate was detected in all the organs of slaughtered cows with no significant difference between the means; hares showed significantly lower glyphosate residues in urine than in fattening rabbits ($p<0.0001$); humans on conventional diet had significantly higher glyphosate levels than

those on organic diet (p<0.0002), and healthy humans had significantly lower glyphosate levels in urine than those with chronic disease (p<0.03). The results clearly show that glyphosate and glyphosate residues could be ingested in food and feed and drinking water (or indeed absorbed through the air or through the skin, see later) and excreted in urine. Furthermore, they can accumulate in all tissues, and at levels known to promote the growth of cancer cells *in vitro* (see below).

Marked deterioration on public health tracks glyphosate and GM crops increase

Although there has been no official health monitoring for glyphosate or GM crops as such, it is possible to examine the health status of countries that have seen the steepest rise in glyphosate use before and after the introduction of GM crops when the rapid increase in glyphosate use began. Plotting the best available government data year to year from the US Centers for Disease Control for the incidence of diseases in the country, and the Department of Agriculture for the GM crops grown and glyphosate herbicides used, Swanson et al [8] showed increases in the incidence of dozens of diseases including six cancers closely tracking the increases in GM crops and glyphosate usage. Figure 2 shows the incidences of liver and thyroid cancers, the former with a distinct pre-1990 trend, the latter without.

When the Pearson correlation coefficients between the incidence of 22 diseases and the amount of glyphosate used and the percentage of GM maize and soy planted respectively, most of the 44 coefficients are greater than 0.91 and none of them fall below 0.81 (see Table 1) (from Chapter 2).

Table 1: Pearson correlation coefficients between the incidence in the US of 22 chronic diseases since 1995 and (a) the amount of glyphosate applied to maize and soy (b) the percentage of maize and soy planted that was GM

Condition	Glyphosate use	%GM
Hypertension	0.923	0.961
Stroke	0.925	0.983
Diabetes prevalence	0.971	0.983
Diabetes incidence	0.935	0.955
Obesity	0.962	0.962
Lipoprotein metabolism disorder	0.973	0.955
Alzheimer's	0.917	0.937
Senile dementia	0.994	0.918
Parkinson's	0.875	0.952
Multiple sclerosis	0.828	0.876
Autism	0.989	0.933
Inflammatory bowel disease	0.938	0.812
Intestinal infections	0.974	0.901
End stage renal disease	0.975	0.958
Acute kidney failure	0.978	0.967
Thyroid cancer	0.988	0.938
Liver cancer	0.960	0.911
Bladder cancer	0.981	0.945
Pancreatic cancer	0.918	0.841
Kidney cancer	0.973	0.940
Myeloid leukaemia	0.878	0.889

In Argentina, where the use of pesticides including especially glyphosate herbicides has increased more than 8.5-fold since GM crops were introduced 20 years ago (see Chapter 2), physicians and local governments have been documenting rapid increases in birth defects and cancers for years. At the 1st National Meeting of physicians in the crop-sprayed towns which took place in the National University of Córdoba 27-28 August 2010, an official report from the province of Chaco recorded a 4.5-fold increase in the incidence of birth defects over 12 years, from 19.1 /10 000 in 1997 to 28.1 /10 000 in 2001 and 85.3/ 10 000 in 2009 [42]. Also, the incidence of childhood cancer rose from 8.03/ 100 000 in 1991 to 11.2/100 000 in 2001 and 15.7/100 000 in 2007. A second report released by the Ministry of Health in Córdoba, entitled "Report on cancer in Córdoba 2004-2009" based on analysis of deaths from cancerous tumours in the province shows that the highest rates of deaths occur in areas where GM crops and agrochemicals are used, and they are almost double

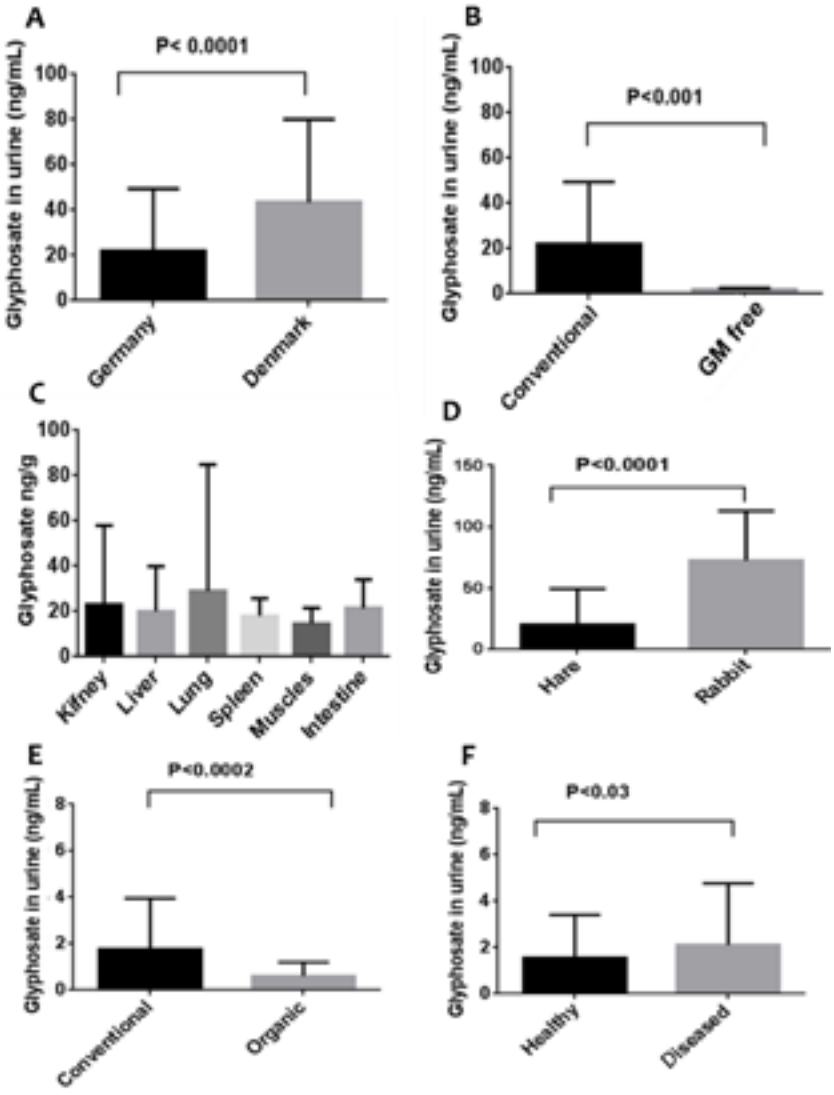


Figure 1 Glyphosate residues in urine and animal tissues: A, urine of cows in Germany and in Denmark; B, urine of cows from conventional and GM free farms; C, levels in different organs and tissues from cattle obtained in a slaughter house; E, urine from humans on conventional and organic diets; F, urine from healthy humans and those chronically disease (redrawn from [41])

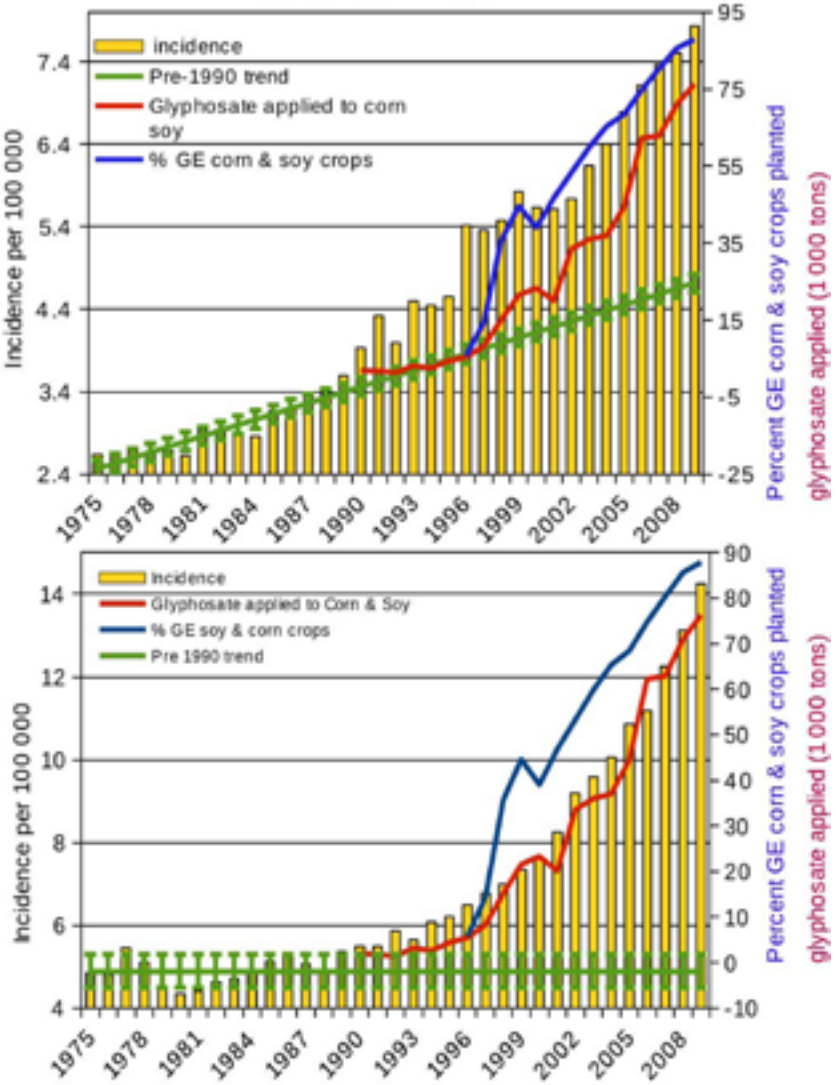


Figure 2 Incidence of liver cancer (top) and thyroid cancer (bottom) closely tracking increases in glyphosate use and GM corn and soy crop planted (redrawn from [8])

the national average [43]. The provincial average is 158 per 100 000, and in Córdoba Capital, the rate is 134.8. But four Córdoba departments are well above those rates: Marcos Juárez, 229.8; Presidente Roque Sáenz Peña, 228.4; Union, 217.4; and San Justo, 216.8. These are the "pampa gringa", the area of Córdoba agriculture. WHO's latest 2012 data for Argentina show that the death rate from cancerous tumours for Argentina as a whole is 115.13, about half of that in Marcos Juárez, where glyphosate and AMPA have been detected in lakes, soils, and rainwater. Apart from the worst affected pampa gringa, the departments of Rio Cuarto, General San Martin, Celman, Tercero Arriba and General Roca, also dedicated to industrial farming, have the second highest cancerous tumour deaths ranging from 180-201 per 100 000, again well above the national average.

Cancer in experimental animals

As described in the IARC report [10], glyphosate was tested for carcinogenicity in two studies by dietary administration on male and female mice, and in male and female rats by dietary administration in 5 studies and by drinking water in one study. The main finding was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma combined in males in one feeding study in CD-1 mice; renal tubule carcinoma being a rare tumour in this strain of mice. In the second feeding study, there was a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice. For the five feeding studies in rats, two in the Sprague-Dawley strain showed a significant increase in the incidence of pancreatic islet cell adenoma in males, one of them also showed a significant positive trend in the incidences of hepatocellular adenoma in males and of thyroid C-cell adenoma in females. Two studies, one in Sprague-Dawley rats, and one in Wistar rats found no significant increase in tumour incidence at any site, but the study on Wistar rats was considered inadequate because of the short duration of exposure. The study in Wistar rats given glyphosate in drinking found no significant increase in tumour incidence.

Many of the significant results came from animal studies submitted to the US EPA, which dismissed them in altering its initial classification of glyphosate as 'possible carcinogen' to 'noncarcinogenic'.

Studies with significant results evaluated by IARC

In the first experiment submitted to the EPA [44], groups of 50 male and 50 female randomized CD-1 mice individually caged were given diets containing 0, 1 000, 5 000, and 30 000 ppm of glyphosate (99.7 % pure) *ad libitum* for 24 months. There was a consistent decrease in body weight in both males and female mice at the highest dose. There was a significant positive trend (p=0.016 in trend test) in the incidence of renal tubule adenoma in the dosed male mice: 0/49, 1/50 1/50 (2 %) 3/50 (6 %). Subsequent to its initial report [45], the EPA recommended that additional renal sections should be cut and evaluated for all male mice in the control and treated groups. The pathology report indicated the same incidence of renal tubule adenoma as originally reported [44]. The EPA then requested that a pathology working group (PWG) be convened to evaluate the tumours of the kidney of the male mice treated with glyphosate, including the additional renal sections [46]. As a result, the PWG reported that the incidence of renal tubule adenoma was 1/49 (2 %), 0/49, 1/50 (2 %), 1/50 (2 %), and not significant by the trend test. However, the incidence of carcinoma of the renal tubule was 0/49, 0/49, 1/50 (2 %), 2/50 (4 %); p=0.037 trend test for carcinoma. The incidence of renal tubule adenoma or carcinoma (combined) was 1/49 (2 %), 0/49, 1/50 (2 %), 3/50 (6 %); p=0.034 trend test for combined. The Working Group considered that the second evaluation indicated a significant increase in the incidence of rare tumours with a dose-related trend that could be attributed to glyphosate. It has been reported that only 1 out of 725 CD-1 male mice in a historical database had developed renal cell tumours (1 carcinoma).

The second study on groups of 50 male and 50 female CD-1 mice was reported in the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). They were given diets containing glyphosate (98.6 % pure) at concentrations adjusted weekly for the first 13 weeks, and every 4 weeks thereafter to give doses of 0, 100, 300, or 1 000 mg/kg by weight *ad libitum* for 104 weeks. There was no effect on survival or body weight in any of the dosed groups. There was a significant increase in the incidence of haemangio-

sarcoma in males, 0/50, 0/50, 0/50, 4/50 (8 %); p<0.001, Cochran-Armitage trend test. There was also a non-significant increase in the incidence of histiocytic sarcoma in the lymphoreticular/haemopoietic tissues in males, 0/50, 2/50 (4 %), 0/50, 2/50 (4 %), and in females, 0/50, 3/50 (6 %), 3/50 (6 %), 1/50 (2 %).

The EPA also provided information on a long-term study of groups of 60 males and 60 female Sprague-Dawley rats (age 8 weeks) given diets containing glyphosate (96.5 % pure) at a concentration of 0, 2 000, 8 000, or 20 000 ppm, *ad libitum* for 24 months [47-49]. Ten animals per group were killed after 12 months. There was no effect on survival, and no significant decrease in body weight gain in males. In females at the highest dose, body weight gain was significantly decreased starting on day 51. In males at the lowest dose, there was a significant increase in the incidence of pancreatic islet cell adenoma compared with controls: 8/57 (14 %) *versus* 1/58 (2 %), p < 0.05 (Fisher exact test). Additional analysis by the EPA [47] using Cochran-Armitage trend test and Fisher exact test, and excluding rats that died or were killed before week 55 gave a statistically significant higher incidence of pancreatic islet cell adenoma in males at the lowest and highest doses compared with controls (1/43, 2 %): lowest dose 8/45 (18 %, p = 0.018, pairwise test), intermediate dose, 5/49 (10 %); highest dose 7/48 (15 %, p= 0.042; pairwise test). The range for historical controls for pancreatic islet cell adenoma reported in males at this laboratory was 1.8-8.5 %. There was also a statistically significant positive trend in the incidence of hepatocellular adenoma in males (p= 0.016) and of thyroid follicular cell adenoma in females (p=0.031).

(Note that in applying the Cochran-Armitage test, the EPA assumed a linear dose response over the entire range. They gave no justification for this; indeed they did not state it explicitly. A less drastic assumption, for example, a logistic-like response, would have reduced the p-values and yielded more significant cases.)

The EPA provided information on another long-term study with groups of 50 male and 50 female Sprague-Dawley rats given diets containing glyphosate (98.7 % pure) at a concentration of 0, 30 100, or 300 ppm (mg/kg body weight per day) *ad libitum* for life (up to 26 months) [47-49]. An increase in the incidence of pancreatic islet cell adenoma was reported in males at the lowest dose: controls 0/50, lowest dose 5/49 (10 %), p < 0.05, Fisher exact test, both intermediate and highest dose were 2/50 (4 %).

A study on Swiss mice (20/group) tested the carcinogenic potential of glyphosate formulation Roundup Original® (glyphosate 41 %, polyethoxylated tallowamine (poea), ~15 %) dissolved in 50 % ethanol and applied onto the shaved back skin [50].
Group 1 - untreated controls;
Group 2 - glyphosate only (25 mg/kg body weight) applied topically three times per week for 32 weeks;
Group 3 - single topical application of the tumour initiator dimethylbenz[a]anthracene (DMBA in ethanol, 52µg/mouse), followed one week later by the tumour promoter 12-O-tetradecanoylphobol-13-acetate (TPA in acetone, 5 µg/mouse) applied topically 3 times a week for 31weeks;
Group 4 – single topical application of glyphosate (25 mg/kg body weight) followed 1 week later by TPA in acetone, 5 µg/mouse) applied topically 3 times a week for 31 weeks.
Group 5 – glyphosate (25 mg/kg body weight) applied topically three times per week for 3 weeks, followed 1 week later by TPA (in acetone, 5 µg/mouse) applied topically 3 times a week for 28 weeks;
Group 6 – single topical application of DMBA (in ethanol, 52 µg/mouse);
Group 7 – TPA (in acetone, 5 µg/mouse) applied topically 3 times a week for 32 weeks;
Group 8 – single topical application of DMBA (in ethanol, 52 µg/mouse), followed one week later by glyphosate (25 mg/kg body weight) applied topically three times per week for 31 weeks.

All mice were killed at the end of the experiment (32 weeks). Skin tumours were observed in group 3, the positive control and in group 8, DMBA + glyphosate, 8/20 p<0.05 *versus* group 6, DMBA only, 0/20. Thus the glyphosate formulation appears to be a tumour promoter. The Working Group decided this was an inadequate study because of the small number of animals and lack of solvent controls. What the IARC report [10] did not take into account was the substantial proteomic analysis in the rest of the paper [50] using 2-dimensional gel electrophoresis and mass spectrometry. The researchers identified 22 spots that were differentially expressed (>2 fold) on glyphosate, DMBA, and TPA application over the untreated control. Among them, 9 proteins - translation elongation factor eEF-1 alpha chain, carbonic anhydrase III, annexin II, calcyclin, fab fragment anti-VEGF antibody, peroxiredoxin-2, superoxide dismutase [Cu–Zn], stefin A3, and calgranulin-B - were common and showed similar expression pattern in glyphosate and TPA-treated mouse skin. These proteins are known to be involved in several key processes such as apoptosis and growth-inhibition, anti-oxidant responses. The up-regulation of calcyclin, calgranulin-B and down-regulation of superoxide dismutase [Cu–Zn] was further confirmed by immunoblotting. The author concluded that [51]: "Altogether, these results suggested that glyphosate has tumor promoting potential in skin carcinogenesis and its mechanism seems to be similar to TPA."

However, as the experiments were carried out with Roundup, it remains unclear whether the cancer promoting activity is due to glyphosate or POEA or both. Experiments on human cancer cells have thrown further light on the issue (see later).

How the EPA changed glyphosate classification from possibly carcinogenic to noncarcinogenic

An excellent review on glyphosate toxicity was written by Caroline Cox of Northwest Coalition for Alternatives to Pesticides, Eugene, Oregon in the US and published in 1995.

The author stated [51]: "It is striking that laboratory studies have identified adverse effects of glyphosate or glyphosate-containing products in *all* standard categories of toxicological testing." Not only is glyphosate acutely toxic to animals including humans, animal studies feeding glyphosate for 3 months resulted in reduced weight gain, diarrhoea, and salivary gland lesions. Lifetime feeding resulted in excess growth and death of liver cells, cataracts, and lens degeneration, and increases in the frequency of thyroid, pancreas, and liver tumours. Glyphosate containing products have caused genetic damage in human blood cells, fruit flies and onion cells. Glyphosate reduced sperm counts in male rats, lengthened the oestrous cycle in female rats, increasing their foetal loss and decreasing the birth weight of their offspring. The paper also revealed two serious cases of fraud in laboratories conducting toxicology and residue testing for glyphosate and glyphosate-containing products.

On carcinogenicity, Cox wrote [51]: "The potential of glyphosate to cause cancer has been a controversial subject since the first lifetime feeding studies were analyzed in the early 1980s. The first study (1979-1981) found an increase in testicular interstitial tumors in male rats at the highest dose tested (30 mg/kg of body weight per day) [52] as well as an increase in the frequency of

a thyroid cancer in females [53] [*this study was not considered by the IARC*]. The second study (completed in 1983) found dose-related increases in the frequency of a rare kidney tumor in male mice [54]. The most recent study (1988-1990) found an increase in the number of pancreas and liver tumors in male rats together with an increase of the same thyroid cancer found in the 1983 study in females [55]."

But the EPA explained all that away. Cox continued [51]: "All of these increases in tumor incidence are "not considered compound-related" [55] according to EPA. In each case, different reasons are given for this conclusion. For the testicular tumors, EPA accepted the interpretation of an industry pathologist who said that the incidence in treated groups (12 percent) was similar to those observed in other control (not glyphosate-fed) rat feeding studies (4.5 percent) [56]. [*This is an illicit use of controls, and 12 percent is clearly well above 4.5 percent in any case.*] For the thyroid cancer, EPA stated that it was not possible to consistently distinguish between cancers and tumors of this type, so that the incidences of the two should be considered together [*a questionable manipulation of data*]. The combined data are not statistically significant [53]. For the kidney tumors, the registrants reexamined slides of kidney tissue, finding an additional tumor in untreated mice so that statistical significance was lost. This was despite a memo from EPA's pathologist stating that the lesion in question was not really a tumor [54] [*and hence amounts to a falsification of data*]. For the pancreatic tumors, EPA stated that there was no dose-related trend and no progression to malignancy [*the lack of linear dose-related trend is frequently the case in endocrine disrupting chemicals*]. For the liver tumors and the thyroid tumors, EPA stated that pairwise comparisons between treated and untreated animals were not statistically significant and there was no progression to malignancy [55]." (Comments between square brackets added).

EPA concluded that glyphosate should be classified as Group E [55], "evidence of non-carcinogenicity for humans." They added that this classification "is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances."

The EPA authorities went against the advice of their own scientists, as Cox revealed [51]. An EPA statistician wrote in a memo concerning one of the carcinogenicity studies [55], "Viewpoint is a key issue. Our viewpoint is one of protecting the public health when we see suspicious data." Unfortunately, EPA has not taken that viewpoint in its assessment of glyphosate's cancer-causing potential. The agency should indeed be held responsible for two decades of people and planet being subjected to chronic glyphosate exposures on a misclassification that has allowed the manufacturer to claim it is 'safe', and perpetrating many other falsehoods to promote its ubiquitous and liberal use.

Carcinogenic potential of glyphosate in human cells

There has been only one *in vivo* study on the potential of glyphosate to promote cancerous growth on skin of mice [50], which suggested from proteomic analysis that the glyphosate formulations used (Roundup) promoted cancerous growth in a similar way to a well-known cancer promoter TPA, but it remained unclear whether it was glyphosate or the adjuvant POEA or both that promoted cancer. Further studies on cancer cells showed that glyphosate is probably the main culprit.

Glyphosate promotes growth of human cancer cells

On account of epidemiological studies showing increased frequency of birth defects in pesticide applicators and general population of the Red River Valley, Minnesota, a selection of 16 agrochemicals including both Roundup and glyphosate (reagent grade monoisopropylamine salt) were investigated for their effects on the growth of the oestrogen-dependent MCF-7 human breast cancer cells [57]. Tests were performed in both growth media contained charcoal-dextran (CD) treated or non-CD treated foetal bovine serum. The researchers found that both glyphosate and its most widely used formulation, Roundup, were able to promote significant proliferation of MCF-7 cells; and the results were similar in CD- and non-CD- treated medium. Maximum induction of cell proliferation occurred at 2.28 µg/mL of glyphosate (135 + 3.5 % with CD, 130 + 7.98 % without CD) or 10 µg/mL Roundup (126 + 5.1 % with CD, 121 + 10.3 % without CD); $p<0.05$ linear regression. The data suggested that non-oestrogenic induction of cell proliferation is involved in glyphosate and Roundup (this is corroborated by strong evidence that glyphosate and AMPA are genotoxic and cause oxidative stress, see later).

In a second more recent and detailed study carried out in Thailand, the researchers found that glyphosate at minute concentrations enhanced the proliferation of human hormone-dependent breast cancer T47D cells, but not hormone-independent breast cancer MDA-MB231 cells. Their detailed experiments showed that glyphosate mimics the action of oestrogen, and uses the same molecular pathways as the natural hormone to promote proliferation of the cancer cells. They also found that glyphosate had synergistic effects in enhancing breast cancer cell growth in combination with genistein, a common phytoestrogen in soybean [58].

Glyphosate at concentrations between 10^{-12} and 10^{-6} M (0.169 ng/L to 0.169 mg/L) boosted the proliferation of T47D cells by 15 to 30 %, about half as effectively as the most potent oestrogen, 17 β-estradiol (E2). The same low concentrations of glyphosate induced the activation of oestrogen response element (ERE) - a specific DNA sequence promoting gene expression with high affinity for the oestrogen receptor (ER) that binds oestrogen - thereby activating gene expression in response to oestrogen. Furthermore, this activation was inhibited by an oestrogen antagonist, ICI 182780, indicating that the estrogenic activity of glyphosate was mediated via ERs.

The highest oestrogen mimicking effect was at 10^{-9}M or 0.169 µg/L and the effect was half that of oestrogen, the most potent growth-promoter in hormone-dependent breast cancer cells. ICI 182780, a specific inhibitor of oestrogen at 1 nM reduced the proliferative effects of both glyphosate and E2. At 10 nM it completely inhibited the growth enhancing effects of glyphosate, suggesting that glyphosate acts via the oestrogen receptor ER.

T47D-KBluc cells, with stably transfected triplet oestrogen response element (ERE) promoter–luciferase reporter gene construct, when treated with glyphosate at the concentration range of 10^{-12} to 10^{-6} M, proliferated at 5-13 fold of the controls without glyphosate or E2, less than half that induced by oestrogen.

The concentration ranges of glyphosate and genistein inducing ERE activity more than 10 fold of control are individually 10^{-11} to 10^{-9}M and 10^{-7} to 10^{-5} M respectively. Glyphosate residues in soybean were found in the range of 0.1-5.6µg/g, while genistein were in the range of 0.01-1.2 mg/g. As mentioned earlier, glyphosate concentrations in human urine could be 1.8×10^{-8} to 1.4×10^{-6} M. Using these concentrations as a guide, the interaction range between the two oestrogenic mimics were set at genistein 10^{-7} to

10^{-5} M, and glyphosate 10^{-11} to 10^{-9}; the concentrations were varied with a fixed ratio of both compounds. The results showed significant enhancement of ERE activation in the combination of 10^{-10} M glyphosate with 10^{-6}M genistein and 10^{-9} M glyphosate with 10^{-5}M genistein. At 10^{-7}M genistein and 10^{-9}M glyphosate, cell proliferation was increased to 169 % of control, where individually, the promotion was 145 %.

The important new finding is that glyphosate mimics oestrogen activity at minute concentrations; it may be inhibitory for oestrogen at high concentrations (while other toxicities including oestrogen-independent carcinogenicity) also come into effect. Nonlinear concentration dependence is characteristic of environmental pollutants with endocrine disrupting effects (see [59]).

Glyphosate is genotoxic and causes oxidative stress

As stated in the IARC review [10], there is strong evidence that both glyphosate and glyphosate formulations cause genotoxicity. The end-points evaluated include biomarkers of DNA adducts and breakage, and various kinds of chromosome damage. Tests in bacteria gave consistently negative results.

The evidence base for glyphosate includes human cells *in vitro*, mammalian models *in vivo* and *in vitro*, and studies in non-mammals. *In vivo* studies in mammals generally gave positive results in the liver and mixed results in kidney and bone marrow.

There were three studies on residents in communities exposed to glyphosate-based formulations, two of which reported positive results. Additional evidence comes from studies that gave largely positive results in human cells *in vitro*, as well as in non-mammalian organisms.

For AMPA, the evidence for genotoxicity is moderate; while the number of relevant studies is not large, all gave positive results.

There is strong evidence that glyphosate, glyphosate-formulations and AMPA cause oxidative stress in human cells *in vitro*, and in non-human mammalian systems and non-mammalian organisms *in vivo*.

Genotoxicity

Studies on humans exposed to glyphosate contamination through aerial or ground spraying clearly show that glyphosate in the air is absorbed into the body and transported into cells.

A study [60] carried out in Ecuador on an exposed group of 24 randomly selected individuals living 3 km or less from an area on the border between Ecuador and Colombia where aerial spraying with a glyphosate formulation (Roundup Ultra) had occurred continuously for three days between December 2000 and March 2001, and sporadic aerial spraying continuing for three weeks following continuous spraying. A clinical history was completed for each of the exposed individuals and a wide-range of reactions were noted, including intestinal pain and vomiting, diarrhoea, fever, heart palpitations, headaches, dizziness, numbness, insomnia, sadness burning of eyes or skin, blurred vision, difficulty in breathing and blisters or rash. The unexposed control group consisted of 21 unrelated healthy individuals living 80 km away from the spraying area; they were similar to the exposed group regarding demographic characteristics and occupation but were not matched controls. Significant increase in DNA damage was found with the comet assay. The migration length of the exposed group was 35.5 ± 6.4 μm, compared with the control of 25.94 ± 0.6 μm. The results were highly significant at $p<0.001$.

A large study on community residents involved 137 women of reproductive age and their 137 spouses from five Colombian regions. In three regions with exposures to glyphosate formulations from aerial spraying, blood samples were taken from the same individuals at three time points (before spraying base line, 5 days and 4 months after spraying) to determine the frequency of micronucleus formation in lymphocytes. The baseline frequency of bi-nucleated cells with micronuclei was significantly higher in subjects from the three regions sprayed with glyphosate formulations and in a fourth region with pesticide exposure but not through aerial spraying, compared with a reference region without pesticides being used. The frequency of micronuclei in peripheral blood lymphocytes was significantly increased compared with baseline level in the same individuals after aerial spraying with glyphosate based formulations in each of the three regions ($p=0.01$ to <0.001) [61].

A study published in 2015 (not included in the IARC report) assesses damage to the genetic material of children exposed to pesticides in the province of Córdoba by determining the frequency of micronuclei in the cells lining the inside of the mouth [62]. The researchers found that children living within 500 m of spraying areas have over 66 % more cells with micronuclei than those living more than 3 000 m away. In addition, 40 % of the exposed children suffer from persistent conditions that may be associated with chronic pesticide exposure including respiratory symptoms, with and without additional symptoms such as skin itching or stains, nose itching or bleeding, lacrimation, eye and ear burning or itching. This study highlights the extensive area (500 km) affected by aerial spraying.

In studies on human cells, glyphosate induced DNA strand breaks (measured by comet assay) in liver Hep-2 cells, lymphocytes, GM38 fibroblasts, HT1080 fibrosarcoma cell line, and TR146 buccal carcinoma cell line. DNA strand breaks were also induced by AMPA in Hep-2 cells, and by a glyphosate-based formulation in TR146 buccal carcinoma cell line. In human lymphocytes, AMPA but not glyphosate induced chromosomal aberrations. Glyphosate did not induce a concentration-dependent increase in micronucleus formation in human lymphocytes at levels estimated to correspond to occupational and residential exposure. Sister chromatid exchange was induced by glyphosate and a glyphosate-based formulation in human lymphocytes (reviewed in [10, p. 46]).

In mammalian model systems *in vivo* conflicting results were obtained for the genotoxicity of glyphosate and glyphosate formulation (reviewed in [10, pp. 46, 48]).

In contrast, the evidence of genotoxicity in non-mammalian organisms is very extensive (reviewed in [10, pp. 48, 51]). For fish strand breaks in comet assay was consistently observed in several species, sabalo, European eel, zebrafish, Nile tilapia. AMPA also induced DNA strand breaks in the comet assay in European eel. A glyphosate-based formulation produced DNA stand breaks in numerous fish species including European eel, sabalo, guppy, bloch, neotropical fish *Corydoras paleatus*, carp, and goldfish. AMPA induced erythocytic nuclear abnormalities in European eel, micronucleus formation by different glyphosate based formulations in various fish.

Glyphosate-based formulations induced DNA strand breaks in caiman, frog, tadpoles and snail, but not in oyster, clam and

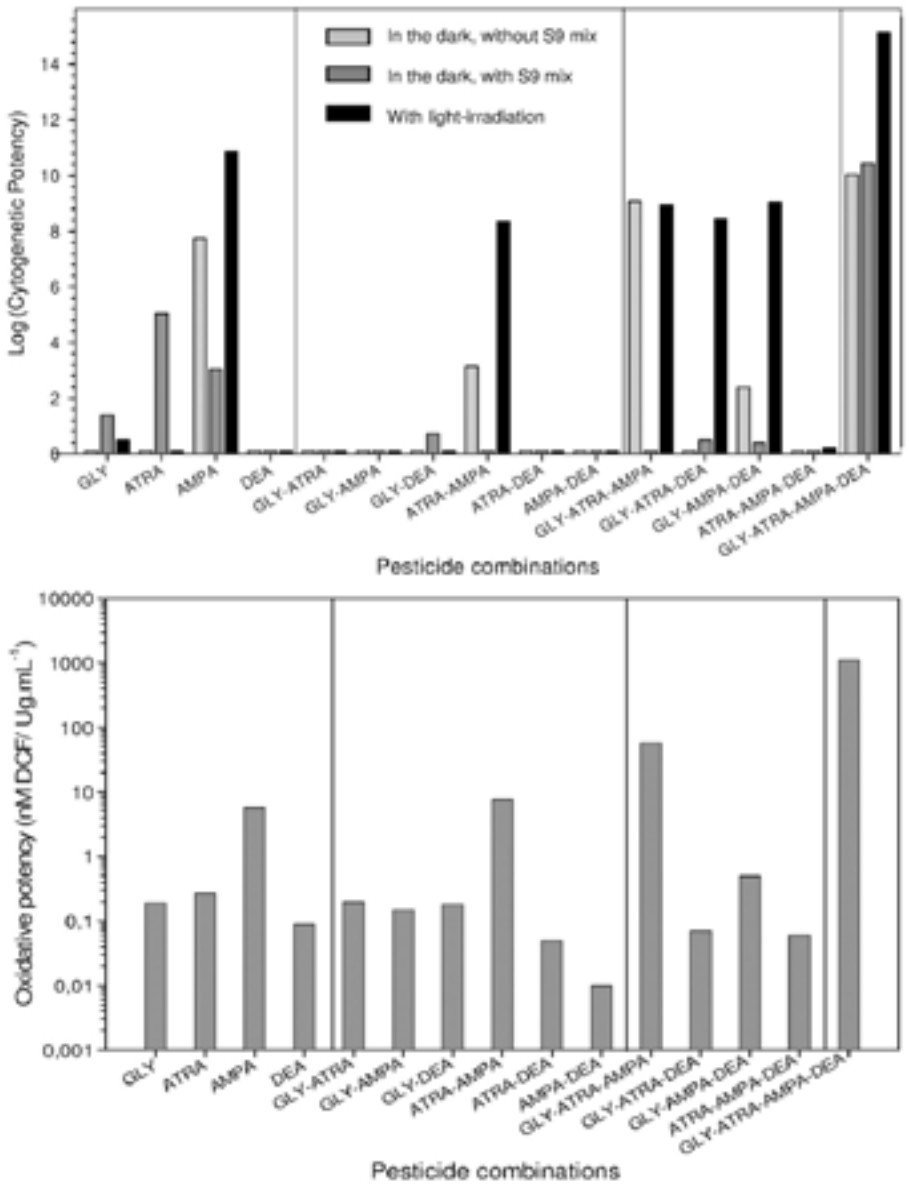


Figure 3 Cytogenetic potential (top) and oxidative potency (bottom) of pesticides and mixtures of pesticides

the mussel larva. In earthworms one glyphosate formulation induced DNA strand breaks while two others did not, highlighting the potential importance of components other than the active ingredient.

Micronucleus formation was induced by a glyphosate formulation in earthworms and by a different glyphosate formulation in caiman and frog.

In the standard *Drosophila melanogaster* test, glyphosate induced mutation, but not in a cross of flies characterized by an increased capacity for CYP450-dependent bio-activation. A glyphosate formulation also caused sex-linked recessive lethal mutations in *Drosophila*.

In plants, glyphosate produced DNA damage in Tradescantia (spiderwort) in comet assay. Chromosomal aberration was induced after glyphosate exposure in fenugreek and in onion in one study but not in another. A glyphosate formulation induced chromosomal aberration in barley roots and onion but not in *Crepis capillaris* (hawksbeard). Micronucleus formation was not induced by glyphosate in *Vicia faba* bean or by a glyphosate formulation in *Crepis capillaris*.

The results from non-human mammalian cells *in vitro* generally gave positive results for genotoxicity (see [10, p.48]). In the most recent publication reviewed, IARC has not fully described the results which are quite important, as they address non-additive, and potential synergistic effects of mixtures of pesticides, as would be encountered frequently in the environment. Researchers at Aix-Marseille Université in France investigated the genotoxicity of mixtures of glyphosate and atrazine (the world's top two herbicides) and their breakdown products AMPA and desethyl-atrazine (DEA) before and after photoactivation in hamster ovarian CHO K1 cells, in order to mimic real environmental conditions of exposure [63]. ROS (reactive oxygen species) were measured in the dark to assess oxidative stress, and micronucleus formation assayed for clastogenic (chromosomal abnormality) effect. They found that AMPA has a strong photo-inducible clastogenic effect, with MCC (minimal clastogenic concentration, the lowest concentration of pesticide that induced a significant increase of micronucleated cells) of 0.006 µg/mL in the dark, and 0.0004 µg/mL after light irradiation. Atrazine and glyphosate displayed cytogenetic activity only after metabolic activation, with MCC of 0.064 µg/mL and 5.8 µg/mL respectively. DEA was inactive in all experimental conditions. Surprisingly, combinations of two pesticides showed globally lower effects than those obtained with the most active individual compounds, AMPA and atrazine. Only atrazine+AMPA giving MCC of 0.39 µg/mL in the dark, and 0.0026 µg/mL after light stimulation and glyphosate+DEA giving MCC of 22.1 µg/mL after metabolic activation. In combinations of three pesticides, glyphosate+atrazine+AMPA gave a strong cytogenetic effect in the dark, with a MCC of 0.001 µg/mL; and all the combinations were activated by light. However, their cytogenetic potentials were close to AMPA, indicating weak synergistic effects. The mixture of 4 pesticides on the other hand exhibited a very powerful cytogenetic activity with MCC < 0.001 µg/mL under all experimental conditions. The MCC of 0.0004 µg/mL was 20-fold lower than that of AMPA in the dark, and at 0.0003 µg/mL, 200-fold lower than that of atrazine after metabolic activation. It was also strongly photo-stimulated, as the MCC was reduced by 100-fold by light to 4. 10^{-6} µg/mL.

The oxidative stress induced by the pesticides and pesticide mixtures measured in the dark showed that only AMPA gave an elevated oxidative effect, whereas the oxidative potencies of glyphosate, atrazine and DEA were very low. Among pesticide mixtures, atrazine+AMPA and glyphosate+atrazine+AMPA showed high oxidative potencies. But the mixture of all four exhibited the strongest oxidative potency of all. The results are summarized in Figure 3, where the Cytogenetic Potency (CP) is defined as the slope of the dose–response curves.

The results confirm that glyphosate, atrazine and AMPA have cytogenetic effects in mammalian cells; they show that mixtures

of pesticides could have enhanced synergistic effects, and that sunlight could greatly amplify those effects. The results also show that the most genotoxic pesticide mixtures induce the most oxidative stress in the cells, suggesting that oxidative stress (see below) could play an important role in genotoxicity.

Oxidative stress

There has been no study on oxidative stress in humans as the result of exposure to glyphosate. Glyphosate and/or its formulations as well as AMPA produce oxidative stress in human cells. Human keratinocyte cell line HaCaT showed signs of oxidative stress in several studies with glyphosate or glyphosate formulation that was relieved or prevented by antioxidants (reviewed in [10, p. 68]).

In a study on human liver carcinoma HepG2 cells at the City University of Buenos Aires, Argentina, the glyphosate formulation Roundup UltraMax, Monsanto produced a 40 % increase in reactive oxygen species at concentrations well below that of agricultural use (40 mg/L), but neither glyphosate nor AMPA did even at concentrations of 900 mg/L [64]. Moreover, the glyphosate formulation induces dose-dependent cytotoxicity with an estimated LC_{50} value of 41.22 mg/L for 24 h exposure, predominantly through a caspase-dependent apoptotic pathway. This shows the importance of 'inert' adjuvants in contributing to the toxicity of glyphosate, or in being toxic themselves, which have been ignored in risk assessment of pesticides so far. In another publication from the same research team using Hep2 cell line (originating from human laryngeal carcinoma), the LC_{50} of Atanor (glyphosate formulation), Impacto (spray adjuvant) and the mixture of both [65]. The results showed that all of the three induced dose and time-dependent cytotoxicity and the toxicity of Atanor and Impacto was additive. All of them also triggered the apoptosis pathway. Furthermore all of them produced an increase in catalase and glutathione levels (markers of oxidative stress), with increase in ROS production in cells treated with Atanor and the mixture.

In primary lymphocyte cultures and plasma obtained from healthy male non-smoking blood donors, oxidative DNA damage in lymphocytes and lipid peroxidation in plasma were both significantly increased at glyphosate concentration of 580 mg/L (~3.4 mM), but not at lower concentrations [66]. In human erythrocytes isolated from healthy donors, production of reactive oxygen species was increased by glyphosate (> 0.25 mM), AMPA (> 0.25 mM), and N-methylglyphosate (> 0. 5 mM) [67].

Most studies of oxidative stress in mammals were conducted in rats and mice. It was found that glyphosate induced production of free radicals and oxidative stress in mouse and rat tissues through alteration of antioxidant enzyme activity, depletion of glutathione and increases in lipid peroxidation (reviewed in [10, p. 69]).

Positive associations between glyphosate and oxidative stress were reported in aquatic organisms; consistently presenting evidence that glyphosate can cause oxidative stress in fish. Similar effects were found in tadpoles and pacific oyster exposed to a pesticide mixture containing glyphosate (reviewed in [10, p. 70]).

The single study on mammalian cells [63] has been described in detail at the end the previous section.

To conclude

The WHO IARC reclassified glyphosate as 'probable carcinogen' based on 'limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals', supported by strong evidence that glyphosate and glyphosate formulations are genotoxic, and strong evidence that glyphosate and its metabolite AMPA, and glyphosate formulations cause oxidative stress; both oxidative stress and genotoxicity being key characteristics of carcinogens.

Regarding carcinogenicity in humans, we have reviewed the main evidence presented in the glyphosate part of the IARC Monograph 112 [10], which showed that glyphosate exposure is associated with increased risk of non-Hodgkin's lymphoma from several large epidemiological studies as well as smaller studies, and single studies have found non-significant RRs or ORs for glyphosate exposure and several cancer sites. In addition, we have presented further relevant evidence from the formal scientific literature as well as reports from non-government organizations.

First, glyphosate use has gone up rapidly and enormously worldwide especially since glyphosate-tolerant genetically modified crops were introduced. The global glyphosate market demand in 2012 was 718 600 tonnes [34], with GM crops accounting for 45.2 % of the total demand, and glyphosate for ~25 % of the global pesticide market [35]. Glyphosate and its residues have heavily contaminated air, soil, and water worldwide, constituting a major increase in pesticide burden on public health. It is to be found not only generally in human and livestock urine through exposure in food and feed (as well as in drinking water, and through inhalation from the air and absorption through the skin), but also in all livestock tissues tested and in mother's milk, contradicting all the claims of the manufacturer that glyphosate does not accumulate in soil or leach into water, and that it does not bio-accumulate in tissues.

Second, although no post-market health monitoring has been done for either GM crops or glyphosate, it is significant that US government data show a marked deterioration of public health, with increase in incidence of 22 diseases *including 6 cancers* – liver, thyroid, bladder, pancreas, kidney and myeloid leukaemia - closely tracking the increase in GM crops planted and glyphosate used in the country [8]. For 22 diseases, the Pearson correlation coefficients were calculated between incidence and % GM crops and between incidence and glyphosate usage. Most of the 44 coefficients are greater than 0.91, with none of them falling below 0.81, and those for incidence of cancers and glyphosate use among the highest.

Similarly, In Argentina, where the use of pesticides including especially glyphosate herbicides has increased more than 8.5-fold since GM crops were introduced 20 years ago (Chapter 3), physicians and local governments have been documenting rapid increases in birth defects and cancers for years. An official report from the province of Chaco recorded a 4.5-fold increase in the incidence of birth defects over 12 years, from 19.1 /10 000 in 1997 to 28.1 /10 000 in 2001 and 85.3/ 10 000 in 2009 [42]. Also, the incidence of childhood cancer almost doubled from 8.03/ 100 000 in 1991 to 11.2/100 000 in 2001 and 15.7/100 000 in 2007. A second report released by the Ministry of Health in Córdoba shows the highest rates of deaths from tumours occur in areas where GM crops and agro-chemicals are used, and they are almost double the national average [43].

Finally, a study in an animal model that includes proteomic analysis suggests that a glyphosate formulation can promote cancer in a similar way to a known cancer promoter [50], while studies in human cells show that glyphosate at minute concentrations can promote the growth of oestrogen dependent breast cancer cells [58], and at much higher concentrations promotes growth

of cancer cells by a hormone independent mechanism [57].

With regard to animal experiments, we have reviewed the long-term feeding studies assessed by the IARC that showed positive results for cancers. These include an experiment submitted to the EPA on male and female mice showing a significant increase in carcinoma of the renal tubule as well as significant increase in combined carcinoma and adenoma of the renal tubule in male mice. A second experiment on mice submitted to Joint FAO/WHO Meeting on Pesticide Residues (JMPR) found a significant increase in the incidence of haemangiosarcoma as well as a non-significant increase in the incidence of histiocytic sarcoma in the lymphoreticular/haemopoietic tissues in males. An experiment on rats submitted to the EPA found a significant increase in the incidence of pancreatic islet cell adenoma compared with controls in males at both the lowest and highest doses. There was also a statistically significant positive trend in the incidence of hepatocellular adenoma in males and of thyroid follicular cell adenoma in females. A second experiment on rats submitted to the EPA also found an increase in the incidence of pancreatic islet cell adenoma in all dosed males, which was statistically significant at the lowest dose.

The experiment on cancer promotion in mice skin [59] has been mentioned above.

In addition, we have drawn attention to a review on glyphosate toxicity published in 1995 [51], which showed how the EPA dismissed successive animal studies (including one that was not assessed by IARC showing testicular tumours in dosed male animals), finally resulting in altering the original classification of glyphosate as 'possible carcinogen' to 'noncarcinogenic' in 1993, against the advice of its own scientists, as documented in memos from the EPA archives. This misclassification has been largely responsible for two decades of people and planet being subjected to chronic glyphosate exposures in allowing the manufacturer to claim glyphosate 'safe', and perpetrating many other falsehoods in promoting its ubiquitous and liberal use.

There is copious evidence on the genotoxicity of glyphosate and glyphosate formulations in human cells *in vivo* and *in vitro*, and non-mammalian organisms *in vivo*. There have been no studies on oxidative stress in human cells *in vivo* as the result of exposure to glyphosate. Many studies showed that glyphosate and/or its formulations as well as AMPA produce oxidative stress in human cells, in mammalian models, as well as various species of fish and other aquatic organisms.

We have added a study published in 2015 (not included in the IARC report), which found that children living within 500 m of spraying areas have over 66 % more cells with micronuclei in in the cells lining the inside of the mouth than those living more than 3 000 m away [62], and 40 % of the exposed children suffer from persistent conditions that may be associated with chronic pesticide exposure. This study highlights the extensive area (500 km) affected by aerial spraying.

Further, we have elaborated on a published study dealing with an aspect ignored in the IARC report, i.e., synergistic effects of mixtures of herbicides most likely to be encountered in the environment. The study investigated the genotoxicity of mixtures of glyphosate and atrazine (the world's top two herbicides) and their breakdown products AMPA and desethyl-atrazine (DEA) before and after photoactivation in hamster ovarian CHO K1 cells [63]. It found that the mixture of 4 pesticides exhibited a very powerful genotoxic activity 20 times that of AMPA (the most genotoxic agent) and 200-fold that of atrazine after metabolic activation, and which was further enhanced 100-fold by light. The genotoxicity of the herbicides and mixtures was accompanied by corresponding level of oxidative stress induced.

We suggest that the additional evidence – had it been taken into proper account – would have been sufficient to classify glyphosate as definitely carcinogenic.

It should be noted that chronic exposure to glyphosate herbicides is associated not only with cancers, but also with infertility, impotence, abortions, birth defects, neurotoxicity, hormonal disruption, immune reactions, an unnamed fatal kidney disease, chronic diarrhoea, autism and other ailments. In addition to human diseases, glyphosate herbicides are linked to more than 40 new and re-emerging major crop diseases. They are causing irreparable harm to the entire food web; including the plant kingdom, beneficial microbes that supply nutrients to our crops and soils, fish and other aquatic life, amphibians, butterflies, bees, birds, mammals, and the human microbiome (reviewed in Chapter 1). Indeed, there is a strong case for a worldwide ban on glyphosate.

Total bans on glyphosate are already in place or announced in El Salvador, Bermuda, and Sri Lanka, and proposed in other countries; while a number of partial bans have also been imposed including a ban on aerial spraying in Columbia (see [68] Fallout from WHO Classification of Glyphosate as Probable Carcinogen, *SiS* 67). The Californian EPA announces it plans to label glyphosate "known to cause cancer" [69]. We need to stop the devastation of people and planet that has gone on for the past 20 years by halting the use of glyphosate and shifting comprehensively to sustainable, organic non-GM agriculture [70] (Food futures now, organic, sustainable and fossil fuel free, ISIS/TWN special report) already shown to be the most effective way to feed the world with healthy uncontaminated food, and to mitigate and adapt to climate change.

6

Sri Lanka Bans Glyphosate for Deadly Kidney Disease Epidemic

Glyphosate's metal-chelating activity causes bioaccumulation of toxic metals in the body, resulting in an estimated 400 000 cases in Sri Lanka and 20 000 deaths

Dr Eva Sirinathsinghji

Sri Lankan Rice Paddy, photo James manners, Flickr

Sri Lanka has banned importation of glyphosate with immediate effect. This decision is prompted by the spread of fatal kidney disease afflicting farmers across the country. The move comes following the WHO declaration of glyphosate as a probable carcinogen, but is the result of a longer standing battle to halt the epidemic that has already claimed an estimated 20 000 lives.

In 2014, a study published by Sri Lankan researchers linked the chemical to the chronic kidney disease. A complete ban was initially proposed [1], but due to plantation sector representatives claiming a shortage of agricultural workers and could not sufficiently manage weeds without glyphosate, the government at first limited the ban to disease endemic areas [2] but then totally reversed the ban due to pressure from industry. December 2014 saw another partial ban put in place for the Northern provinces though enforcement remained murky until the most recent total ban was announced in the wake of the WHO classification, to take effect immediately from May 2015 [3, 4].

Similar kidney problems have been documented in other global regions, prompting an earlier complete ban of glyphosate by El Salvador in 2013, but has yet to be written into law [5].Even Brazil, one of the largest growers of glyphosate-tolerant genetically modified (GM) crops has now filed a law suit by Federal Prosecutors to ban glyphosate along with 8 other dangerous pesticides [6]. It is becoming increasingly difficult for government regulators and glyphosate producers to justify the use of this herbicide when other nations are banning the chemical outright in order to protect their citizens.

Glyphosate can impact human health in a number of ways, one of which is through its potent metal chelating abilities. Indeed, glyphosate was originally patented by Stauffer Chemical Co. in 1964 (U.S. Patent No. 3,160,632) [7] for this very function. Chelating mineral ions can lead to nutritional depletion in

Starting in the mid-1990s, this Chronic Kidney Disease of unknown aetiology (CKDu) was discovered among the rice paddy farmers in the North Central Province (NCP) of Sri Lanka. Over the next two decades, the disease spread rapidly to the other farming areas. The prevalence of the disease is estimated at 15 % [10] affecting a total of 400 000 patients with an estimated death toll of around 20 000

plants and animals, which has already been shown to cause health problems in both. In the case of this kidney disease epidemic, its chelation of metals such as arsenic in the water supplies is now thought to lead to their bioaccumulation in the body, resulting in kidney failure and even death, as proposed in a new study [8] by Channa Jayasumana (Rajarata University, Sri Lanka), Sarath Gunatilake (California State University, USA) and Priyantha Senanayake (Hela Suwaya Organization, Sri Lanka) published in *the International Journal of Environmental Research and Public Health*. The theory has been validated by the researchers' follow-up publications finding CDKu to be positively associated with spraying glyphosate (5.12 fold increased risk), drinking from wells (2.52 fold increased risk) and even worse, from abandoned wells (4.69 fold increased risk); being male (4.69 fold increase risk versus women) [9], and a significantly higher level of glyphosate and heavy metals in CKDu patients compared to controls [10]. Glyphosate has also been linked to many other health problems including cancers (see Chapter 5), infertility (see Chapter 4), along with neurotoxicity, reproductive problems, birth defects, and other problems (see Chapter 1).

Starting in the mid-1990s, this Chronic Kidney Disease of unknown aetiology (CKDu) was discovered among the rice paddy farmers in the North Central Province (NCP) of Sri Lanka. Over the next two decades, the disease spread rapidly to the other farming areas. The prevalence of the disease is estimated at 15 % [11] affecting a total of 400 000 patients with an estimated death toll of around 20 000 [12]. The Sri Lankan Ministry of Health have since defined CKDu with the following criteria:

(1) No past history of, or current treatment for diabetes mellitus or chronic and/or severe hypertension, snake bites, urological disease of known aetiology or glomerulonephritis.

(2) Normal glycosylated haemoglobin levels (HbA1C < 6.5%).

(3) Blood pressure <160/100 mmHg untreated or <140/90 mmHg on up to two antihypertensive agents.

The disease seems to progress slowly, with tubular interstitial nephritis (inflammation of the spaces between renal tubules) associated with mononuclear cell infiltration (infiltration of immune cells – indicative of inflammatory lesions), glomerular sclerosis (hardening or scarring of the renal glomeruli) and tubular atrophy [13]. It is further characterized by tubular proteinurea (excess, unabsorbed protein buildup), usually alpha-1 and beta-2 microglobulinuria proteins, and high urine Neutrophil Gelatinase-associated lipocalin (NGal) levels (>300 ng/mg creatinine).

CKDu previously linked to hard water, arsenic and unidentified pesticides

Different groups including members of the World Health Organisation have already researched the disease and acknowledged a multifactorial cause, with the main causative factors being exposure to arsenic, cadmium and pesticides. Consumption of hard water, low water intake and exposure to high temperatures resulting in significant dehydration, are among the other factors.

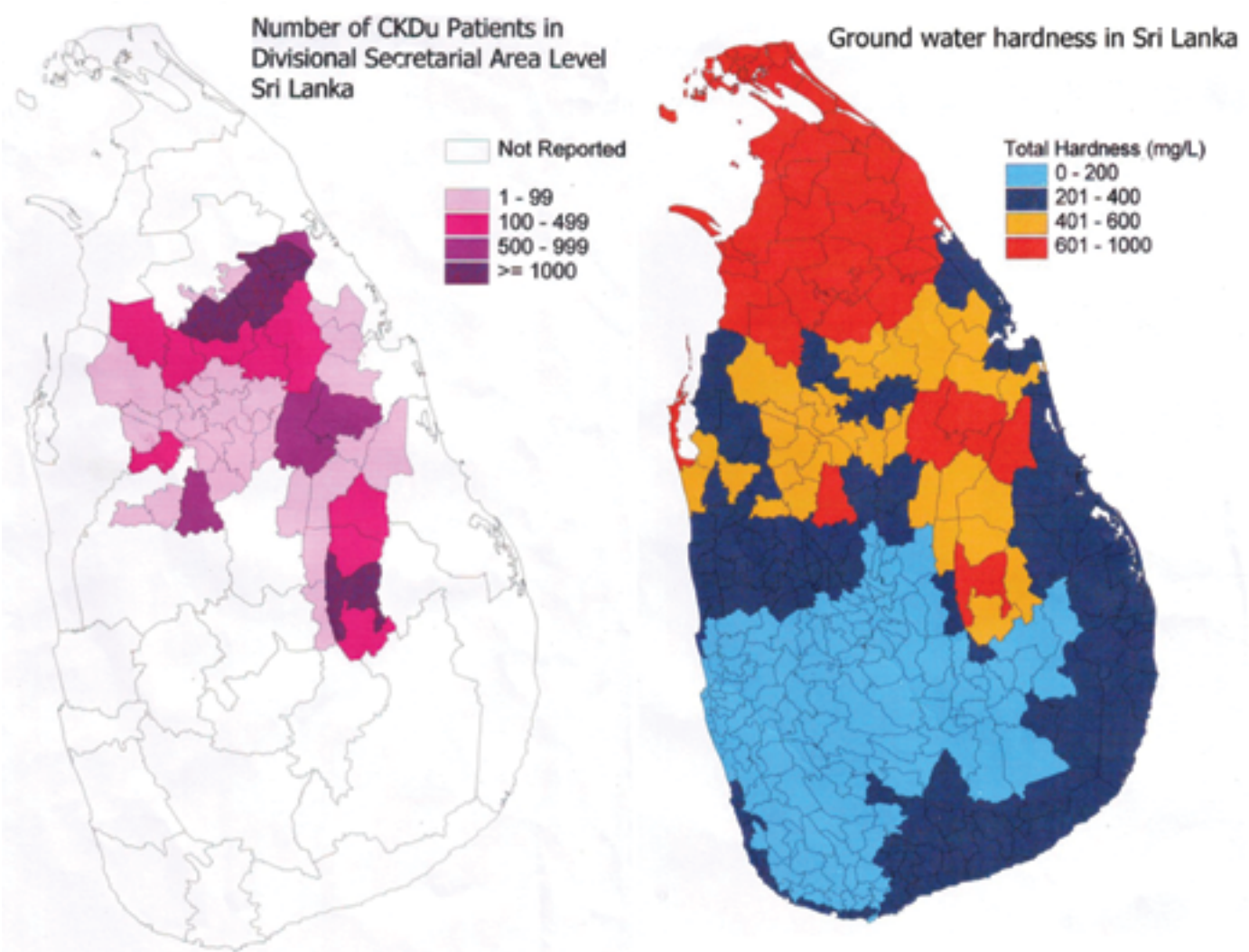


Figure 1 Map of Sri Lanka correlating prevalence of CKDu disease by region (left), with regions of hard or very hard water

However, as the authors of the new study state, "whatever hypothesis that is propounded should be able to answer the questions as to why CKDu is confined to certain geographical areas of Sri Lanka and why there was no CKDu in Sri Lanka prior to the 1990s."

The authors first present a well-documented, statistically significant correlation between water hardness and CKDu. Ninety six percent of the CKDu patients had consumed hard or very hard water for at least five years, which is also clearly illustrated by the maps of Sri Lankan regions showing those most affected by the disease to reside in hard water regions (see Figure 1). They also noted further observations in the affected regions:

(a) The number of villagers who complain that the ground water hardness in CKDu endemic area has increased steadily over the last two decades.

(b) Certain shallow wells (2–5 m), previously used for drinking purposes are now abandoned due to high hardness and bad taste.

(c) There are a few natural springs located in the CKDu endemic area where water is not hard. People who consume water from these sources have been determined to be free from the disease.

(d) Individuals who drink treated water from large water supply schemes (especially in the two cities of Anuradhapura and Polonnaruwa), while living in the same endemic areas, do not have the disease.

(e) In the adjoining farming areas of the Northern Province of Sri Lanka, where the ground water hardness level is known also to be hard or very hard, there have not been any significant number of CKDu cases reported.

Previous evidence has shown that CKDu patients accumulated arsenic in their bodies, with toxic levels of arsenic in urine, hair and nail samples, while healthy people in CKDu endemic regions also show signs of high arsenic levels, suggesting that hard water is linked to CKDu onset [12]. It has been further suggested that the arsenic originates from tainted agrochemicals including pesticides and fertilizers, though the source has not yet been fully determined.

CKDu caused by 'compound X' – now discovered to be glyphosate

The study reveals that a previously unknown factor, referred to by the authors as 'compound X', originates from agrochemicals and that compound X, when combined with hard water containing toxic levels of calcium and magnesium, causes serious kidney damage. In support of the hypothesis that compound X derives from agrochemicals and is indeed glyphosate, are the observations that CKDu emerged in the 1990s, which fits with the massive influx of agrochemicals in Sri Lanka since the 1970s following changes in economic policies. Further, low concentrations can lead to bioaccumulation of a toxic substance, which would explain the 12-15 year lag time before symptoms emerge. This coincides with the shifting age of patients, with prevalence of disease increasing in younger people in recent years, suggesting a cumulative nature of the toxin. In addition, regions of Sri Lanka that have restricted agrochemical use, as in the North where the concern of political, violent conflict meant that governments wanted to prevent people from using agrochemicals to make explosives, high levels of CKDu do not exist. These areas also have

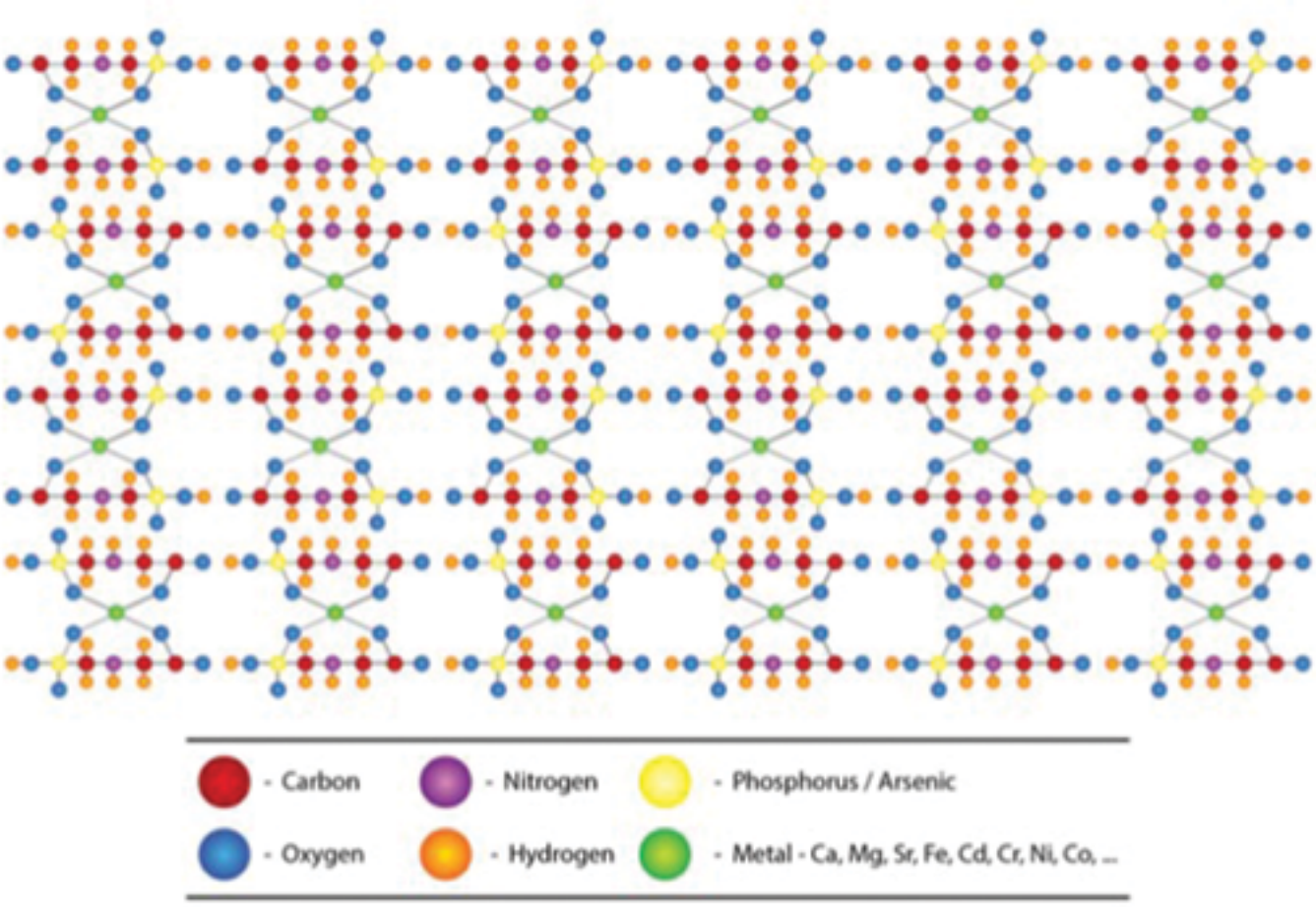


Figure 2 Proposed glyphosate/heavy metal lattice structure

Glyphosate alone has also been shown in numerous studies to cause kidney toxicity. Nile tilapia exposed to glyphosate show changes in proximal tubular cells. Exposed juvenile African catfish develop haematopoietic cell death and kidney histopathological changes including dilatation of Bowman's space (a region of the kidney involved in the first filtration of the blood to form urine) as well as degenerated tubules. Mammalian studies found increased serum creatinine, blood urea and reduced kidney weight of rats fed with glyphosate exposed maize. Oral exposure increases blood urea levels and leads to renal dysfunction in rats and dairy cows

hard water, showing that hard water alone is not sufficient to cause CKDu. The authors used these observations to describe the expected properties of compound X listed below:
(a) A compound made of recently (2–3 decades) introduced chemicals to the CKDu endemic area
(b) Ability to form stable complexes with hard water
(c) Ability to capture and retain arsenic and nephrotoxic metals and act as a "carrier" in delivering these toxins to the kidney
(d) Possible multiple routes of exposure: ingestion, dermal and respiratory absorption.
(e) Not having a significant first pass effect when complexed with hard water (a phenomenon of drug metabolism, usually by the liver, whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation)
(f) Presenting difficulties in identification when using conventional analytical methods.

Glyphosate is further implicated by the fact that it is by far the most commonly used herbicide in Sri Lanka, with quantities of glyphosate use exceeding all other pesticides combined.

Glyphosate forms metal complexes that bioaccumulate in the body

Glyphosate was first used as a descaling agent to clean out calcium and other mineral deposits from pipes and boilers, aided by the chemical's high water solubility. Descaling agents bind to metals, making them water soluble and removable. Its stability in water depends on a number of factors, including phosphate which competes with glyphosate for soil absorption. Further, its binding to metals can result in strong complexes that affect its biodegradability, with glyphosate degradation time increasing to 7-22 years depending on pH. In water above pH 6.5, glyphosate turns into a dianion (an anion with a -2 negative charge), suggesting it forms metal complexes in alkaline conditions, increasing its solubility and thus leaching deep into soils [14, 15]. Alkaline conditions are known to reduce the weed killing capacity of glyphosate, as glyphosate-metal complexes are stable in basic but not acidic conditions. The effects of pH are also important in understanding the stability of the lattice structure in the acidic conditions of the kidney, as will be explained below.

Studies using nuclear magnetic resonance (NMR) techniques shows that glyphosate interacts with calcium, magnesium and other metals, and that the resulting complexes become more stable with time [16, 17]. Further, the paddy farming soil in regions endemic for CKDu are rich in metals including calcium, magnesium, iron, nickel, chromium and cobalt. Ferric irons alter soil absorption of glyphosate and its metabolite, AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). This problem is confounded by the application of triple phosphate (TSP) fertiliser to paddy fields, which have been found contaminated with certain metal ions as well as high levels of arsenic. This leaves people highly vulnerable from exposure to stable, toxic glyphosate-metal complexes in drinking water. Glyphosate exposure also occurs through the skin; farmers are found to have glyphosate in urine following spraying. Glyphosate can mix with sweat in hot and humid climates before being absorbed through the skin. Further, Sri Lankan farmers do not often wear protective gear to prevent respiratory exposure. Arsenic and cadmium also commonly contaminate rice, vegetables and tobacco leaves which are often chewed along with betel leaves by Sri Lankans. This transdermal and respiratory exposure therefore provides an additional opportunity for glyphosate to bind to nephrotoxic metals consumed in foods and bioaccumulate in the body.

Based on previously published studies on how glyphosate forms metal complexes and matrices [14-17], the authors propose the formation of stable glyphosate metal lattices, which can explain how glyphosate, hard water, arsenic and other nephrotoxic metals cause kidney disease in Sri Lanka. This proposed glyphosate metal lattice, depicted in Figure 2, is based on previous NMR studies showing the ability of hard water ions to bind to both the phosphonate and carboxyl functional groups of the glyphosate molecule to form complexes.

It is worth noting that glyphosate's causative role in CKDu has previously eluded researchers due to its chemical properties including its ionic character, high polarity, high solubility in water, low volatility, insolubility in organic solvents and strong complexion behaviour, which make it very difficult to detect in the lab.

Mechanism of glyphosate's role in kidney disease

The glyphosate metal lattice hypothesis is supported by the observation that people who drink natural spring water do not suffer the disease, with these waters being devoid of magnesium and calcium, making the water unable to retain glyphosate. It also explains why regions with hard water but low levels of herbicide and chemical fertilizer are free of CKDu. Further, CKDu patients show accumulation of metals (As and Cd) in the hair and nail samples, but low levels of urinary excretion of metals (compared

Rice at Market in Sri Lanka, photo 4Neus, Flickr

with control subjects in the same regions), suggesting that the kidney is unable to properly rid these chemicals from the body. Urine from controls as well as CKDu patients in endemic areas also show the presence of glyphosate and heavy metals, indicative of the glyphosate metal lattice accumulated in their bodies. Evidence from El Salvador similarly points to toxic heavy metals as a culprit in the disease that largely affects poor, agricultural workers.

The glyphosate-metal lattice is thought to accumulate in the kidney where acidic conditions from the breakdown of ammonia cause the breakdown of the lattice. Ammonium sulphate is already used by agriculturalists as a buffer to release glyphosate from metal ions in hard water conditions, suggesting that the same mechanism may underlie the effects seen in the kidney proximal tubules in CKDu patients. The lattice breakdown can then release glyphosate and its metabolite AMPA as well arsenic, which may damage the glomeruli. Other heavy metals can be partially reabsorbed by the kidneys resulting in further tubular damage. Nephrotoxicity of heavy metals is already well known, with long-term exposure causing oxidative stress, nitrosative stress (cell damage caused by reactive nitrogen oxygen species acting together with reactive oxygen species), apoptosis and necrosis in the glomerular and proximal tubular cells [18-20]. Glomerular sclerosis (hardening and inflammation of the kidneys), glomerular collapse and tubular interstitial damage are the result of these pathological mechanisms. Glyphosate alone has also been shown in numerous studies to cause kidney toxicity. Nile tilapia exposed to glyphosate show changes in proximal tubular cells [21]. Exposed juvenile African catfish develop haematopoietic cell death and kidney histopathological changes including dilatation of Bowman's space (a region of the kidney involved in the first filtration of the blood to form urine) as well as degenerated tubules [22]. Mammalian studies found increased serum creatinine, blood urea and reduced kidney weight of rats fed with glyphosate exposed maize [23]. Oral exposure increases blood urea levels and leads to renal dysfunction in rats [24] and dairy cows [25].

Studies on the effects of glyphosate and hard water metals combined would provide crucial insight into this hypothesis, though there is no publication on this matter despite the known association of glyphosate with such metals.

Previously described alternative pathways of glyphosate-induced kidney damage

Other studies have noted alternative mechanisms whereby glyphosate can cause kidney damage. Indeed, glyphosate can induce toxicity through a number of mechanisms including the disruption of cytochrome P450 and aromatase pathways that may be responsible for the genotoxic and teratogenic effects seen under glyphosate exposure. A recent review [26] explains how glyphosate has been patented as an antibiotic and shown to kill beneficial gut bacteria in poultry, leading to dysbiosis (microbial imbalance). This may go on to promote the growth of pathogenic bacteria such *Clostridium difficile*, which produce excessive amounts of p-Cresol sulphate, a toxic phenol associated with chronic kidney disease and can induce activation of inflammatory cytokines and chemokines, with inflammation playing a key role in kidney disease.

Glyphosate also induces a switch from aerobic to anaerobic respiration in *E. coli* and other gut bacterial species, causing the increased production of indole, a derivative of the aromatic amino acid tryptophan, the breakdown of which also requires cytochrome P450. Tryptophan, an aromatic amino acid produced by the shikimate pathway that glyphosate inhibits, contains an indole ring. Therefore, disruption of tryptophan synthesis by gut microbes may well lead to the accumulation of indole in the body. Indole is an important signalling molecule for many bacteria, and along with p-Cresol, is associated with kidney disease.

To conclude

National governments are beginning to take long overdue steps to protect their citizens from glyphosate, the most commonly used herbicide in the world. Its links to diseases in humans, crops, and livestock can no longer be ignored. Other governments need to follow the examples of El Salvador and Sri Lanka in protecting their citizens from a highly toxic chemical.

7

Changing from GMO to Non-GMO Natural Soy, Farming Experiences from Denmark

Healthier, more productive pigs, more profit, and much less birth deformities; an important lesson for all farmers not to use GMO feed or glyphosate on their land

Ib Borup Pederson

I want to tell you what I have seen on my farm and about the on-farm and lab investigations carried out in collaboration with Professor Monika Krüger and other scientists.

My farm "Pilegaarden" (Willow Farm) is an average Danish farm in the small village of Hvidsten. Our pigs are raised according-ly to United Kingdom regulations for pig housing, and exported to the UK for consumption. Inside the pig farm is a straw-based system for the sows as well as a standard farrowing house.

Healthier, more productive sows, less medication, more piglets and much more profit

I had read about the effects that GM feed has on rats in lab experiments (see [1] GM Soya Fed Rats: Stunted, Dead, or Sterile, *SiS* 33), so I decided to change the feed from GM to non-GM soy in April 2011 without telling the herdsman on the farm. Two days afterwards, he said to me: "You have changed the food." He always notices whenever there is any problem with the feed and tells me. This time was different. Something very good was happening with the food as the pigs were not getting diarrhoea any more. The farm was saving 2/3 of the medicine or £7.88 per sow; not just my farm but three other farms in Denmark that switched from GMO to non GMO feed have also seen the same. Medication after the changeover in the weaners barn also went down dra-matically by 66 %, with one type of antibiotics not being used since.

"Pilegaarden" (Willow Farm)

The sows have higher milk production; we can tell because the sows are suckling 1, 2 or 3 more piglets and have more live born pigs, on average 1.8 piglets more per sow. They wean 1,8 pigs more per litter, and have more live born pigs. We have seen a certain aggressive diarrhoea disappear altogether that affected young piglets in the first week of life, killing up to 30 % of the pigs. It has completely gone for over 3 years. Sows no longer suffer from bloating or ulcers and they also live longer in high production, only dropping in effectivity after 8 layers compared to 6 on GM soy.

So, a change to non-GM soy makes the herd easier to manage, improves the health of the herd, reduces medicine usage, increases production and is very profitable.

Severe birth deformities in piglets

Deformities in the pigs used to be very rare and I used to be proud to send Siamese twins to schools for classes because it would only happen one in a million. But then they became too frequent. So I read a lot on the subject and my suspicion fell on glyphosate. I read how glyphosate had been shown in scientific studies (see [2] Lab Study Establishes Glyphosate Link to Birth Defects, *SiS* 48, [3]) to cause deformities and noted it was the same type of deformities that I was seeing in my pigs, and the same as those found in anencephaly babies in Washington counties in US [4] that Don Huber talked about as well as the birth defects in Argentina [5, 6] (Argentina's Roundup Human Tragedy , *SiS* 48) as described by Dr Medardo Ávila-Vázquez where high levels of glyphosate are used. I had looked at studies showing that a 2-day exposure to 3.07 mg/l glyphosate herbicide caused only 10 % mortality but caused malformations in 55 % of test animals [7]. A toxicological study in 2003 led by Dr Dallegrave [8] found bone abnormalities, absence of bones or parts of bones, shortened and bent bones, asymmetry, fusions, and clefts in rats. So, after this I began to list all the deformities I saw in my pigs.

I decided to be on the safe side, by listing the clear deformities that cannot be missed, like a back that is totally kinked over (see Box 1). I have pictures of all the deformed piglets, which are born alive in most cases. One had a 180° bend in one of its vertebra. There were also deformities in the soft tissue, and one without an anus. One had kidney problems; another had its stomach outside the body. One had a cranial deformity, with no eyes and its brain outside the head; this is very typical. One had no cranium at all. Some are even messier. There was a piglet with only one eye, and one completely headless. There was a little nose, but it had no bones to grow on so it probably would have died just after birth. We also started counting deformities of the tail, which are never fatal but are actually spinal deformities.

Box 1

Type of deformities seen

Cranial	Tail	Stomach
Spinal	Kidneys	Ears
Limbs	Misplaced sex organ	Eye
Dual sex	Motor problems	Feet
No rectum	Tongue	

So, a change to non-GM soy makes the herd easier to manage, improves the health of the herd, reduces medicine usage, increases production and is very profitable

Box 2

Glyphosate detected in malformed piglets [9]

A total of 38 deformed Danish one-day old piglets were euthanized and the tissues analysed for glyphosate using ELISA (enzyme-linked immunosorbent assay). All organs or tissues had glyphosate in different concentrations. The highest concentrations were seen in the lungs ((0.4-80 µg/ml) and heart (0.15-80 µg/ml); the lowest in muscles (4.4-6.4 µg/g).

Rate of malformation increased to one out of 260 born piglets if sow feeds contain 0.87-1.13 ppm glyphosate in the first 40 days of pregnancy. In case of 0.25 ppm glyphosate one out of 1 432 piglets was malformed. These piglets showed different abnormalities as ear atrophy, spinal and cranial deformations, cranium hole in head and leg atrophy; in one piglet only a single large eye developed. Piglets without trunk, with elephant tongue, and female piglet with testes were also present. One malformed piglet showed a swollen belly and fore gut and hind gut were not connected.

The researchers note: "Further investigations are urgently needed to prove or exclude glyphosate in malformations in piglets and other animals."

I sent the deformed piglets to Germany to be analysed by Professor Krüger at Leipzig University. She opened them up and took the organs including the lungs, liver, kidneys, muscles, nervous system, intestines and heart; and she found glyphosate in all of the organs (see Box). You can see some of the piglets in the scientific paper I published with Krüger and other scientists [9].

Teratogenic dose much lower than the regulatory allowed dose

In addition to these experiments, I had over 30 000 piglets born over 2 years and therefore have statistical data that are not easily available in the lab and this is where farmers have the ideal opportunity to do their own testing. I tested the food, the foetuses, the urine and the grains that came into the farm. To do the tests, take representing samples from the batches of food, mix them, and take 100 grams in a plastic bag of each to be tested, or 100 ml of liquids. When taking muck and urine for testing, you need patience; blood tests can be done by a vet. Send it for analyses to a lab that has the facilities to test glyphosate down to about 0.1ppb = 0.1 milligram per tonne. If tests are only detecting at above 0.1ppm = 0.1 grams per ton, it cannot show you what is in urine and muck. It costs about £30-50 for one test. Tests in oils might not be possible; you need to ask beforehand.

The results of the tests showed that with 0.06 mg/kg of glyphosate residue in the feed - much lower than the allowed 20 mg/kg - I was getting cranial and spinal deformities after 2 months of feeding (see Figure 1). At 0.1 mg/kg I was also getting deformities, but not many so that one pig could alter the numbers. But, at 0.2 mg/kg the deformities start to go up. At the maximum of 2.26 mg/kg the numbers start to get very high.

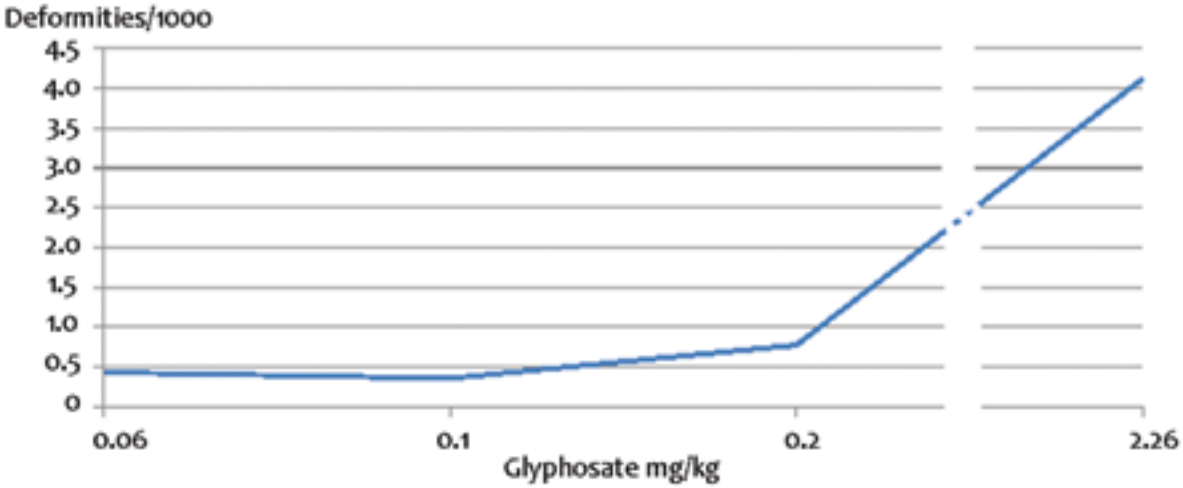


Figure 1 Rates of cranial and spinal deformities in pigs fed increasing levels of glyphosate in feed

I also got help from Dr Thomas Böhn from Norway who told me to look at longer intervals. We got numbers after 6 months to see an accumulative effect. The story is exactly the same. There is a very clear difference between low and high levels of glyphosate. We also looked at the numbers of pigs born, which was significantly less after eating food with higher levels of glyphosate (see Figure 2) with a significant difference of 1 less pig born per sow between low levels of glyphosate in feed accumulative intake over a 35 days period (<3 mg/kg body weight) and high levels (3-9 mg/kg body weight), consumed just in the last 5 weeks of pregnancy. So we have less born as well as the odd ones that are deformed.

In short, the differences we saw with having 5 times difference in glyphosate levels from 0.2 to 1 part per million (ppm) was a 5 times increase in cranial and spinal deformities at birth, as well as 5 times more abortions as well as 0.95 less piglets born per litter.

Glyphosate has known toxicities down to extremely low concentrations

We can also relate the actual levels of glyphosate in feed to the level in the urine. So for 1 132 ppb (or 1.13 ppm), there is 44 ppb (~4 %) in the urine and 246.33 ppb (~22 %) in dung. When I tested my own urine, I found that I had 2.58 ppb and that is not from eating GM contaminated feed but from eating normal food from the Danish shops. This is already at the level of higher rates of abortions and deformities and probably also fertility problems. Is this why in the Western world we have a very big problem with fertility (see Chapter 4)? And at 1000 ppb, glyphosate is patented by Monsanto as an antibiotic, actually killing the beneficial microorganisms. At 0.1 ppb (less than 1/25 the level measured in my urine) Roundup caused tumours in 80% of rats compared to 20 % in the controls [10], which only developed them at 700 days. To have that high level of glyphosate in my urine, I must have consumed at the level of about 0.2ppm or 2000 times more than the test rats. So what does that mean for the rates of cancer (see Chapter 5)?

I have a short film about how it is to be a farmer, I always feel very bad about my pigs getting ill so I leave the film for people to see. These same things must be happening in Chinese farms also, as they are using the same feed as I used to. Even non-GM soya contains glyphosate and we as farmers need to demand that it is not sprayed down with glyphosate because it can affect people as well as pigs.

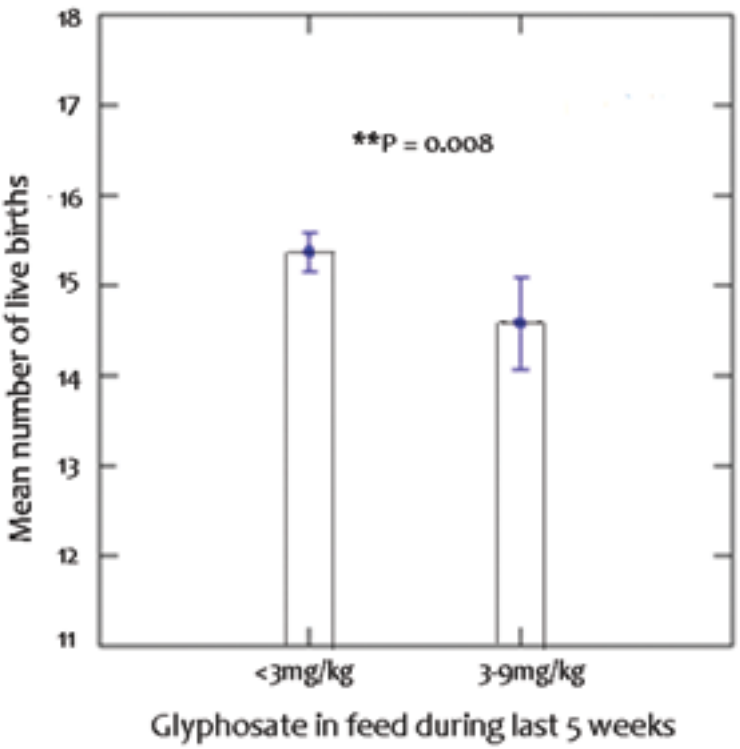


Figure 2 Rates of liveborn per sow after consuming low and high levels of glyphosate in feed in last 5 weeks of pregnancy

To conclude

Any farmer who switches away from GMOs and Roundup will experience improved health in their herd and crops. What I have seen in my pigs, knowing about the scientific studies on malformations due to the chemical Roundup and the fact that 1/80 people in certain towns in Argentina have the same defects after being exposed to the chemical and the fact that I know of 14 Danish people born with deformities of the same type makes me wonder what we are doing. And it scares me. A farmer's task is to provide nutritious and healthy food for consumers, GMOs and Roundup provide neither. Thinking about DDT and how we thought that was healthy , that should reminds us that we cannot ignore the warning signs for glyphosate.

8

Glyphosate and Metal Chelation – A Mechanism of Toxicity

Don Huber painted a devastating picture of glyphosate and GM crops at UK Parliament

Dr Eva Sirinathsinghji

In 2012, Don Huber, professor emeritus at Purdue University and USDA senior scientist (see Box) delivered to the UK Houses of Parliament a damning indictment of glyphosate agriculture as a most serious threat to the environment, livestock, and human health [1].

Since his letter to the US Secretary of State Tom Vilsak was leaked in February 2011, there has been a great deal of controversy over what Huber described as a pathogen "new to science" and abundant in glyphosate-tolerant GM crops (see [2] Emergency! Pathogen New to Science Found in Roundup Ready GM Crops?, *SiS* 50). As he concluded in the letter: "We are now seeing an unprecedented trend of increasing plant and animal diseases and disorders. This pathogen may be instrumental to understanding and solving this problem".

Don Huber

Don Huber, Emeritus Professor at Purdue University and senior scientist on USDA's National Plant Disease Recovery System, has been a plant physiologist and pathologist for over 40 years. His academic career began with 8 years as a cereal pathologist at the University of Idaho, and the next 35 years at Purdue University where he specialised in soil-borne disease control, physiology of disease, and microbial ecology. For the past 20 years, he has conducted extensive research into the effects of glyphosate on crops, in response to the increase in crop diseases on glyphosate-applied fields.

His talk linked glyphosate to reduced nutrient availability in plants, increasing plant diseases, the emergence of a new pathogen, animal illness and possible effects on human health (see [3, 4] Glyphosate Tolerant Crops Bring Death and Disease, Scientists Reveal Glyphosate Poisons Crops and Soil, *SiS* 47).

Pathogen new to science

The conversion of US agriculture to monochemical herbicide practice has resulted in the extensive use of glyphosate herbicides. Coincidentally, farmers have been witnessing deterioration in the health of corn, soybean, wheat and other crops, and epidemics of diseases in small grain crops. All are associated with the extensive use of glyphosate, which has increased further since the introduction of glyphosate-tolerant, Roundup Ready (RR) crops.

Glyphosate immobilises nutrients required to maintain plant health and resistance to disease. This weakening of the plants defence could explain the infestation of GM crops with the new pathogen, which has now been observed in horse, sheep, pigs, cows, chicken, multiple animal tissues including reproductive parts (semen, amniotic fluid), manure, soil, eggs, milk, as well as the common fungal pathogen that is currently infesting RR crops, *Fusarium solani fsp glycines mycelium*. All are coming into contact with glyphosate either through direct exposure or consumption through animal feed. It is also highly abundant in crops suffering from plant Goss' wilt and sudden death syndrome.

The pathogen can be cultured in the lab, and has been isolated from livestock foetal tissue, replicated in the lab and re-introduced back into the animals. It appears to be very common and may well be interacting with the effects of glyphosate on both plants and animals, exacerbating disease and causing reproductive failure in livestock (see below). Although great expectations have been placed on Huber to publish his findings, he insists that before this can be done, further resources are necessary to be able to characterise the 'entity' and identify what type of species it is, including sequencing of its genome. This is a slow process and once complete, it is his intention to publish the work in a peer-reviewed journal.

Understanding glyphosate's mode of action

Recognising glyphosate's mechanism of action is the key to understanding how it may exert detrimental effects on the health of crops, animals, and the environment alike. Glyphosate is a broad-spectrum herbicide that interacts with a range of physiological processes in the plant and its environment. Although it is most commonly recognised to work through inhibition of the plant enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) involved in the production of aromatic amino acids in the shikimate pathway, it was actually first patented as a strong metal-chelator that binds to metals including manganese, magnesium, iron, nickel, zinc and calcium, many of which are important micronutrients acting as co-factors for plant enzymes in different physiological processes including the plants' defence system. Indeed, it is actually through chelation of manganese that the EPSPS enzyme is inhibited.

Rendering plants more susceptible to disease through glyphosate's pathogenic activity is actually the way it exerts its herbicidal activity. This is done not just through immobilising nutrients in the plant but also impacting the agricultural system as a whole. Consistently, if glyphosate does not reach the root of a plant or the plant is grown in a sterile soil, the plant is not killed.

Once in the soil, glyphosate is later immobilised through the chelation of cations, and is therefore very stable and not easily degraded. However, phosphorus (including phosphorus fertilisers) can desorb the herbicide, making it active once again in the soil.

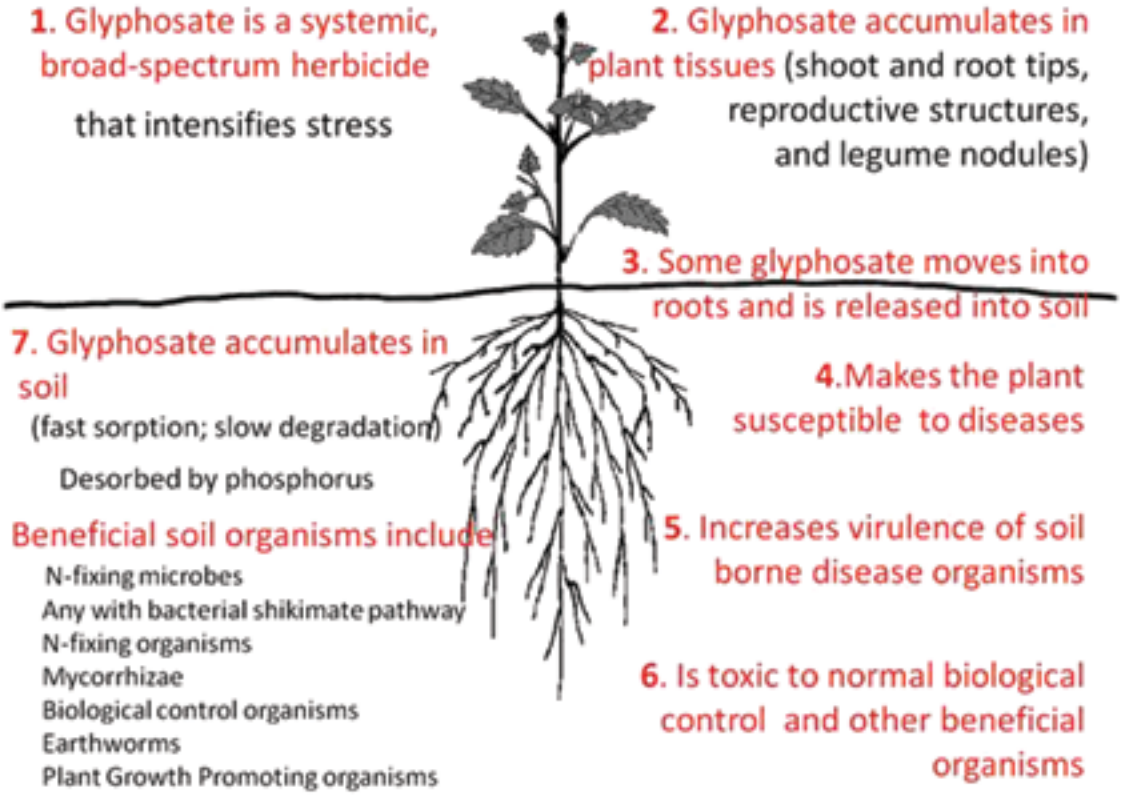


Figure 1 Interactions of glyphosate with plant and soil biology; adapted from Huber's presentation

Glyphosate interferes negatively with many components of agriculture

Huber stressed that agriculture is an integrated system of many interacting components, which together determine crop health and therefore yield. This concept is undervalued, and the sooner this is recognised, the sooner we will be able to reap the full genetic potential of our crops.

The three main components of an agricultural system are 1) the biotic environment including beneficial organisms for example, nitrogen-fixing microbes and mineralizers; 2) the abiotic environment including nutrients, moisture, pH; and 3), defence against pathogens that damage crops. The genetic potential of a plant can be achieved by minimising the stress placed on these components through improving plant nutrition and physiology and prevention of diseases and pests.

We have been repeatedly told that to meet the world's needs for food production we must resort to GM crops and chemical agriculture. However, glyphosate detrimentally interacts with all the agricultural components, so much so that an estimated 50 percent of the potential crop yields are currently being lost (see Figure 1).

As shown in Figure 1, glyphosate interacts with a wide range of health determinants, which intensifies stress and reduces crop yields. Not only does it accumulate in the plant tissues (shoot and root tips, reproductive structures and legume nodules), it accumulates in the roots where it then leaks into the soil and harms beneficial microorganisms in the soil including those that act as biological controls of pathogens. The obvious consequence is the increased virulence of soil-borne pathogens that lead to disease.

Glyphosate immobilises nutrients critical for plant defence system and other functions

One of Huber's important discoveries was the close correlation of all the known conditions affecting the disease 'take-all' with the availability of manganese to the plant and its physiological effect on resistance to this pathogen.

Micronutrients are the activators or inhibitors of many critical physiological functions. Thus, a deficiency or change in availability of these regulatory elements can greatly affect plant growth and resistance to diseases and pests. Those metabolic pathways producing secondary anti-microbial compounds, pathogen-inhibiting amino acids and peptides, hormones involved in cicatrisation (walling off pathogens), callusing, and disease escape mechanisms can all be compromised by glyphosate.

Micronutrients are also necessary for other processes in a plant. Manganese for example is not only involved in co-activating the EPSPS enzyme, with up to 25 other enzymes known to be affected by manganese chelation. Such enzymes are necessary for photosynthesis, in assimilating carbon dioxide in the electron transport chain, along with zinc. It also helps in the synthesis of chlorophyll and in nitrate assimilation. Numerous enzymes requiring other mineral co-factors are also affected, among them enzymes of the shikimate pathway, to which EPSPS belongs, are responsible for plant responses to stress and the synthesis of defence molecules against pathogens, such as amino acids, lignins, hormones, phytoalexins, flavenoids and phenols.

Consistent with what is known about the role of micronutrients and glyphosate, the levels of key minerals have been measured in transgenic RR soybeans and found to be lower than those in isogenic non-transgenic varieties. Manganese was reduced by as much as 45 %, while iron was reduced by 49 % [5]. Similar deficiencies in mineral content have been found in non-GM varieties, suggesting that the glyphosate, and not the RR transgene, is responsible for reducing mineral availability [6]. Glyphosate reduces photosynthesis, water uptake, amino acid production as well as lignin, a molecule conferring mechanical strength of the

Figure 2 Effects of long-term glyphosate on crop health; adapted from Huber's presentation

plant and crucial for conducting water through plant stems [7, 8].

As Huber stated, the consequences of these nutrient deficiencies is that "crops don't look as good, are not as productive or rigorous, and are slower growing" (see Figure 2). He noted yield drags of 26 % for RR soybeans. Furthermore, with current concerns for global warming, plants that are up to 50 % less water-efficient, such as RR crops, are counter-productive and can only exacerbate problems.

Huber stressed that there is nothing in the glyphosate tolerant crops that operates on the glyphosate applied to them. Consequently, although they have enough resistance to prevent them from dying (conferred by the EPSPS transgene), their overall physiological function is compromised by glyphosate. It therefore affects GM as well as non-GM crops through residual levels of glyphosate in the ground.

In addition to chelating nutrients in the plants, glyphosate can lower mineral content through damaging beneficial soil organisms, including microbes producing indole-acetic acid (a growth-promoting auxin), earthworms, mycorrhizae associations, phosphorus & zinc uptake, microbes such as *Pseudomonads, Bacillus* that convert insoluble soil oxides to plant-available forms of manganese and iron, nitrogen-fixing bacteria *Bradyrhizobium, Rhizobium*, and organisms involved in the biological control of soil-borne diseases that reduce root uptake of nutrients.

Glyphosate increases incidence and virulence of soil-borne pathogens

Thirty-four diseases have been reported in the scientific literature to increase in incidence as a result of glyphosate weed-eradication programmes. They affect a wide variety of crops from cereals to bananas, tomatoes, soybean, cotton, canola, melon and grapes [9]. Some of these diseases are considered 'emerging' or 're-emerging' as they had not caused serious economic losses in the past. This has worrying implications for the agricultural sector with the US now in its fourth year of epidemics of Goss' wilt and sudden death syndrome and eighteenth year of epidemic of *Fusarium* fungal colonisation resulting in root rot and *Fusarium* wilt. Not only does glyphosate affect disease susceptibility, there is also evidence of increased disease severity. Examples include 'take-all'; *Corynespora* root rot in soybean; *Fusarium* spp diseases, including those caused by *Fusarium* species that are ordinarily non-pathogenic. Head-scab caused by *Fusarium* spp of cereals increases following glyphosate application, which is also now prevalent in cooler climates when previously it was limited to warmer climates.

Food and feed safety concerns

Nutrient-deficient, transgenic plants suffering from disease that also harbour herbicide residues, presents an array of possible safety hazards to animals and humans. According to Huber, possible harm include direct toxicity of glyphosate itself, which has been shown to cause endocrine disruption, DNA damage, reproductive and developmental toxicities, neurotoxicity, cancer, and birth defects (see [10] Glyphosate Toxic and Roundup Worse, *SiS* 26; [11] Death by Multiple Poisoning, Glyphosate and Roundup, *SiS* 42; [12] Ban Glyphosate Herbicide *Now*, *SiS* 43; [13] Lab Study Establishes Glyphosate Link to Birth Defects, *SiS* 48). Furthermore, allergies are on the rise, and animals are showing allergy responses, including inflamed irritated stomachs (Figure 3), discoloration of stomach lining, leakage of intestines as well as behavioural symptoms of irritability and anti-social behaviour in

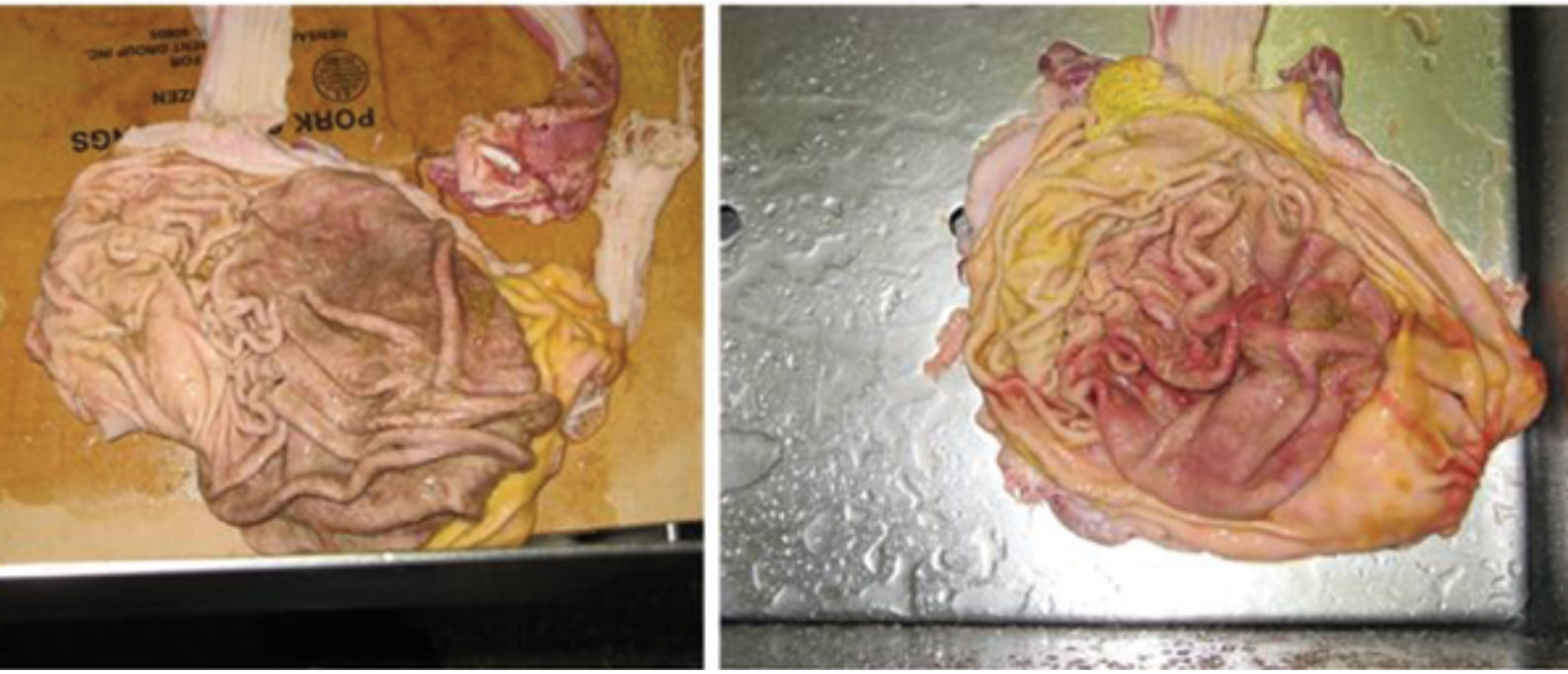


Figure 3 Stomach shows allergic response of discolouration and inflammation in GMO fed pig (right) compared with control (left)

cows (abnormal for herd animals). Inflammatory bowel disease in humans has risen 40 percent since 1992, which may be related to consumption of GM foods, although this has not yet been proven.

The increase in infestation of crops with fungal pathogens that produce toxins is an added concern. Mycotoxins, including fusarium toxins as well as aflatoxins released by *Aspergillus* fungi are carcinogenic and have forced imports of wheat into the US due to unsafe levels found in domestic harvests.

Triple whammy of reproductive toxicity caused by glyphosate

In 2002, the Cattlemen's Association gave a statement to US Congress on the serious and puzzling rises in reproductive problems. It said: "high numbers of foetuses are aborting for no apparent reason. Other farmers successfully raise what look to be normal young cattle, only to learn when the animals are butchered that their carcasses appear old and, therefore, less valuable...The sporadic problem is so bad both in the United States and abroad that in some herds around 40-50 percent of pregnancies are being lost.. [and] the viability of this important industry is threatened."

Glyphosate appears to be able to induce reproductive failures through three separate mechanisms. The first, mentioned above is the endocrine dysfunction caused by direct toxicity of glyphosate.

The second is the reduced nutrient content having consequential effects on the nutritional status of animals. Manganese in animals, as in plants, is an essential nutrient, and deficiencies have been associated with a variety of diseases as well as reproductive failures, which are becoming increasingly common in livestock. One study performed in Australia following two seasons of high levels of stillbirths in cattle found that all dead calves were manganese deficient [14]. Furthermore, 63 percent of babies with birth defects were also deficient. Manganese is known to be important for mobilising calcium into bones, correlating with abnormal bone formation in these calves.

Third, the unknown pathogenic 'entity' may be associated with inducing pseudo-pregnancies. As far back as 1998, a suspect agent was found in reproductive tissue of livestock. It has now been isolated in high concentrations from semen, amniotic fluid as well as placental tissue. It has also been found in aborted foetal tissue. Some farms are reporting up to 50 percent fewer conceptions in animals due to increased miscarriages and pseudo-pregnancies. Although evidence of the widespread presence of this new pathogen is clear, Don Huber suggested the need for further research to understand not only what kind of pathogen it is, but importantly, the effects it is having on the health of plants as well as animals.

To conclude

Over 100 peer reviewed papers have been published by Huber and other scientists on the detrimental effects of glyphosate. Glyphosate increases disease in plants (as well as animals), prompting Huber to write to the Secretary of Agriculture. It may be linked to many health problems in animals and humans, which are an added cost to all the failed promises of a new agricultural technology that would feed the world. As Huber concluded, the "public trust has been betrayed."

9

Glyphosate & Crops Diseases Old and New

Glyphosate is responsible for micronutrient deficiencies at the basis of numerous crop diseases

Dr Don M. Huber

Micronutrients are regulators, inhibitors and activators of physiological processes, and plants provide a primary dietary source of these elements for animals and people Micronutrient deficiency symptoms are often indistinct ("hidden hunger") and commonly ascribed to other causes such as drought, extreme temperatures, soil pH, etc. The sporadic nature of distinct visual symptoms, except under severe deficiency conditions, has resulted in a reluctance of many producers to remediate micronutrient deficiency. Lost yield, reduced quality, and increased disease are the unfortunate consequences of untreated micronutrient deficiency. The shift to less tillage, herbicide resistant crops and extensive application of glyphosate has significantly changed nutrient availability and plant efficiency for a number of essential plant nutrients. Some of these changes are through direct toxicity of glyphosate while others are more indirect through changes in soil organisms important for nutrient access, availability, or plant uptake. Compensation for these effects on nutrition can maintain optimum crop production efficiency, maximize yield, improve disease resistance, increase nutritional value, and insure food and feed safety.

US conversion to monochemical herbicide programme

More than thirty years ago, US agriculture started a conversion to a monochemical herbicide programme focused around glyphosate (Roundup®). The near simultaneous shift from conventional tillage to no-till or minimum tillage stimulated this conversion and the introduction of genetically modified (GM) crops tolerant to glyphosate. The introduction of GM (Roundup Ready®) crops has greatly increased the volume and scope of glyphosate usage, and conversion of major segments of crop production to a monochemical herbicide strategy. Interactions of glyphosate with plant nutrition and increased disease have been previously overlooked, but become more obvious each year as glyphosate residual effects become more apparent.

The extensive use of glyphosate and the rapid adoption of GM glyphosate-tolerant crops such as soybean, corn, cotton, canola, sugar beets, and alfalfa, with their greatly increased application of glyphosate for simplified weed control, have intensified deficiencies of numerous essential micronutrients and some macronutrients. Additive nutrient inefficiency of the Roundup Ready® (RR) gene and glyphosate herbicide increase the need for micronutrient remediation, and established soil and tissue levels for nutrients considered sufficient for specific crop production may be inadequate indicators in a less nutrient efficient glyphosate weed management programme.

Understanding glyphosate's mode of action and impact of the RR gene indicate strategies to offset negative impacts of this monochemical system on plant nutrition and its predisposition to disease. A basic consideration in this regard should be a much more judicious use of glyphosate. Glyphosate damage is often attributed to other causes such as drought, cool soils, deep seeding, high temperatures, crop residues, water fluctuations, etc. Table 1 provides some of the common symptoms of drift and residual glyphosate damage to crops. This paper is an update of information on nutrient and disease interactions affected by glyphosate and the RR gene(s), and includes recently published research in the European *Journal of Agronomy* and other international scientific publications.

Box 1 Some things we know about glyphosate influences on plant nutrition and disease

1. Glyphosate is a strong metal chelator (for Ca, Co, Cu, Fe, Mn, Mg, Ni, Zn) – in the spray tank, in soil and in plants.
2. It is rapidly absorbed by roots, stems, and leaves, and moves systemically throughout the plant (normal and RR).
3. Accumulates in meristematic tissues (root, shoot, legume nodules, and reproductive sites) of normal and RR plants.
4. Inhibits EPSPS in the Shikimate metabolic pathway and many other plant essential enzymes.
5. Increases susceptibility to drought and disease.
6. Non-specific herbicidal activity (broad-spectrum weed control).
7. Some of the applied glyphosate is exuded from roots into soil.
8. Immobilized in soil by chelating with soil cat-ions (Ca, Co, Cu, Fe, Mg, Mn, Ni, Zn).
9. Persists and accumulates in soil and plants for extended periods (years) – it is not 'biodegradable,' but is rapidly immobilized by chelation generally.
10. Desorbed from soil particles by phosphorus and is available for root uptake by all plants.
11. Toxic to soil organisms that facilitate nutrient access, availability, or absorption of nutrients.
12. Inhibits the uptake and translocation of Fe, Mn, and Zn at very low, non-herbicidal rates.
13. Stimulates soil-borne pathogenic and other soil microbes to reduce nutrient availability.
14. Reduces secondary cell wall formation and lignin in RR and non-RR plants.
15. Inhibits nitrogen fixation by chelating Ni for ureide synthesis and is toxic to *Rhizoiaceae*.
16. Reduces physiological availability and concentration of Ca, Cu, Fe, K, Mg, Mn, and Zn in plant tissues and seed.
17. Residual soil activity can damage plants through root uptake.
18. Increases mycotoxins in stems, straw, grain, and fruit.
19. Reduces photosynthesis (CO_2 fixation).
20. Causes fruit (bud) drop and other hormonal effects.
21. Accumulates in food and feed products to enter the food chain as an item of food safety.

Box 2 Some things we know about the glyphosate-tolerance (RR) gene(s)

1. Provides selective herbicidal activity for glyphosate.
2. Inserts an alternative EPSPS pathway that is not sensitive to glyphosate action in mature tissue.
3. Reduces the plant's physiological efficiency of Fe, Mn, Ni, Zn, etc.
4. Inactive (silent) in meristematic tissues (root and shoot tips, legume root nodules, and reproductive tissues).
5. Reduces nutrient uptake and efficiency.
6. Increases drought stress.
7. Reduces N-fixation.
8. Lowers seed nutrient content.
9. Transferred in pollen to plants, and from degrading plant tissues to microbes.
10. Generally causes a yield 'drag' compared with near-isogenic normal plants from which it was derived.
11. Has greatly increased the application of glyphosate.
12. Permanent in plants once it is introduced

Understanding glyphosate

Glyphosate (N-(phosphomonomethyl)glycine) is a strong metal chelator and was first patented as such by Stauffer Chemical Co. in 1964 (US Patent No. 3,160,632). Metal chelates are used extensively in agriculture to increase solubility or uptake of essential micronutrients that are essential for plant physiological processes. They are also used as herbicides and other biocides (nitrification inhibitors, fungicides, plant growth regulators, etc.) where they immobilize specific metal co-factors (Cu, Fe, Mn, Ni, Zn) essential for enzyme activity. In contrast to some compounds that chelate with a single or few metal species, glyphosate is a broad-spectrum chelator of both macro and micronutrients (Ca, Mg, Cu, Fe, Mn, Ni, Zn). It is this strong, broad-spectrum chelating ability that also makes glyphosate a broad-spectrum herbicide and a potent anti-microbial agent since the function of numerous essential enzymes is affected [1].

Primary emphasis in understanding glyphosate's herbicidal activity has been on inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) at the start of the Shikimate physiological pathway for secondary metabolism. This enzyme requires reduced Flavin mononucleotide (FMN) as a co-factor (catalyst) whose reduction requires manganese (Mn). Thus, by immobilizing Mn by chelation, glyphosate denies the availability of reduced FMN for the EPSPS enzyme. It also can affect up to 25 other plant enzymes that require Mn as a co-factor and numerous other enzymes in both primary and secondary metabolism that require other metal co-factors (Co, Cu, Fe, Mg, Ni, Zn). Several of these enzymes also function with Mn in the Shikimate pathway that is responsible for plant responses to stress and defence against pathogens (amino acids, hormones, lignin, phytoalexins, flavenoids, phenols, etc.). By inhibiting enzymes in the Shikimate pathway, a plant becomes highly susceptible to various ubiquitous soil-borne pathogens (*Fusarium*, *Pythium*, *Phytophthora*, *Rhizoctonia*, etc.). It is this pathogenic activity that actually kills the plant as "the herbicidal mode of action" [2-4]. If glyphosate is not translocated to the roots because of stem boring insects or other disruption of the vascular system, aerial parts of the plant may be stunted, but the plant is not killed.

Recognizing that glyphosate is a strong chelator to immobilize essential plant micronutrients provides an understanding for the various non-herbicidal and herbicidal effects of glyphosate. Glyphosate is a phloem-mobile, systemic chemical in plants that accumulates in meristematic tissues (root, shoot tip, reproductive, legume nodules) and is released into the rhizosphere through root exudation (from RR as well as non-RR plants) or mineralization of treated plant residues. Degradation of glyphosate in most soils is slow or non-existent since it is not 'biodegradable' and is primarily by microbial co-metabolism when it does occur. Although glyphosate can be rapidly immobilized in soil (also spray tank mixtures, and plants) through chelation with various cat-ions (Ca, Mg, Cu, Fe, Mn, Ni, Zn), it is not readily degraded and can accumulate for years (in both soils and perennial plants). Very limited degradation may be a "safety" feature with glyphosate since most degradation products are toxic to normal as well as RR plants. Phosphorus fertilizers can desorb accumulated glyphosate that is immobilized in soil to damage and reduce the physiological efficiency of subsequent crops. Some of the observed effects of glyphosate are presented in box 1.

Understanding the Roundup Ready® gene

Plants genetically engineered for glyphosate-tolerance contain the Roundup Ready® gene(s) that provide an alternate EPSPS pathway (EPSPS-II) that is not blocked by glyphosate. The purpose of these gene inserts is to provide herbicidal selectivity so glyphosate can be applied directly to these plants rather than only

for pre-plant applications. As an additional physiological mechanism, activity of this duplicate pathway requires energy from the plant that could be used for yield. The RR genes are 'silent' in meristematic tissues where glyphosate accumulates so that these rapidly metabolizing tissues are not provided an active alternative EPSPS pathway to counter the physiological effects of glyphosate's inhibition of EPSPS. Meristematic tissues also are areas of high physiologic activity requiring a higher availability of the essential micronutrients needed for cell division and growth that glyphosate immobilizes by chelation.

Residual glyphosate in RR plant tissues can immobilize Fe, Mn, Zn or other nutrients applied as foliar amendments for 8-35 days after it has been applied. This reduces the availability of micronutrients required for photosynthesis, disease resistance, and other critical physiological functions. The presence of the RR gene(s) reduces nutrient uptake and physiological efficiency and may account for some of the 'yield drag' reported for RR crops when compared with the 'normal' isolines from which they were derived. Reduced physiological efficiency from the RR gene is also reflected in reduced water use efficiency (WUE) and increased drought stress (Box 2).

It should be recognized that:

1. There is nothing in the glyphosate-tolerant plant that operates on the glyphosate applied to the plant.
2. All the technology does is to insert an alternative enzyme (EPSPS-II) that is not blocked by glyphosate in mature tissue.
3. When glyphosate enters the plant, it is not selective; it chelates with a host of elements influencing nutrient availability, disease resistance, and the plant's other physiological functions.
4. Glyphosate is present for the life of the plant or until it is exuded into soil or groundwater through the roots. Degradation products are toxic to both RR and non-RR plants.

Interactions of glyphosate with plant nutrition

Glyphosate can affect nutrient efficiency in the plant by chelating essential nutrient co-factors after application as there is many times more 'free' glyphosate in the plant than all of the unbound cations. Chelation of Mn and other micronutrients after application of glyphosate is frequently observed as a 'flashing' or yellowing that persists until the plant can 'resupply' the immobilized nutrients. The duration of 'flashing' is correlated with the availability of micronutrients in soil. Symptom remission indicates a resumption of physiological processes, but is not an indicator of plant nutrient sufficiency since micronutrient deficiencies are commonly referred to as 'hidden hunger.' As a strong nutrient chelator, glyphosate can reduce physiological efficiency by immobilizing elements required as components, co-factors or regulators of physiological functions at very low rates. Thus, plant uptake and or translocation of Fe, Mn and Zn are drastically reduced (up to 80 %) by commonly observed 'drift' rates of glyphosate (<1/40 the herbicidal rate). This is reflected in reduced physiological efficiency, lower mineral nutrient levels in vegetative and reproductive tissues, and increased susceptibility to disease. Microbial and plant production of siderophores and ferric reductase in root exudates under nutrient stress are inhibited by glyphosate to exacerbate plant nutrient stress common in low-available micronutrient soils.

Glyphosate is not readily degraded in soil and can probably accumulate for many years chelated with soil cat-ions. Degradation products of glyphosate are as damaging to RR crops as to non-RR crops. Persistence and accumulation of glyphosate in perennial plants, soil, and root meristems, can significantly reduce root growth and the development of nutrient absorptive tissue of RR as well as non-RR plants to further impair nutrient uptake and efficiency. Impaired root uptake not only reduces the availability of specific nutrients, but also affects the natural ability of plants to compensate for low levels of many other nutrients. Glyphosate also reduces nutrient uptake from soil indirectly through its toxicity to many soil microorganisms responsible for increasing the availability and access to nutrients through mineralization, reduction, symbiosis, etc.

Degradation of plant tissues through growth, necrosis, or mineralization of residues can release accumulated glyphosate from meristematic tissues in toxic concentrations to plants. The most damaging time to plant wheat in ryegrass 'burned down' by glyphosate is two weeks after glyphosate application to correspond with the release of accumulated glyphosate from decomposing meristematic tissues. This is contrasted with the need to delay seeding of winter wheat for 2-3 weeks after a regular weed burn-down' to permit time for immobilization of glyphosate from root exudates and direct application through chelation with soil cat-ions. The Roundup® label for Israel lists recommended waiting times before planting a susceptible crop on that soil. One of the benefits of crop rotation is an increased availability of nutrients for a subsequent crop in the rotation. The high level of available Mn (130 ppm) after a normal corn crop is not observed after glyphosate-treated RR corn. The lower nutrient availability after specific RR crop sequences may need to be compensated for through micronutrient application in order to optimize yield and reduce disease in a subsequent crop.

Box 3 Some plant pathogens stimulated by glyphosate

Botryospheara dothidea
Corynespora cassicola
Fusarium species
F. avenaceum
F. graminearum
F. oxysporum f.sp. cubense
F. oxysporum f.sp. (canola)
F. oxysporum f.sp. glycines
F. oxysporum f.sp. vasinfectum
F. solani f.sp. glycines
F. solani f.sp. phaseoli
F. solani f.sp. pisi
Gaeumannomyces graminis
Magnaporthe grisea
Marasmius spp.
Monosporascus cannonbalus
Myrothecium verucaria
Phaeomoniella chlamydospora
Phytophthora spp.
Pythium spp.
Rhizoctonia solani
Septoria nodorum
Thielaviopsis bassicola
Xylella fastidiosa
Clavibacter michiganensis subsp. nebraskensis (Goss' wilt)

The influence of glyphosate on soil organisms important for access, mineralization, solubilisation, and fixation of essential plant nutrients

Glyphosate is a potent microbiocide and is toxic to earthworms, mycorrhizae (P & Zn uptake), reducing microbes that convert insoluble soil oxides to plant available forms (Mn and Fe, *Pseudomonads*, *Bacillus*, etc.), nitrogen-fixing organisms

(*Bradyrhizobium*, *Rhizobium*), and organisms involved in the 'natural,' biological control of soil-borne diseases that reduce root uptake of nutrients. Although glyphosate contact with these organisms is limited by rapid chelation-immobilization when applied on fallow soil; glyphosate in root exudates, or from decaying weed tissues or RR plants, contacts these organisms in their most active ecological habitat throughout the rhizosphere. It is not uncommon to see Cu, Fe, Mg, Mn, Ni, and Zn deficiencies intensify and show in soils that were once considered fully sufficient for these nutrients. Increasing the supply and availability of Co, Cu, Fe, Mg, Mn, Ni, and Zn have reduced some of the deleterious effects of glyphosate on these organisms and increased crop yields.

In contrast to microbial toxicity, glyphosate in soil and root exudates stimulates oxidative soil microbes that reduce nutrient availability by decreasing their solubility for plant uptake, immobilize nutrients such as K in microbial sinks to deny availability for plants, and deny access to soil nutrients through pathogenic activity. Plant pathogens stimulated by glyphosate (Box 3) include ubiquitous bacterial and fungal root, crown, and stalk rotting fungi; vascular colonizing organisms that disrupt nutrient transport to cause wilt and die-back; and root nibblers that impair access or uptake of soil nutrients

Herbicidal mode of action of glyphosate

As a strong metal micronutrient chelator, glyphosate inhibits activity of EPSPS and other enzymes in the Shikimate metabolic pathway responsible for plant resistance to various

pathogens. Plant death is through greatly increased plant susceptibility of non-RR plants to common soil-borne fungi such as *Fusarium*, *Rhizoctonia*, *Pythium*, *Phytophthora*, etc. that are also stimulated by glyphosate [2-4]. It is very difficult to kill a plant in sterile soil by merely shutting down the Shikimate pathway (secondary metabolism) unless soil-borne pathogens are also present. It is the increased susceptibility to soil-borne pathogens, and increased virulence of the pathogens, that actually kills the plants after applying glyphosate. Disease resistance in plants is manifest through various active and passive physiological mechanisms requiring micronutrients. Those metabolic pathways producing secondary anti-microbial compounds (phytoalexins, flavenoids, etc.), pathogen inhibiting amino acids and peptides, hormones involved in cicatrisation (walling off pathogens), callusing, and disease escape mechanisms can all be compromised by glyphosate chelation of micronutrient co-factors critical for enzyme function. Genetic modification of plants for glyphosate tolerance partially restores Shikimate pathway function to provide a selective herbicidal effect.

Box 4 Some symptoms of glyphosate damage to non-target plants

1. Micronutrient (and often some macronutrient) deficiency
2. Low vigour, slow growth, stunting
3. Leaf chlorosis (yellowing) – complete or between the veins
4. Leaf mottling with or without necrotic spots
5. Leaf distortion – small, curling, strap-like, wrinkling, or 'mouse ear'
6. Abnormal bud break, stem proliferation – witches broom
7. Retarded, slow regrowth after cutting or running (alfalfa, perennial plants)
8. Lower yields, lower mineral value – vegetative parts and reproductive (grain, seeds)
9. Early fruit, bud, or leaf drop
10. Early maturity, death before physiological maturity, tip die-back
11. Predisposition to infectious diseases and extended infection/ susceptible period– numerous
12. Predisposition to insect damage
13. Induced abiotic diseases – drought, winter kill, sun scald, bark cracking (perennial plants)
14. Root stunting, inefficient N-fixation and uptake
15. Poor root nodulation in legumes

Interactions of glyphosate with plant disease

Micronutrients are the regulators, activators, and inhibitors of plant defence mechanisms that provide resistance to stress and disease. Chelation of these nutrients by glyphosate compromises plant defences and increases pathogenesis to increase the severity of many abiotic (bark cracking, nutrient deficiencies) as well as infectious diseases of both RR and non-RR plants in the crop production system (Box 4). Many of these diseases are referred to as 'emerging' or re-emerging' diseases because they rarely caused economic losses in the past, or were effectively controlled through management practices.

Non-infectious (abiotic) diseases

Research at Ohio State University has shown that bark cracking, sunscald, and winter-kill of trees and perennial ornamentals is caused by glyphosate used for under-story weed control, and that glyphosate can accumulate for 8-10 years in perennial plants. This accumulation of glyphosate can be from the inadvertent uptake of glyphosate from contact with bark (drift) or by root uptake from glyphosate in weed root exudates in soil. Severe glyphosate damage to trees adjacent to stumps of cut trees treated with glyphosate (to prevent sprouting in an effort to eradicate citrus greening or CVC) can occur through root translocation and exudation several years after tree removal.

Infectious diseases

Increased severity of the take-all root and crown rot of cereals (*Gaeumannomyces graminis*) after prior glyphosate usage has been observed for over 20 years and take-all is now a 're-emerging' disease in many wheat producing areas of the world where glyphosate is used for weed control prior to cereal planting. A related disease of cereals, and the cause of rice blast (*Magnaporthe grisea*), is becoming very severe in Brazil and is especially severe when wheat follows a RR crop in the rotation. Like take-all and *Fusarium* root rot, this soil-borne pathogen also infects wheat and barley roots, and is a concern for U.S. cereal production.

Fusarium species causing head scab are common root and crown rot pathogens of cereals everywhere; however, *Fusarium* head scab (FHB) has generally been a serious disease of wheat and barley only in warm temperate regions of the US. With the extensive use of glyphosate, it is now of epidemic proportions and prevalent throughout most of the cereal producing areas of North America. Canadian research has shown that the application of glyphosate one or more times in the three years previous to planting wheat was the most important agronomic factor associated with high FHB in wheat, with a 75 % increase in FHB for all crops and a 122 % increase for crops under minimum-till where more glyphosate is used. The most severe FHB occurs where a RR crop precedes wheat in the rotation for the same reason. Glyphosate altered plant physiology (carbon and nitrogen metabolism) increasing susceptibility of wheat and barley to FHB and increased toxin production, is also associated with a transient tolerance

of wheat and soybeans to rust diseases.

The increased FHB with glyphosate results in a dramatic increase in tricothecene (deoxynivalenol, nivalenol, 'vomitoxins') and estrogenic (zaeralenone) mycotoxins in grain; however, the high concentrations of mycotoxin in grain are not always associated with *Fusarium* infection of kernels. Quite often overlooked is the increase in root and crown rot by FHB Fusaria with glyphosate and the production of mycotoxins in root and crown tissues with subsequent translocation to stems, chaff and grain. Caution has been expressed in using straw and chaff as bedding for pigs or roughage for cattle because of mycotoxin levels that far exceeded clinically significant levels for infertility and toxicity. This also poses a health and safety concern for grain entering the food chain for humans. The list of diseases affected by glyphosate (see reference No. 18 of this chapter) is increasing as growers and pathologists recognize the cause effect relationship.

Special nutrient considerations in a glyphosate-dominant weed management ecological system

There are two things that should be understood in order to remediate nutrient deficiencies in a glyphosate usage program: 1) the effects of glyphosate on nutrient availability and function and 2) the effect of the RR gene on nutrient efficiency. With this understanding, there are four objectives for fertilization in a glyphosate environment – ***all of which indicate a more judicious use of glyphosate as part of the remediation process.***

These four objectives are to:

1. Provide adequate nutrient availability for full functional sufficiency to compensate for glyphosate and RR reduced availability or physiological efficiency of micronutrients (esp. Mn and Zn but also Cu, Fe, Ni).
2. Detoxify residual glyphosate in meristematic and other tissues, in root exudates, and in soil by adding appropriate elements for chelation with the residual glyphosate.
3. Restore soil microbial activity to enhance nutrient availability, supply, and balance that are inhibited by residual glyphosate in soil and glyphosate in root exudates.
4. Increase plant resistance to root infecting and re-emerging diseases through physiological plant defence mechanisms dependent on the Shikimate, amino acid, and other pathways that are compromised by micronutrient inefficiency in a glyphosate environment.

Meeting nutrient sufficiency

Extensive research has shown that increased levels and availability of micronutrients such as Mn, Zn, Cu, Fe, Ni, etc can compensate for reduced nutrient efficiency and the inefficiency of RR crops. This need may not be manifest in high fertility or nutrient toxic soils for a few years after moving to a predominantly monochemical strategy. The timing for correcting micronutrient defi-

ciencies is generally more critical for cereal plants (barley, corn, wheat) than for legumes in order to prevent irreversible yield and/or quality loss. Nutrient sufficiency levels from soil and tissue analysis that are considered adequate for non-GM crops may need to be increased for RR crops to be at full physiological sufficiency. Since residual 'free' glyphosate in RR plant tissues can immobilize most regular sources of foliar-applied micronutrients for 8-15 days, and thereby reduce the future availability of these materials, it may be best to apply some micronutrients 1-2 weeks after glyphosate is applied to RR crops.

The expense of an additional trip across the field for foliar application frequently deters micronutrient fertilization for optimum crop yield and quality. There are newly available micronutrient formulations (nutrient phosphites) that maintain plant availability without impacting herbicidal activity of the glyphosate in a tank-mix, and plants have responded well from these micronutrient-glyphosate mixes. Simultaneous application of some micronutrients with glyphosate might provide an efficient means to overcome deficiencies in low fertility soils, as well as mitigate the reduced physiological efficiency inherent with the glyphosate-tolerant gene and glyphosate immobilization of essential nutrients in the plant.

Under severe micronutrient deficiency conditions, selecting seed high in nutrient content or a micronutrient seed treatment to provide early nutrient sufficiency, establish a well-developed root system, and insure a vigorous seedling plant with increased tolerance to glyphosate applied later, has been beneficial even though excess nutrient applied at this time may be immobilized by glyphosate from root exudates and not available for subsequent plant uptake. Micronutrients such as Mn are not efficiently broadcast applied to soil for plant uptake because of microbial immobilization to non-available oxidized Mn, but could be applied in a band or to seed or foliage.

Detoxifying residual glyphosate

Some nutrients are relatively immobile in plant tissues (Ca, Mn) so that a combination of micronutrients may be more beneficial than any individual one to chelate with residual glyphosate and 'detoxify' it in meristematic and mature tissues. Thus, foliar application of Mn could remediate for glyphosate immobilization of the nutrient; however, it may be more effective when applied in combination with the more mobile Zn to detoxify sequestered glyphosate in meristematic tissues even though Zn levels may appear sufficient. Gypsum applied in the seed row has shown some promise for detoxifying glyphosate from root exudates since Ca is a good chelator with glyphosate (one of the reasons that ammonium sulphate is recommended in spray solutions with hard water is to prevent chelation with Ca and Mg which would inhibit herbicidal activity). Although bioremediation of accumulating glyphosate in soil may be possible in the future, initial degradation products of glyphosate are toxic to both RR and non-RR plants. This is an area that needs greater effort since the application of phosphorus fertilizers can desorb immobilized glyphosate to be toxic to plants through root uptake. Micronutrient seed treatment can provide some detoxification during seed germination, and stimulate vigour and root growth to enhance recovery from later glyphosate applications.

Biological remediation

The selection and use of plants for glyphosate-tolerance that have greater nutrient efficiency for uptake or physiological function has improved the performance of some RR crops, and further improvements are possible in this area. Enhancing soil microbial activity to increase nutrient availability and plant uptake has been possible through seed inoculation, environmental modification to favour certain groups of organisms, and implementation of various management practices. There are many organisms that have been used to promote plant growth, with the most recognized being legume inoculants (*Rhizobia*, *Bradyrhizobia* species); however, glyphosate is toxic to these beneficial microorganisms. Continued use of glyphosate in a cereal-legume rotation has greatly reduced the population of these organisms in soil so that annual inoculation of legume seed is frequently recommended. Biological remediation to compensate for glyphosate's impact on soil organisms important in nutrient cycles may be possible if the remediating organism is also glyphosate-tolerant and capable of over-coming the soils natural biological buffering capacity. This would be especially important for nitrogen-fixing, mycorrhizae, and mineral reducing organisms, but will be of limited benefit unless the introduced organisms are also tolerant of glyphosate. Modification of the soil biological environment through tillage, crop sequence, or other cultural management practices might also be a viable way to stimulate the desired soil biological activity.

Increasing plant resistance to stress and root-infecting pathogens

Maintaining plant health is a basic requirement for crop yield and quality. Plant tolerance to stress and many pathogens is dependent on a full sufficiency of micronutrients to maintain physiological processes mediated through the Shikimate or other pathways that are compromised in a glyphosate environment. Sequential application(s) of specific micronutrients (esp. Ca, Cu, Fe, Mn, Zn) may be required to compensate for those nutrients physiologically lost through glyphosate chelation. Breeding for increased nutrient efficiency and disease resistance will be an important contributor to this objective.

To conclude

Glyphosate is a strong, broad-spectrum nutrient chelator that inhibits plant enzymes responsible for disease resistance so that plants succumb from pathogenic attack. This also predisposes RR and non-RR plants to other pathogens. The introduction of such an intense mineral chelator as glyphosate into the food chain through accumulation in feed, forage, and food, and root exudation into ground water, could pose significant health concerns for animals and humans and needs further evaluation. Chelation immobilization of such essential elements as Ca (bone), Fe (blood), Mn, Zn (liver, kidney), Cu, Mg (brain) could directly inhibit vital functions and predispose to disease. The lower mineral nutrient content of feeds and forage from a glyphosate-intense weed management program can generally be compensated for through mineral supplementation. The various interactions of glyphosate with nutrition are represented in Figure 1 of Chapter 8.

10

How Roundup® Poisoned my Nature Reserve

A personal witness to the devastating demise of wild pollinators and other species as glyphosate herbicides increase in the environment

Rosemary Mason MB ChB FRCA

In March 2006, UK's Natural Environment Research Council (NERC) announced the closure of its wildlife research centres [1], a decision opposed by 99% of 1 327 stakeholders. Monks Wood centre, which hosted BBC's Spring Watch, pioneered work on DDT and pesticides in the 1960s, and more recently revealed how climate change is affecting wildlife, with spring arriving three weeks earlier. The research centres were also involved in assessing the impacts of GM (genetically modified) crops on wildlife, with findings contradicting industry claims that no harm would be caused.

In response to that and to the unexplained disappearance of birds and invertebrates (such as bumblebees, honeybees and other pollinators), we set aside one acre of the field next to our house in South Wales to make a chemical-free nature reserve.

Progress

To begin with we had considerable success. We photographed many insects that were clearly benefitting from wild flowers, often insignificant ones, which supplied nectar and pollen resources but which had been eliminated from many conventional arable fields. The reserve also provided larval food plants for several species of moths, butterflies and bush crickets.

In 2009, I had major surgery followed by radiotherapy. The work on the reserve diverted me from dark thoughts, and insomnia allowed me to make nocturnal visits around the reserve and adjacent fields to see speckled bush crickets in their most active periods. With a bat detector set at 40 kHz, a torch and recording device, I followed the 'singing' adult bush crickets and recorded the progress of their courtships. In fact 'stridulation' is a sound produced by the males rubbing a tooth-bearing left wing across a scraper on the right wing. Courtship and mating takes place at the highest point. It was amazing how many I heard and saw. The same frequency picked up the staccato discharge of pipistrelle bats performing their erratic aerobatics as they hunted insects along the hedge above my head. I would hear tawny owls calling to each other, such a haunting sound, and follow the voice with my ears, as the owl moved on silent wings between groups of trees.

After observations made during the summer of 2009, we published a photo-journal: *Speckled Bush Crickets. Observations in a small nature reserve* [2] (see Box 1). On 10 February 2010, Dr David Robinson, who is studying the behaviour and acoustics of *Leptophyes punctatissima* (Speckled Bush Crickets) at the Open University, said: "*I think that it is probably the first time anybody has produced a book about a single species*." He gave a copy to Dr Judith Marshall, who is the British expert on grasshoppers and

Box 1

Extracts from photo-journals [2, 3] & other observations

***Mating strategy in the female spider* Araneus quadratus**

"At fence post 22 on 16th August 2010, I was lucky enough to witness and photograph the courtship and mating of Araneus quadratus, an orb web spider, in our 1-metre high hedge." Spiders reconstruct their webs during the night. *"An early morning photograph illuminated by a torch, showing the previous night's work. The prey catching web of an orb web spider is amazingly intricate. It was much more complex than her courtship web, which looked as if it had been thrown together in a hurry! There are strong frame threads and radial threads, after which the spider lays down a temporary auxiliary spiral which she takes down as she constructs the sticky prey- catching spiral. This ends before the central hub, leaving a free zone."*

The first pollen of the year for the* Bombus Terrestris *March 5th 2010

"She descended like a helicopter, feet first into a large, purple crocus flower and disappeared completely. Apart from a faint tremor of the petals you would have been unaware she was there if you hadn't actually seen her go in. Some 5-10 s later she emerged head first over the threshold, liberally powdered with pollen and crawled out like a drunk, narcotised by the first decent meal of the year."

Moulting in a Speckled Bush Cricket nymph, August 8th 2009

"She sat with her right hind leg extended and braced against the leaf below with the left leg flexed and acting as a counterbalance. The forelegs grasped the shroud and the two mid legs were used as stabilisers. The external mouthparts, mandibles and palps were clearly visible and this time I could see the mouthparts moving. She had chosen a perfect day on which to perform her ecdysis. She and her other self were poised like ballet dancers caught in the spotlight of the sun, casting surreal shadows on the scabious leaf below. At the end of 16 minutes all that remained was a pair of tibia, still hooked by their tarsi to a trefoil leaf above. Presumably she must have mentally calculated that the nutritional gain from climbing up and unhooking them was hardly worth the effort."

The Ladybird Ball

For two weeks in April 2010 we studied 7-spot ladybirds. They are remarkable predators and natural pest removers! They steadily graze their way through aphids and mildew spores. We made counts three times a day; morning, afternoon and evening. During those periods they migrated from positions in the field during the day and usually gathered on shrubs in the western hedge in the early evening sunshine; field maple, hawthorn, blackthorn, hornbeam and hazel. Here they fed, rested and mated. Although they meet by accident, the factors that govern their behaviour (they are attracted by light and move against the force of gravity) meant that they climb upwards and are drawn to the same places. In those 2 weeks we counted 348 ladybirds.

Three plant species that supported the insects

August 5th 2009: Male speckled bush cricket nymph on devil's bit scabious leaf; 'proof of grazing'.

July 7th 2010: 'The Teasels grew and grew, like Jack's beanstalk, and had to be staked up against the July gales!' Teasels were the favourite flower of the new bumblebee queens. They were used for both feeding and roosting.

August 18th 2010: *Bombus terrestris*, buff-tailed bumblebee, has a short tongue which cannot reach the inside of the bell-shaped flowers of the Comfrey. She solves the problem of a short tongue by 'stealing' it. The short tongue penetrates the base of the flower.

crickets at the Natural History Museum.

At the end of 2010, we published another photo-journal, *The Year of the Bumblebee. Observations in a small nature reserve* [3] (see Box 1). The United Nations had declared 2010 the International Year of Biodiversity, to celebrate the diversity of life on earth. It also marked the year by which 200 countries had promised to halt biodiversity loss. In 2010 we set ourselves the task of identifying the six common types of bumblebees, their emergence, behaviour and the species of flower from which they took pollen and nectar.

By 2013 we knew that something was wrong. The numbers and species of invertebrates in our reserve were declining. Their behaviour was abnormal. In August, some of their food plants were uniformly affected with mildew

Biodiversity started to decrease rapidly in 2013. What was the cause?

By 2013 we knew that something was wrong. The numbers and species of invertebrates in our reserve were declining. Their behaviour was abnormal. In August, some of their food plants were uniformly affected with mildew.

In 2006, we had commissioned an overnight moth count [4] from a professional naturalist. The next morning at about 6 am when he emptied the traps, he recorded (while we photographed) 143 species of moths, attracted to the bright lights from a wide radius. Some species trapped were in numbers up to 500. We were astounded by the variety of species and asked if it was to do with the sunflowers which we had grown in the field as a winter crop for birds. No, he replied, it was because we weren't using pesticides and we had allowed the small wildflowers to flourish.

In 2013 we asked him to repeat the count. He confirmed our worse fears, the biodiversity had declined. He counted only 51 species and the maximum number of the same species was 50. By August 2014, a naturalist friend with a reserve 3 miles away had stopped doing moth counts. He said there were so few that it wasn't worth the effort.

In April 2013, we were sent a scientific paper by Anthony Samsel and Stephanie Seneff, which showed that glyphosate's suppression of Cytochrome P450 enzymes and amino acid biosynthesis by beneficial gut microbes has led to a variety of human diseases that globally reach epidemic proportions in populations on a Western diet, including gastrointestinal disorders, obesity, depression, autism, infertility, cancer and Alzheimer's disease [5].

Glyphosate liberally used as herbicide on GM crops and as a drying agent on conventional crops, aided and abetted by UK and European regulatory agencies

We had no idea that glyphosate and other pesticide residues had been contaminating our staple foods since before 2002, according to UK Defra (Department for Environment, Food & Rural Affairs) Expert Committee on Pesticide Residues in Food (PRiF) [6] and neither had our friends in Wales and in Denmark. Following the recommendations by Monsanto, farmers had been using glyphosate as herbicide throughout the crop growth cycle; and at the end they were also desiccating (drying) or ripening crops with glyphosate sprayed about 7-10 days before harvest [7]. So, some of us in Europe are receiving glyphosate residues in all our *non-organic* staple foods, such as bread, cereals, potatoes, pasta, pulses, rice, sugar, beer, whisky, *etc.*[6] and many foods from the US made from corn or soya (mostly GM).

Not only that, a collusion between UK's PRiF, European Food Safety Authority (EFSA) and Germany as Rapporteur Nation for European Union with Monsanto led to a 100-fold increase in the permitted glyphosate levels in lentils "In order to accommodate the authorized desiccation use of glyphosate on lentils in the United States and Canada" without consultation with European Parliament or the public (see Box 2).

When humans ingest glyphosate residues in staple foods, or animals get them in GM feed, beneficial bacteria are continually being destroyed causing failure of absorption of nutrients and minerals. Worse yet, the toxic bacteria on the other hand can thrive.

We learned later from colleagues in the US that Monsanto has a total of four patents filed on the chemical. They bought it as a chelator of heavy metals (used for cleaning boilers by 'grabbing' minerals) [10] and then marketed it as herbicide [11]. In addition they filed a patent on it as an antibiotic in 2002 [12] and as an antiprotozoal against

Box 2

Collusion between the UK Expert Committee on Pesticide Residues in Food (PriF), the European Food Safety Authority (EFSA) and the German Rapporteur Member State with Monsanto to raise glyphosate levels in lentils 100-fold without consulting European Parliament or the public

In the PriF Report of Quarter 4 of 2011 on lentils [8, p. 27] 16 samples were above the Maximum Residue Limit (MRL) of 0.1 mg/kg. [The highest level was 0.9 mg/kg]. Its risk assessment concluded that none of the residues detected would be expected to have an effect on health. The main reason: "A new, higher MRL for glyphosate on lentils is expected to come into force in summer 2012. None of the residues detected in this survey would be above this new proposed MRL."

EFSA published the following paragraph on its website [9] soon afterwards:

"According to Article 6 of the Regulation (EC) No 396/2005, Germany, herewith referred to as the Rapporteur Member State (RMS), received an application from the company Monsanto Europe to set an import tolerance for glyphosate in lentils. In order to accommodate the authorized desiccation use of glyphosate on lentils in the United States and Canada, the RMS proposes to raise the existing MRL for lentils [0.1 mg/kg] to 10 mg/kg. The RMS Germany drafted an evaluation report according to Article 8 of Regulation (EC) No 396/2005 which was submitted to the European Commission and forwarded to EFSA on 1 August 2011." This was granted by EFSA in January 2012.

There was no public consultation; the request from Monsanto was granted as a matter of routine.

malaria in 2003 [13]. Samsel & Seneff subsequently published another paper on the chemical: Glyphosate, pathways to modern diseases II: celiac sprue and gluten intolerance [14].

Some additional sources of glyphosate in South Wales: use on streets and pavements [15], Japanese knotweed [16] bracken [17] and rhododendron [18]

According to Monsanto, the glyphosate herbicide formulations Roundup® Pro Biactive and Roundup® Pro Biactive 450 are [15] "approved for weed control in amenity, industrial and forestry and aquatic areas. It can be used at any time of the year as long as weeds are green and actively growing. Monsanto advises re-spraying if die-back is not observed at 6 weeks [16].

New rules from the regulator Chemicals Regulation Directorate (CRD) in 2012 prohibits blanket spraying of any herbicide on non-porous hard surfaces. But "targeted treatment" is recommended on roads and pavements in the spring, and higher rates in autumn, and even a late autumn application [15].

With such comprehensive recommendations from Monsanto, it would not be surprising if glyphosate has saturated the environment, not only in agricultural areas but within cities in all residential areas. People and wildlife are exposed to unprecedented and still largely unknown levels of what is now known to be a highly toxic herbicide (see [19] Why Glyphosate Should Be Banned, and chapter 1 in [20] Ban GMOs Now, both ISIS special reports).

Glyphosate found in our tap and river water in 2013

In August 2013, when the Roundup® spraying season was into its 5th month, we commissioned BioCheck to measure glyphosate in tap water and river water. This is a company attached to the Veterinary School in Leipzig where the Department, headed by Prof Dr Monika Krüger, had been doing glyphosate levels in the urine of pigs, dairy cows, chickens and farmers (they all had increased

Box 3

August 29th 2014: left, devil's bit scabious, leaves with mildew, in flower, but few insects; middle, teasel: leaves with mildew, no insects taking pollen; right, comfrey, leaves with mildew, no insects taking nectar/pollen.

levels in their urine, in particular cattle with chronic botulism) [21, 22].

The level of glyphosate in one Welsh river draining from areas of Japanese knotweed spraying was 190 parts per trillion (ppt) and in local tap water was 30 ppt. These were of the order of concentrations found in a study in 2013 which showed that breast cancer cell proliferation is accelerated by glyphosate in extremely low concentrations [23]: "The present study used pure glyphosate substance at log intervals from 10^{-12} to 10^{-6} M. These concentrations are in a crucial range which correlated to the potential biological levels at part per trillion (ppt) to part per billion (ppb) which have been reported in epidemiological studies." In the UK the incidence of breast cancer has almost doubled between 1975 and 2010 [24].

We failed to discover how much Roundup® has been, or is being used, in the Swansea area

No-one can tell us (not the contractor, Complete Weed Control Ltd [25] nor the City and County Council) how much Roundup® has been used in the Swansea area over the last 10 years.

Chemicals Regulation Directorate (CRD) admits to the widespread use of Amenity Pesticides but fails to monitor them. CRD had commissioned Risk & Policy Analysts in association with Britt Vegetation Management to undertake studies on the usage of amenity pesticides. In 2010, none of the questionnaires were returned by the Contractors or Councils in Wales or Ireland [26]. The most alarming aspect was the extent of Amenity use of Herbicides. The surface types treated by Amenity Plant Protection Product (PPP) users in 2008 were specified on p. 11 of the document [26] as amenity grass, sports turf, woodland, tree/shrub beds, riparian areas/areas beside water, open water/aquatic areas, gravel ballast surfaces, pavement kerbs, road and other hard surfaces, construction sites with 'a weed issue' and broken surfaces covered with rubble.

Between 2006 and 2010, we photographed many invertebrate species; by 2014 most had vanished

In 2006, for example, at least 8 species of the family of shield bugs (Order: Hemiptera), 5mm to 15mm, were identified. Some are named after a specific shrub; e.g. hawthorn, birch, juniper, sloe or gorse, but all can be seen on other deciduous trees or types of vegetation.

In April 2014, a few shield bug young were seen. After April we saw a small number of adult shield bugs but no ladybirds. On 22 August in the early morning, I walked down the path between the fence posts and the hedge; there was not a single spider's web.

In March 2014, a red-tailed queen that had over-wintered from 2013 was seen searching for nest sites, but no new queens appeared in July 2014. The leaves of several of their food plants had mildew, the spores of which are secondary food of the 7-spot ladybirds. These natural 'pesticides' had vanished. Species which we had grown as food plants for moths and butterflies were uneaten. The sorry state of affairs is shown in Box 3.

Glyphosate increased 10 fold between August 2013 and August 2014

Analysis in local tap water in August 2014 revealed a 10-fold increase since August 2013; from 30 ppt to 300 ppt. If Roundup® continues to be sprayed in the same quantities (whatever they are), this area of South Wales will become a biological desert. At the same time, Glyphosate-resistant Japanese knotweed has appeared in August 2014, regrown after spraying early in 2014. We have photographed these in fields and along the roadside (not shown).

Monsanto found guilty of false claims about Roundup® in 1996 but still perpetrating them

We discovered that in 1996, the Attorney General of the State of New York, Consumer Frauds and Protection Bureau, Environmental Protection Bureau successfully brought a case against Monsanto with regard to: ***False advertising by Monsanto regarding the safety of Roundup® herbicide (glyphosate)*** [27].

Despite having been convicted of false claims in 1996, Monsanto repeated the same lies in a document published 2010 entitled "The agronomic benefits of glyphosate in Europe" [28, p.3]: "Since its discovery in the early 1970's the unique herbicidal active ingredient glyphosate has become the world's most widely used herbicide because it is efficacious, economical and *environmentally benign*. These properties have enabled a plethora of uses which *continue to expand to this day providing excellent weed control both in agricultural and non-crop uses to benefit mankind and the environment*." Further, it states that glyphosate has an "*excellent safety profile to operators, the public and the environment*." (italics added)

On page 4 [28] Monsanto makes another fraudulent claim about the use of glyphosate in increasing wildlife and biodiversity: "**Increased wildlife and biodiversity:** Use of glyphosate instead of mechanical weed control techniques on non-cropped/amenity land preserves wildlife like small mammals and birds. Adoption of Conservation agriculture encourages earthworms and other invertebrates as well as birds. Judicious use of glyphosate to control excessive plant growth and invasive weeds on or around waterways and lakes encourages wildfowl and much other wildlife."

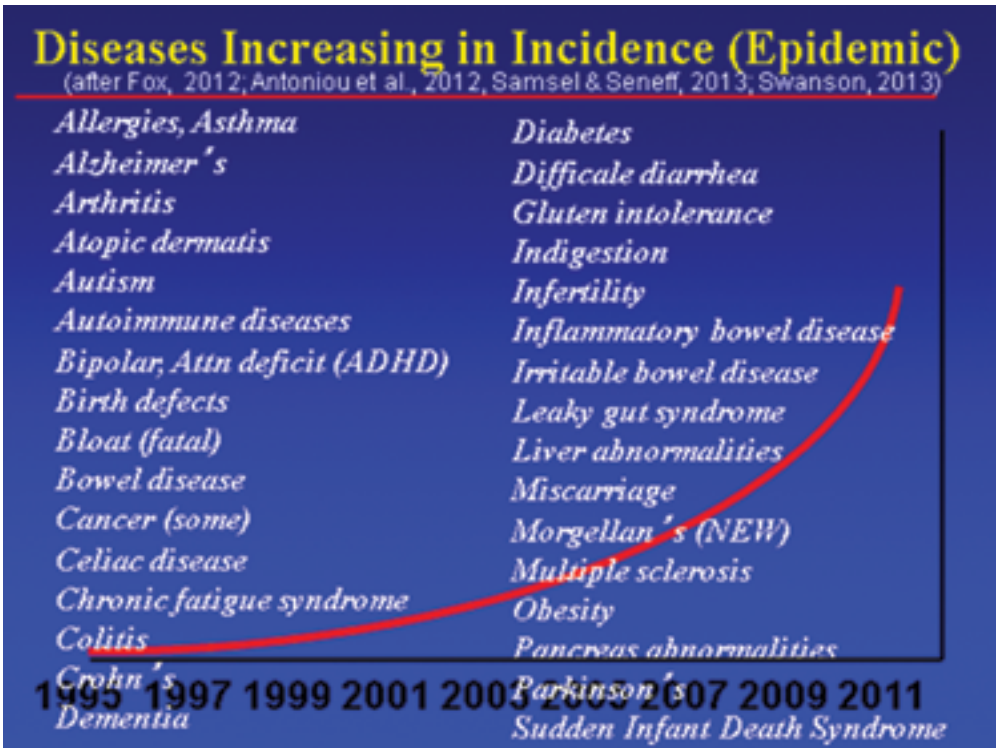
An additional claim was made for GM Crops (p. 4): "Use of glyphosate tolerant crops allows later control of weeds providing early food sources for many invertebrates and birds and thus increases animal numbers."

I am not alone in having Roundup® poisoning my reserve

Craig Childs, author of *Apocalyptic Planet*, describes searching for signs of life in 2012 on a farm in Grundy Count, Iowa, which was growing Monsanto's GM Bt Roundup® Ready corn [29]: "I had come to a different type of planetary evolution. I listened and heard nothing, no bird, no click of an insect."

American journalist Robert Krulwich reviewed *Apocalyptic Planet* [30]:

"Yet, 100 years ago, these same fields, these prairies, were home to 300 species of plants, 60 mammals, 300 birds, hundreds and hundreds of insects. This soil was the richest, the loamiest in the state. And now, in these patches, there is almost literally nothing but one kind of living thing. We've erased everything else. There's something strange about a farm that intentionally creates a biological desert to produce food for one species: us. It's efficient, yes. But it's so efficient that the ants are missing, the bees are missing, and even the birds stay away. Something's not right here. Our cornfields are too quiet."



Slide from Dr Don Huber's presentation to UK All-Party Parliamentary Group on Agroecology

Everyone said that we must: "*Wait for the European Reassessment of Glyphosate in 2015*"

We wrote to many people (the Council, the Welsh Assembly, the Chemicals Regulation Directorate and the HSE among others) to tell them about glyphosate in our drinking water. We begged them all to stop its use, but the replies were virtually identical; "*The German Rapporteur Member State and EFSA are doing a reassessment for 2015.*"

But it has been shown that glyphosate reassessment in Europe is fraudulent

On 9 July 2014, ISIS circulated Scandal of Glyphosate Re-assessment in Europe (*SiS* 63) [31] (see Chapter 11), revealing that the German Rapporteur Member State's Federal Institute of Risk Assessment (BfR) and its federal agency partners did not actually review the published toxicology studies, but relied on a summary provided to them by the Glyphosate Task Force (GTF), a consortium consisting of Monsanto and chemical companies all over Europe, including Syngenta UK and Dow Italy, with an odd one from Taiwan. GTF describes itself as [32] "a consortium of companies joining resources and efforts in order to renew the European glyphosate registration with a joint submission." ***Hence***

Monsanto and other companies who stood to gain from selling glyphosate herbicides were given free rein to pronounce glyphosate effectively even safer than before [33]***, hence the increase in Acceptable Daily Intake (ADI)*** recommended in the RAR.

GTF systematically excluded all independent peer-reviewed studies that reported congenital birth defects, reproductive problems and cancers in humans and animals; studies reporting the presence of glyphosate in human or animal urine; long term (24-month) feeding studies in rats that showed liver damage, kidney damage, tumours and endocrine disruption, and any study reporting high levels of AMPA, a toxic metabolite of glyphosate, in the environment. It also excluded all studies using Roundup, as only the 'active ingredient' pure glyphosate was risk assessed for toxicology, despite the fact that Roundup is the most widely used glyphosate herbicide in Europe, and adjuvants in the formulations are known to be highly toxic and have synergistic effects on glyphosate toxicity (see [19, 20]).

Renewal Assessment Report (RAR) on Ecotoxicity

Unsurprisingly, GTF's evaluation of peer-reviewed literature regarding ecotoxicity [34] also broadly concluded that ***glyphosate is not harmful to the environment.***

We strongly challenge this conclusion; we believe glyphosate is likely responsible for destroying biodiversity in our small nature reserve in South Wales. There is also already evidence of glyphosate/Roundup toxicity to frogs, aquatic ecosystems, soil ecosystems, and link to demise of Monarch butterflies, as well as diseases and birth defects of livestock [20]. The relevant evidence for ecotoxicity was dismissed in the RAR [34] in the same cavalier way as toxicity of glyphosate for humans [31]. The disappearance of wildlife hardly bodes well for human health [5, 14] as already suggested, and as epidemiological evidence shows (see below).

Worsening health since glyphosate use increased

Studies published in 2013 in the *Journal of American Medical Association* (*JAMA*) [35] and the *Lancet* [36] respectively show that between 1990 and 2010, US and Britain have slipped down the scale of health compared with other wealthy nations.

An All-Party Parliamentary Group (APPG) on Agroecology meeting on 18 June 2014 brought together world experts on glyphosate. One of them, senior scientist at US Department of Agriculture and world expert on glyphosate Dr Don Huber showed a slide [37] summarising diseases that have increased in incidence since 1995, correlated with the red line representing the increasing use of glyphosate in the US.

Huber ended a talk he has given all over the world as follows [38]:

"Future historians may well look back upon our time and write, not about how many pounds of pesticide we did or didn't apply, but by how willing we are to sacrifice our children and future generations for this massive genetic engineering experiment that is based on flawed science and failed promises just to benefit the bottom line of a commercial enterprise."

11

Scandal of Glyphosate Re-assessment in Europe

EU rapporteur state Germany recommends re-approval with daily intake increased by 67 %; its re-assessment was carried out by Monsanto and a consortium of chemical companies in Europe based almost entirely on studies from industry; it should be rejected outright

Dr Nancy Swanson and Dr Mae Wan Ho

Preposterous verdict of "acceptable" risks for glyphosate

Germany, acting as the European Union rapporteur member state (RMS) submitted their glyphosate renewal assessment report (RAR) to the European Food Safety Authority (EFSA) in January 2014, recommending re-approval of glyphosate for use in Europe with increase in the acceptable daily intake (ADI) from 0.3 to 0.5 mg per kg body weight per day [1].

The overall findings of the RAR are that glyphosate poses no unacceptable risks. Glyphosate is not metabolized or accumulated in the body, not genotoxic, not carcinogenic, not endocrine disrupting, and not considered persistent or bioaccumulative; it has no reproductive toxicity, no toxic effects on hormone-producing or hormone-dependent organs, and no unacceptable effect on bees. Therefore any risks are within acceptable standards. The only risks noted were that glyphosate is a severe eye irritant and is persistent in soil. We are yet to find out how the final decision will be affected by the WHO assessment (see Chapter 12) of glyphosate as a 'probable carcinogen', though the glyphosate task force involved in the renewal process (see later) have responded by stating they do not accept the decision [2].

Issues that could not be finalized in the assessment were: relevance of impurities, effects on microorganisms, effects on non-targeted plants, and indirect effects on biodiversity - non-targeted organisms, particularly birds.

The Proposed Decision at the end of Vol. 1 is completely blacked out.

Scandalous conclusion amid overwhelming evidence of toxicities

How did they arrive at such a preposterous conclusion when the evidence for glyphosate herbicides toxicity has accumulated worldwide to such an extent that a number of countries are already banning its use? Denmark took the lead to ban the herbicide back in 2003 [3] The Dutch Parliament banned it in April 2014 for non-commercial use [4], to take effect by the end of 2015; France is set to follow. Brazil, one of the largest growers of glyphosate-tolerant genetically modified (GM) crops has now filed a law suit by Federal Prosecutors to ban glyphosate along with 8 other dangerous pesticides [5]. El Salvador imposed a complete ban in February 2013, linking glyphosate herbicides to an epidemic of chronic kidney disease that has struck the region [6]. Sri Lanka's

Mountainside agriculture in El Salvador, photo Oisin Prendiville, Flickr

scientists have provided evidence for glyphosate accumulation in the body especially in the presence of hard water. Its ability to capture and retain arsenic and nephrotoxic metals enables it to act as a carrier to deliver the toxins to the kidney [7] (see Chapter 6).

Glyphosate has also been linked to many other health problems including cancers (see Chapter 5), infertility (see Chapter 4), along with neurotoxicity, reproductive problems, birth defects, genotoxicity, and other human health problems as well as ecotoxicity (see Chapter 1), and many have considered a world-wide ban long overdue.

A severely restrictive electronic-only and biased comment process

EFSA had put the RAR on their website for public consultation, which ended 11 May 2014. The response was electronic only on a rigid template with predetermined categories of answers, and severe limitations on space. Neither e-mail, nor ordinary mail was accepted. Commenters had to sign an agreement to have their comments deleted if deemed unsuitable. Thus, all comments relating to Roundup were ignored, even though Roundup is the most widely used glyphosate herbicide in Europe. The consultation was strictly limited to pure glyphosate. Dr Brian John of GM-Free Cymru lodged a complaint with the European Ombudsman saying that EFSA had no right to impose those conditions, accusing the process of being [8] "biased, and heavily weighted towards those who want to see glyphosate continue in use" and "entirely unfit for purpose."

The entire process of risk assessment was also completely non-transparent.

Who were the authors of the risk assessment report?

The German Federal Institute for Risk Assessment (BfR-- Bundesinstitut für Risikobewertung) is responsible for the RAR. There is no information on authorship anywhere within the 15 documents totalling 3 744 pages [9]. Between April and June of 2014, the BfR was contacted and asked on four separate occasions to provide information on who authored the report and which committee at BfR was responsible for the report. To date, they have not responded.

The BfR Committee for Pesticides and Their Residues (CPTR), which might be expected to be responsible for preparing the RAR, has 3 out of 12 of its 2014 members and 4 out of its 16 2011-2013 members from either BASF or Bayer CropScience [10, 11]. This serious conflict of interest in a regulatory agency is not restricted to BfR, it is endemic to the EU regulatory agency.

EFSA has a history of conflicts of interest. The Corporate Europe Observatory report 'Unhappy Meal' published in October 2013 [12], revealed that some 59 % of EFSA's scientific panel members still had direct or indirect links to companies whose activities fell under EFSA's remit. As a result the European Parliament voted in April 2014 for a resolution to ban scientists with ties to the agriculture and food industries from working at the agency, and has given EFSA two years to clean up its act [13].

How did they arrive at such a preposterous conclusion when the evidence for glyphosate herbicides toxicity has accumulated worldwide to such an extent that a number of countries are already banning its use?

The entire process of risk assessment for re-approval was flawed and corrupt to the core. It is rife with conflict of interest, non-transparent and heavily biased towards unpublished, non-peer reviewed studies from industry. The RAR is worse than useless, and should be rejected outright. All available evidence including studies on commercial formulations of glyphosate herbicides should be seriously considered in any risk assessment, and by a truly independent, unbiased panel free from any conflict of interest

But the conflict of interest is even more blatant than anyone could have imagined. It is Monsanto and a consortium of European chemical companies that performed the risk assessment for the re-approval of glyphosate.

Monsanto & a consortium of European chemical companies did the risk assessment

The BfR stated in its press release [14]: "Apart from the BfR, other institutes involved in the new assessment of glyphosate were the Federal Environment Agency, the Julius Kühn Institute and the Federal Office of Consumer Protection and Food Safety, the latter as risk management authority." That was designed to add undue respectability and gravitas to the risk assessment.

But BfR and its federal agency partners did not actually review the published toxicology studies. Instead they relied on a summary provided to them by the Glyphosate Task Force (GTF) [15]. And the GTF consists of Monsanto and a consortium of chemical companies all over Europe, including Syngenta UK and Dow Italy, with an odd one from Taiwan thrown in for good measure (see pp. 9-13 of Vol. 1 of the RAR [9]). Although the BfR added comments here and there, all the assessments of the toxicological studies were from the GTF. Hence Monsanto and other companies who stood to gain from selling glyphosate herbicides were given free rein to pronounce glyphosate effectively even safer than before, hence the increase in ADI.

Let us be clear: even the industry's studies found toxic effects for acute (single dose), subchronic (short-term) and chronic (long-term) exposures at some dosage. The way the game is played is to vary the dose and find the maximum dose where no adverse effects are observed (NOAL). Then divide that by 100 to obtain the ADI and declare the substance "safe". The chemical industries ***already know*** that glyphosate is toxic and can cause a host of physical problems.

Selective 'expert' rejection of counter-evidence

The GTF used a scheme devised by H.J. Klimisch and other scientists working for BASF in 1997 to assess the reliability of toxicological studies [16]. The method aims to classify toxicological data into one of four categories: reliable without restriction, reliable with restrictions, not reliable, and not assignable. However, the assignment is weighted toward industry studies and is heavily dependent on the judgment of the human toxicologists involved. It can certainly not overcome human bias.

Consequently, the rapporteur member state (RMS) has accepted, without question, virtually all of the unpublished reports given to them by the chemical companies. Much of the information is blacked out (author, report title, laboratory) but the sponsoring company is named (Monsanto, Syngenta etc.) and the reports are referred to by a number.

When the industry toxicology reports were in conflict with each other, they chose to sanction the ones that reported less toxic responses, relegating others to "supplementary" status. When the toxic effects were significant compared to their own controls, they used illicit "historical controls" instead to make them appear less significant.

Of the published reports, with the exception of genotoxicity, they only used those that tested for glyphosate alone. The glyphosate was "supplied by Monsanto at 99% purity." That, despite the fact that the public has been using nothing but formulations, especially Roundup!

The GTF took all of the peer-reviewed studies and proceeded to find excuses to throw out the ones that didn't agree with the already-accepted industry studies. First they threw out all studies that used the actual product (Roundup, Rodeo, Lasso etc.) because the active ingredient percentage is not the same from product to product and the surfactants used vary from product to product so the results cannot be compared and are thus inconclusive. They threw out any studies where they deemed that the dosage was unreasonably high, compared to their "safe" levels, although their own toxicology studies showed the same results at the higher dosages. They threw out any that they decided were inapplicable to mammals (frog embryos, insect larvae etc.) or that were administered in a non-natural way (injection). They took issue with how many rats/mice/dogs/guinea pigs were or were not used and how things were or were not measured or reported.

For human studies, the GTF argued that the dose/response could not be determined; the toxic effect could not be traced to glyphosate alone, the application rates were unreasonable for Europe, or there were reporting deficiencies of some sort.

For more details see a synopsis of the toxicology section of the RAR prepared by Nancy Swanson [17].

To conclude

The entire process of risk assessment for re-approval was flawed and corrupt to the core. It is rife with conflict of interest, non-transparent and heavily biased towards unpublished, non-peer reviewed studies from industry. The RAR is worse than useless, and should be rejected outright. All available evidence including studies on commercial formulations of glyphosate herbicides should be seriously considered in any risk assessment, and by a truly independent, unbiased panel free from any conflict of interest.

12

Glyphosate 'Probably Carcinogenic to Humans' Latest WHO Assessment

The world authority on cancer's evidence-based assessment is pitched against the Monsanto-led corrupt approvals in US and Europe

Dr Mae-Wan Ho and Dr Nancy Swanson

World authority experts selected free from conflict of interest

The world authority on cancer, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) declared the herbicide glyphosate 'probably carcinogenic to humans' in its latest expert assessment [1, 2]. A Working Group of 17 experts from 11 countries met at IARC headquarters 3-10 March 2015 in Lyon, France. The meeting followed almost a year of review and preparation, including a comprehensive review of the latest available scientific evidence. The experts were selected on the basis of their expertise and most importantly, *the absence of real or apparent conflicts of interest*. The Working Group considered "reports that have been published or accepted for publication in the openly available scientific literature" as well as "data from governmental reports that are publicly available". They evaluated five organophosphate insecticides and herbicides including glyphosate. The results, announced 20 March were as follows. The herbicide **glyphosate** and the insecticides **malathion** and **diazinon** were classified as probably carcinogenic to humans (Group 2A). The insecticides **tetrachlorvinphos** and **parathion** were classified as possibly carcinogenic to humans (Group 2B).

Significance of the assessment

To understand the real significance of the new assessment, some background information is needed. Substances and exposures that can lead to cancer are called carcinogens.

The IARC is part of the WHO, its major goal is to identify causes of cancer, and its classification for carcinogens is the most widely used and accepted in the world [3]. In the past 30 years, the IARC has evaluated the cancer-causing potential of more than 900 likely candidates, placing them into the following categories:

Group 1: Carcinogenic to humans
Group 2A: Probably carcinogenic to humans
Group 2B: Possibly carcinogenic to humans

Group 3: Unclassifiable as to carcinogenicity in humans
Group 4: Probably not carcinogenic to humans

Commenting on the classification system, the American Cancer Society stated [3]: "Perhaps not surprisingly, based on how hard it can be to test these candidate carcinogen, most are listed as being of probable, possible, or unknown risk. Only a little over 100 are classified as "carcinogenic to humans.""

The Environmental Protection Agency uses a rating system similar to that of IARC [3]:

Group A: Carcinogenic to humans
Group B: Likely to be carcinogenic to humans
Group C: Suggestive evidence of carcinogenic potential
Group D: Inadequate information to assess carcinogenic potential
Group E: Not likely to be carcinogenic humans

The world authority on cancer, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) declared the herbicide glyphosate 'probably carcinogenic to humans' in its latest expert assessment [1, 2]. A Working Group of 17 experts from 11 countries met at IARC headquarters 3-10 March 2015 in Lyon, France

Thus, a classification of 2A in cancer-causing potential for glyphosate on the IARC is almost the highest possible categorization.

As stated in the IARC press release [1]: "Group 2A means that the agent is ***probably*** *carcinogenic to humans*. This category is used when there is limited evidence of carcinogenicity in humans and *sufficient evidence of carcinogenicity* in experimental animals."

It should also be noted that the two insecticides placed in the lower category (2B) in terms of cancer-causing potential are both in restricted use. Tetrachlorvinphos is banned in the European Union, but continues to be used in the US; while parathion has been severely restricted since the 1980s, and all authorized uses were cancelled in the European Union and USA by 2003.

Of the organophosphates in Group 2 A, diazinon has been used in agriculture and home and garden insect-control. It has been in low production especially after 2006 due to restrictions in the USA and the EU. Malathion is used in agriculture, public health and residential insect control, and continues to be produced in substantial volumes throughout the world. But it is minor league compared with glyphosate. As highlighted in the assessment [1, 2], glyphosate has the highest global production volume of all herbicides. The agricultural use of glyphosate has increased sharply since the introduction of genetically modified (GM) crops tolerant to glyphosate. The largest use worldwide is in agriculture, but it is also deployed in forestry, urban, and home applications in more than 750 different commercial products. Consequently, glyphosate has been detected in the air during spraying, in water, and in food. The general population is exposed primarily through residence near sprayed areas, home use, and diet.

Evidence of glyphosate's cancer-causing potential including that suppressed by EPA

The assessment cited the main evidence on which the classification of glyphosate as probably carcinogenic to humans is based [1] as follows:

"For the herbicide glyphosate, there was limited evidence of carcinogenicity in human for non-Hodgkin lymphoma. The evidence in humans is from studies of exposures, mostly agricultural in the US, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. On the basis of tumours in mice, the United States Environmental Protection Agency (USEPA) originally classified glyphosate as possibly carcinogenic to humans (Group C) in 1985 [equivalent to IARC group 2C]. After a re-evaluation of that mouse study, the US EPA changes its classification to evidence to non-carcinogenicity in humans (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is sufficient evidence of carcinogenicity in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby."

Note the pointed reference to US EPA evidence that has been suppressed. This happened through a litany of outright fraud committed by testing companies working for the corporations, deception, and half-truths (see Chapter 5). It should be seen in the light of EPA's decision in 2013 to raise the allowable limits of glyphosate contamination in farm-grown food and animal feed [4]. The amount of allowable glyphosate in oilseed crops (except for canola and soy) went up from 20 ppm to 40 ppm, 100 000 times the amount needed to induce breast cancer cells.

Yet more evidence was cited for animal experiments with glyphosate [2]. These included glyphosate induced positive trend in the incidence of a rare renal tubule carcinoma in male CD-1 mice, a positive trend for haemangiosarcoma in male mice, pancreatic islet-cell adenoma in male rats in two studies, and a promotion of skin tumours in an initiation-promotion study in mice [5].

Also pointed out in the assessment [2], glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption into the body. Soil microbes are known to degrade glyphosate to aminomethylphosphoric acid (AMPA). Blood AMPA detection after poisonings therefore suggests intestinal microbial metabolism in humans.

Glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells

in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations. Bacterial mutagenesis tests were negative, but glyphosate, glyphosate formulations, and AMPA induced oxidative stress in rodents and *in vitro*. Oxidative stress induces reactive oxygen species that can damage DNA [6].

Since our last review on glyphosate and cancer (Chapter 5) new evidence has emerged. Leah Schinasi and Maria Leon at IARC, Lyon, France carried out a systematic review and a series of meta-analyses of nearly three decades worth of epidemiologic research on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to agricultural pesticide active ingredients and chemical groups. Estimates of associations of NHL with 21 pesticides and 80 active ingredients were extracted from 44 papers, all reporting studies conducted in high-income countries (12 countries, majority in Europe or N. America) [7]. Random effects meta-analyses (allowing heterogeneity between studies to contribute to the variance) showed that phenoxyherbicides, carbamate insecticides, organophosphorus insecticide and the active ingredient lindane, an organochlorine insecticide, were positively associated with NHL. In addition, in a handful of papers, associations between pesticides and NHL subtypes were reported: B cell lymphoma was positively associated with phenoxy herbicides and glyphosate. Diffuse large B-cell lymphoma was positively associated with phenoxy herbicide exposure.

New evidence has also come from Argentina, where a team of researchers at Universidad Nacional de Rio Cuarto used a recently established method for monitoring genetic damage resulting from chemical exposure by determining the frequency of micronuclei in the cells lining the inside of the mouth [8]. They found that children living within 500 m of spraying areas have over 66 % more cells with micronuclei than those living more than 3 000 m away. In addition, 40 % of the exposed children suffer from persistent conditions that may be associated with chronic pesticide exposure including respiratory symptoms, with and without additional symptoms such skin itching or stains, nose itching or bleeding, lacrimation, eye and ear burning or itching.

The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is sufficient evidence of carcinogenicity in experimental animals

Monsanto, the Glyphosate Task Force, and the Joint Glyphosate Task Force protest against classification

Monsanto, whose $15.9 billion of annual sales are closely tied to glyphosate [9], protested that the scientific data did not support the conclusions and called on WHO to hold an urgent meeting to explain the findings [10]. "We don't know how IARC could reach a conclusion that is such a dramatic departure from the conclusion reached by all regulatory agencies around the globe," Philip Miller, Monsanto's vice-president of global regulatory affairs, told the press. Apart from the EPA's 2013 hike of allowable glyphosate contamination levels [4], the German government completed a four year evaluation of glyphosate for the EU, concluding that it was "unlikely to pose a carcinogenic risk in humans" [11].

The Glyphosate Task Force (GTF) is a consortium of chemical companies, including Monsanto, formed to promote glyphosate in Europe. The Joint Glyphosate Task Force (JGTF) is the US counterpart. On the same day that the *Lancet* article [2] was published, both the GTF and the JGTF published announcements decrying the WHO classification [12]. They accuse the IARC of only taking into account "a narrow selection of studies and was therefore made without the benefit of analyzing the extensive and relevant database on glyphosate relied upon by the world's regulatory authorities..." They then lauded the German glyphosate re-assessment report (RAR) saying, "As recently as January, the German government completed a four-year study of glyphosate on behalf of the European Union and concluded that glyphosate was unlikely to pose a carcinogenic risk in humans. It is baffling that IARC arrived at such a different conclusion than all these other scientific reviews."

Of course they would refer to the RAR. They wrote it. The GTF prepared the dossier on glyphosate renewal for the German member state and submitted it to the Federal Institute for Risk Assessment (BfR) in Germany. The BfR rubber-stamped it and sent it on to the European Food Safety Authority (EFSA), adding only a few comments here and there.

Finally, the GTF accuses the IARC of not taking into account all of the data available, particularly the industry-sponsored studies [13]. "Most peer reviewed literature and other publicly available information such as the evaluations, opinions and conclusions of regulatory competent authorities were also dismissed by IARC."

Corrupt assessment in the European Union

It is supreme irony for GTF to accuse IARC of not taking into account all of the data available, as the GTF's assessment on behalf of the German government was most narrowly based on industry studies and others that concurred with the findings from industry.

In the carcinogenicity section of toxicology portion of the RAR, 13 industry-sponsored studies were evaluated. All were deemed "acceptable" and all found no significant carcinogenetic effects. Two published studies on rodents were considered. One found no significant results and the other was "considered by the authors to indicate a tumour promoting potential of glyphosate. However, the formulation Roundup was used in the study and not the active substance glyphosate." All studies that used an actual product were disqualified because they claim that only the active ingredient, glyphosate, needs to be evaluated [14].

Twelve peer-reviewed studies, most of which were based on data from a single study (the Agricultural Health Study), found no evidence of carcinogenicity. These studies were all deemed reliable and used in the evaluation.

Only six studies finding a link between glyphosate and cancer were included in the RAR but were disqualified and deemed unreliable, mostly because exact exposures to glyphosate could not be identified in the epidemiological studies. The one lab

study (Séralini) was disqualified because they didn't follow OECD guidelines. And this was only the cancer section. For more details see (Chapter 11) [15].

Glyphosate bans already under consideration

Fortunately, there are non-corrupt regulatory agencies in the world that look at the whole range of evidence on glyphosate toxicity, of which being a probable human carcinogen is just one aspect (see Chapter 1). Glyphosate and in particular the Monsanto formulations Roundup is a wide-spectrum weed killer with wide-spectrum toxicities on organisms and cells. A number of countries have already imposed bans on the herbicide.

Sri Lanka is the latest to impose a ban, effective immediately following the WHO assessment [16], after it had already issued a partial ban following the epidemic of fatal kidney disease in the country [17].

El Salvador, stricken with the same lethal kidney disease epidemic, has voted to ban glyphosate along with 52 other chemicals since 2013 [18], though it has yet to be written into law, again under great pressure from industry.

Brazil's Federal Public Prosecutor has requested the Justice Department to ban glyphosate along with 8 other chemicals [19]. Finally, the Dutch Parliament voted for a ban on non-agricultural uses [20].

To conclude

Individuals, farmers, gardeners, restaurants, shops, local communities should now stop using glyphosate herbicides in defiance of the corrupt approvals given, in order to safeguard the health of people and planet.

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Chapter 1

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About The Institute of Science in Society

The Institute of Science in Society (ISIS) was co-founded in 1999 by scientists Mae-Wan Ho and Peter Saunders to provide critical yet accessible and reliable information to the public and policy makers.

ISIS aims to reclaim science for the public good; to promote a contemporary, holistic science of the organism and sustainable systems; and influence social and policy changes towards a sustainable, equitable world. ISIS is a partner organisation of the Third World Network based in Penang, Malaysia, and works informally with many scientists who are members of ISIS or of the Independent Science Panel that ISIS initiated (see below).

ISIS works through lively reports posted on its popular website www.i-sis.org.uk, archived by the British Library since 2009 as part of UK's national documentary heritage. The reports are circulated to a large e-mail list that includes all sectors of civil society worldwide, from small farmers in India to policy-makers in the United Nations. We publish an art/science, trend-setting quarterly magazine Science in Society, and topical in-depth, influential, and timely reports (see below) as well as monographs including *Genetic Engineering Dream or Nightmare* (1998, 1999, 2000, 2007), *Living with the Fluid Genome* (2003), *Unravelling AIDS* (2005), The *Rainbow and the Worm, the Physics of Organisms*, 3rd edition (2008); *Living Rainbow H2O* (2012).

ISIS also initiates major campaigns from time to time:

World Scientists Open Letter, February 1999, calling for a moratorium on genetically modified (GM) organisms, ban on patents on life, and support for sustainable agriculture; eventually signed by 828 scientists from 84 countries http://www.i-sis.org.uk/list.php

Independent Science Panel, constituted May 2003, consists of dozens of scientists from many disciplines. Its report, *The Case for a GM-Free Sustainable World*, calling for a ban on GM crops and a comprehensive shift to sustainable agriculture was presented in the UK Parliament and European Parliament, circulated worldwide, and translated into 5 or more languages. As a follow up, a special report *Ban GMOs Now* was published in 2012 and widely circulated and distributed worldwide.

Sustainable World Global Initiative, launched April 2005, http://www.i-sis.org.uk/SustainableWorldInitiativeF.php, held its first international conference 14/15 July 2005 in UK Parliament, followed by a weekend workshop 21 January 2006, out of which came a proposal for an innovative food and energy self-sufficient 'Dream Farm 2' for demonstration/education/research purposes. Its first report, *Which Energies?*, appeared in 2006, followed by a second definitive report, *Food Futures Now* (2008) showing how organic agriculture and localized food and energy systems can provide food and energy security and free us from fossil fuels. The third and final report, Green Energies - 100% Renewable by 2050 (2009) was also launched in UK Parliament November 2009, and struck a chord among politicians and opinion formers. It marks the turning point in the world's commitment to green renewable energies.

Reclaiming Beauty and Truth in Science and Art was launched in a unique art/science event 26-27 March 2011, when a whole-foods factory was transformed overnight into an art gallery and music/lecture hall around the theme of 'quantum jazz', the sublime aesthetics of quantum coherence in living systems and the living universe http://www.i-sis.org.uk/Avant_Garde_ArtScience_Event.php. The event was marked by a commemorative volume of essays and artworks, *Celebrating ISIS, Quantum Jazz Biology *Medicine*Art*, a Quantum Jazz Art DVD of artworks with a special selection of music, plus four DVDs of performances and interviews at the actual event itself. Our second act was an extended art/science/music festival, Colours of Water, 12-28 March 2013, a resounding success featuring an amazing cast of scientists, artists, musician, and other social leaders from around the world, all inspired by water and aiming to raise awareness on sustainable water use and conservation (http://www.i-sis.org.uk/coloursofwater/).

Science & Democracy began as an Open Letter on Retraction and Pledge to Boycott Elsevier in December 2013 to support independent scientific research and publication (signed by **1398** scientists and **4025** non-scientists from 100 different countries) followed by the launch in April 2014 of THESPARC www.thesparc.net 'a floating knowledge archive for the survival of people and planet'. THESPARC identifies and provides both scientists and the general public free open access to key scientific papers and preprint. It is a knowledge archive, a systematic collection of papers that are classified by subject areas and searchable by subject, authors, and key words. It is 'floating' in that the papers are stored on other websites. In June 2015, we launched the Independent Scientists Manifesto on Glyphosate calling on governments at all levels to ban the spraying of glyphosate based on overwhelming evidence of harm compiled by an internal group of 81 scientists.

Glyphosate/Roundup, falsely claimed by Monsanto to be safe and harmless, has become the world's most widely and pervasively used herbicide, especially with glyphosate tolerant GM crops

It has brought rising tides of birth defects, cancers, fatal kidney disease, sterility and dozens of other illnesses

Read the devastating evidence
&
BAN glyphosate herbicides from your home & local community

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