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INGSA CASE STUDIES

"ROUNDUP READY"? REGULATING GLYPHOSATES AMIDST HEALTH, ECONOMIC AND PUBLIC CONCERNS ABOUT GM

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CHAFER SENTRY APPLYING GLYPHOSATE TO STUBBLES IN NORTH YORKSHIRE ON A SUNNY DECEMBER DAY

"ROUNDUP READY"? REGULATING GLYPHOSATES AMIDST HEALTH, ECONOMIC AND PUBLIC CONCERNS ABOUT GM

Glyphosate is a leading herbicide, most notably sold as the compound Roundup, which is used in conjuction with crops genetically engineered to be resistant to its effects to reduce pesticide use and increase yields. However, Roundup is also used in maintenance of public parks, pest control in forests, and is sold in gardening centres for household use. Glyphosate itself is used in hundreds of products, making it difficult to fully test in combination with other chemicals which might be used. In light of this, its exact toxicity to humans, bees and the environment in general has been difficult to determine, and has formed a significant area of public resistance to genetically modified organisms. Recently, the licence for glyphosate has come up for renewal in the European Union, opening up the debate about a blanket ban once again. This debate has been recently complicated by the WHO's reclassification of glyphosate as a probable carcinogen, a conclusion that was subsequently challenged by the renewal process, during which the report on acceptable risk issued by EFSA concluded that glyphosate was in fact not carcinogenic if used according to the limits set.

Background and context

In 1974, the multinational biotechnology corporation Monsanto launched a new broad-spectrum herbicide based on the active substance glyphosate.[1] Marketed under the trade name 'Roundup', this herbicide was part of the corporation's large scale involvement in the "green revolution", a global project supported by the World Bank that aimed to increase food production in developing countries through the industrialization of agriculture and extensive use of fertilizers and pesticides. At its introduction Roundup could help clear land for cultivation, but it could not be used on arable crops because crop species as well as weeds succumbed (Duke and Powles 2008).

In the early 1980s Monsanto scientists began working on genetically modified plants which would be engineered for resistance to Roundup, thus allowing use of the compound to remove invasive weed species without damaging the crops. This was done using genetic modification to insert a bacterial gene which produced an enzyme to bypass the toxic effects of glyphosate. In 1994 the corporation released the first transgenic glyphosate-resistant crops—soybeans and canola, followed rapidly by cotton, maize and sugar beets (Cerdeira & Duke 2006). The uptake of these transgenic crops was spectacularly fast and wide, first in North and South America but also globally (James 2015). Monsanto claimed this combination of herbicide and GM seed modified to resist the herbicide enabled food producers to reduce the use of other weed-control tools (chemical or mechanical). Furthermore, glyphosate was claimed to be relatively harmless because it bound tightly to soil constituents with little movement through either soil or groundwater, and had a short environmental half-life with no atmospheric contamination because it is not volatile.

[1] (N-(phosphonomethyl)glycine)

Initially, the WHO classified glyphosate as "probably not carcinogenic to humans". Multiple studies found it was not retained in animal tissue, while reports of potential toxicity in humans were generally blamed on surfactants (chemical additives to the Roundup compound), not on the glyphosate molecule itself, which was deemed non-carcinogenic and not developmentally toxic (Williams *et al*. 2000). However, many of the studies reviewed at that time were carried out by Monsanto, and the structure of risk evaluation studies could leave questions about longer-term exposure unanswered.

A highly controversial paper was published in 2012 by a French scientist, Gilles-Éric Séralini, who had a history of publishing anti-GM claims. To immense and controversial publicity by the author at the time of its release, the paper suggested that Roundup did indeed cause tumours in rats when studied over a longer period. This paper was withdrawn by the publisher a year later after vigorous criticism of its statistical and scientific validity by the scientific community (including several French Académies). It was eventually republished without any further peer review in a different journal along with the raw data (Séralini et al. 2014).

As time went on, it was noted that resistance to glyphosate was beginning to increase in both GM crops (Gilbert 2013) and in related weeds through exchange of genetic material, causing farmers to apply other herbicides along with glyphosate-derived products and thus increasing rather than lowering the total volume of herbicide use (Cerdeira & Duke 2006).[2] Resistance is also driving development of new herbicidal formulations that carry multiple active ingredients (Freedonia 2012 in IARC 2012), which may bring new risks to the environment and animal/human health.

Monsanto now controls 26% of the global seed market (Jones 2015), while 89% of corn and 94% of soybeans grown in the US are from patented GM seeds (USDA 2016). These increasingly include 'stacked' traits (i.e. resistance to insects as well as herbicides), particularly in corn and cotton. Monsanto's market dominance is presented by activists as an exemplar of an agro-industrial business model which is pushing smallhold farmers into debt for the purpose of increasing profit (Zacune 2012).

The dilemma

Although there has been widespread uptake of GM crops by farmers in the USA and South America, this has been countered by widespread public resistance in Europe and other regions. In 2015, the EU voted to allow countries to block GM and to date 19 of the 28 member states have enacted bans, including of Monsanto's bt maize, which at present is grown only in very small amounts in Portugal and Spain.[3]

[2] A report by respected consultants PG Economics concludes that pesticide use has in fact decreased by 8.2% due to adoption of GM (Brookes & Barfoot 2016). However, this company has also been flagged by Lobbywatch.org for having undeclared interests, and its research is often funded by industry lobby groups which include Bayer, Dow, DuPont, Monsanto and Syngenta (see http://www.lobbywatch.org/profile1.asp?PrId=308).

[3] However, many EU countries which ban cultivation do allow import of GM products.

At the same time, the active ingredient in Roundup, glyphosate, was coming to the end of its approved licensing period in Europe, having been authorised in 2002. While Roundup accounts for a significant share of the agro-industrial market, including use by home gardeners, glyphosate is also used in a number of other products - more than 750 in the US alone (IARC 2012). It is therefore impossible to test each and every compound, particularly as new products continue to enter the market.

In Europe glyphosate must first be approved at EU level before member states can authorise its use in products for their own markets, and expiry of the approval would require all member states to withdraw authorisation for the sale of products containing it.[4] Periodic renewal of this approval is required, and in this instance began in 2012. Although any person can submit information during preparation of the draft assessment report which is prepared by the Rapporteur Member State (in this case, Germany), EFSA is expected to make an active assessment only of the *technical* evidence it receives.

The role of scientific advice

In March 2015, the International Agency for Research on Cancer (IARC), the cancer-research arm of the WHO,[5] released a report that assessed the carcinogenicity of five major herbicides, including glyphosate (Guyton, Loomis et al. 2015). The commission used evidence from human, animal, and mechanistic studies, i.e. those seeking to explain causative processes. The IARC concluded that there was "limited evidence" from human epidemiological studies to suggest a positive association between exposure to glyphosate and increased risk of non-Hodgkin lymphoma (NHL), as well as increased risk of childhood cancers associated with application of the herbicide by their parents, but other factors could not be confidently ruled out. Indeed, a large cohort Agricultural Health Study that follows thousands of agricultural workers found no significant increase of NHL. Animal studies (in mice) showed an increase in the incidence of a rare kidney cancer, and of connective tissue as well as skin cancer. "Mechanistic evidence" referred to the increase of blood markers of chromosomal damage in people after spraying of glyphosate, and evidence of glyphosate, glyphosate-formulations and oxidative stress induced by AMPA, a glyphosate metabolite in rodent and in vitro studies. While accepting that other factors could not be completely ruled out in the association with NHL, the report did conclude that there was sufficient evidence of carcinogenicity from experimental animals and from human *in vitro* mechanistic data to warrant reclassifying glyphosate from possibly to "probably carcinogenic to humans (category 2A[6])" (IARC 2012). This is because the IARC used a hazard-based approach rather than a risk based approach – the former considers the potential of a substance to induce cancer independent of considerations of exposure and dose (Gluckman 2016).

[4] See European Commission—Fact Sheet. FAQs Glyphosate. Brussels, 29 June 2016. http://europa.eu/rapid/press-release_MEMO-16-2012_en.htm

[5] From http://www.iarc.fr/en/about: 'The main objective of the IARC is to promote international collaboration in cancer research…[and] identify the causes of cancer so that preventive measures may be adopted … The IARC Monographs Programme is a core element of the Agency's portfolio of activities, with international expert working groups evaluating the evidence of the carcinogenicity of specific exposures.'

[6] A category that also includes eating red meat , shift work, ingested nitraties and nitrites and many chemicals.

The IARC report provoked strong response. The agricultural industry and the farming sector were highly critical (Cressey 2015), with Monsanto accusing the IARC of bias (Levitt 2015). But a number of other stakeholders—environmental groups, opponents of GM crops, anti-globalization advocates—used the IARC report in new campaigns to mobilize public opinion, particularly in the European Union where there has been longstanding hostility towards GMO. In the face of rising media attention, with retail outlets removing Roundup and similar products entirely (Levitt 2015), the European Commission pushed for faster completion of the regular regulatory review of glyphosate that it had begun in 2012.

In November 2015, the relevant regulator, the European Food Safety Authority (EFSA), released a report that - in contrast to the IARC report - concluded that glyphosate was 'unlikely to be carcinogenic'. However, EFSA used a risk based approach, taking into account likely exposure, rather than general potential for harm. Thus it set for the first time safety thresholds for exposure, at 0.5mg per kg of body weight for consumers and 0.1 mg/kg for agricultural operators (EFSA 2015). The US Environmental Protection Agency has also recently concluded that glyphosate is not carcinogenic (EPA 2016).

The differences in the two reports can partly be explained by the hazard versus risk approaches of the two different agencies.[7] While the IARC determines whether there is sufficient evidence to link a particular substance to a higher incidence of cancer, EFSA's brief is to determine the definition and criteria for "acceptable risk", rather than seeking definitive proof of absolute safety.[8] In other words, the underlying questions and classification schemes are different, as are the statistical methods for for determining toxicity, and the substances investigated (EFSA's mandate is for glyphosate alone, whereas IARC also considered its use as part of a compound). Additionally, while the IARC report was based only upon publicly available reports, EFSA had access to a much wider range of studies, including proprietary studies carried out by industry, and a different system for weighting the conclusions. Thus, while the available data for human carcinogenicity was 'limited', the IARC assessed the **likelihood** that the chemical **might cause cancer** in humans to be of sufficient concern, while EFSA studies "whether there is sufficient **confidence** that a pesticide, when used according to the conditions of its approval (i.e. exposure patterns), **will not pose an unacceptable risk** to human health or the environment" (EFSA 2015).

Following release of the EFSA report, a group of 96 leading scientists sent a letter to the European Commissioner for Health and Food Safety, objecting to the EFSA decision on the grounds that the IARC had assessed evidence that was in the public domain and available to independent scientists to review, while the renewal assessment report provided to EFSA by the German Federal Institute for Risk Assessment (BfR) was partially based upon confidential studies conducted by industry groups which were not available to IARC to review. EFSA was also accused of using inappropriate criteria to dismiss positively correlative data. The letter further argued that while IARC had carefully evaluated the strength and weakness of each study assessed, weighted findings according to quality of the data, and clearly identified all studies considered, the BfR study provided no justification for their findings, all citations having been redacted from their report. Moreover, the determination of "no

[7] https://ec.europa.eu/research/sam/index.cfm?pg=glyphosate

[8] The sheer number of products on the market using glyphosate is beyond the capacity of any single agency to test, particularly as compounds such as Roundup can also include toxic additives, such as the surfactant POEA, or produce unexpected effects due to interactions between chemicals.

unequivocal evidence" was misleading, as IARC's determination of "sufficient evidence" in the animal and mechanical data indicates that a causal relationship *has* been definitively established.[9] The letter concluded that EFSA's evaluation did not, therefore, "reflect the available science" and should be disregarded (Portier et al 2015).

Although EFSA did not categorize glyphosate as a possible or probable carcinogen, it still recommended restricting its use. Sweden, France and the Netherlands requested that the licence not be renewed. Several meetings of the EU member states failed to reach a qualified majority to either renew or refuse approval by the deadline of 30th of June, and the EU commission instead extended the current license for a further 18 months to allow another EU agency, the European Chemicals Agency (ECHA), to complete its own review (Stokstad 2016). It also recommended a ban on the surfactant polyethoxylated tallow amine (POEA) from glyphosate-based formulations; minimizing the use of glyphosate in public parks, public playgrounds and gardens; and minimizing pre-harvest use.[10] Although none of these recommendations were binding, POEA – the ingredient in Roundup about which the IARC report showed most concern – was banned in early July 2016 (Michalopoulos 2016).

The issue remains ongoing: in the absence of clear consensus on the carcinogenicity of glyphosate to humans and with regard to the important role of glyphosate in the current model of food production, the potential impact of either continuing or discontinuing the use of glyphosate is profound. Additionally, reaction to the IARC report has reinforced the difficulty of separating what is an otherwise common herbicide from the seemingly intractable debates about the dangers of GM, and resistance to Monsanto itself as the symbol of industrialised agriculture. The differing conclusions of the two reports also suggests the complexities of risk assessment.

Wider lessons and insights

This case highlights a number of issues in the interaction between policy, regulatory agencies, the private sector and the public: issues where a science advisory mechanism has an important but complex role.

In the absence of clear consensus on the carcinogenicity of glyphosate to humans and with regard to the important role of glyphosate in the current model of food production, the potential impact of either continuing or discontinuing the use of glyphosate is profound. Additionally, reaction to the IARC report has reinforced the difficulty of separating what is an otherwise common herbicide from the seemingly intractable debates about the dangers of GM, and resistance to Monsanto itself as the symbol of industrialised agriculture. The differing conclusions of the two reports suggested that glyphosate must be assessed from multiple viewpoints.

First, there is the broader biological and environmental impact. Other than direct toxicity to humans and animals, glyphosate may have impact by reducing resources for certain organisms. For instance, glyphosate toxicity to milkweed may be the reason for the 80% drop in the population of monarch

[9] The letter points out that in terms of public health evaluations, 'limited evidence' in the human data does not mean that the risk is negligible, but rather that causality is, while not unequivocal, credible enough to warrant concern.

[10] http://europa.eu/rapid/press-release_MEMO-16-2012_en.htm

butterflies in North America in the last two decades—starting, strikingly, at the time of the introduction of glyphosate-resistant crops (Semmens, Semmens et al. 2016). The rise of 'superweeds' resistant to glyphosate (among other herbicides) dates from the introduction of GM crops in 1995 and there are now 23 resistant species in 18 countries (Heap 2014), the rise of which has been partly driven by Monsanto's insistence as late as 2004 that continued use of Roundup on GM crops year after year would *not* produce resistance (Gilbert 2013). Both suggest an overall reluctance on the part of industry to accept scientific findings that require a change to corporate practice or to the chemical composition of the pesticides used.

Alternatives to glyphosate-based herbicides in general may be more productive for non-agricultural uses, for example in home gardens, and in parks and playgrounds. Some European countries have already limited the use of glyphosate for home use, leaving commercial applications intact. Weeds in home gardens and small green areas may be better managed by hand weeding and hoeing. Using "traditional" methods such as crop rotations, cover crops, crop management (crop competition, nutrition etc.) in commercial crop production would be more difficult as this could incur considerable cost, but has been recommended as a way of avoiding resistance even when planting GM crops.

The controversy has also shown the strength of the association of glyphosate with Monsanto and its problematic history as a supplier of the defoliant "Agent Orange" to the U.S. Army during the Vietnam War, which was later shown to have catastrophic consequences on the environment and human and animal health. Although Monsanto has attempted to separate its chemical and agricultural interests in recent years, and now proclaims itself a saviour of the honey-bee,[11] other practices – such as its lobbying of the US government to insert a clause called the Farmer Assurance Provision, which aimed to prevent judicial review of any genetically engineered crops,[12] into a short-term spending bill in 2013, have tended to cast a shadow over the entire sector in the public eye, particularly in Europe.

The case also points out the need for transparency in regulatory organisations, particularly the need to avoid the appearance of conflict of interest through use of confidential industrial reports. As most of the controversy around GM is values-based, and public confidence in regulatory agencies in general is low, any scientific advice given requires the utmost transparency in order to avoid provoking yet further conflict.

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[11] http://www.monsanto.com/improvingagriculture/pages/honey-bee-health.aspx.

[12] The provision, which became popularly known as the 'Monsanto Protection Act', was dropped when the bill expired.

QUESTIONS FOR REFLECTION

- Much of the controversy over GM is values-based, in particular critiques over seed patenting, industrial agriculture in general and the practices of some corporations in particular. How can good scientific advice be given in that context?

- Policymakers and the public may have different needs, and different levels of understanding about the function of regulatory agencies. Given that the EFSA report relies upon confidential information and does not cite the source of the studies it evaluated to come to its conclusion, how can regulatory science be best explained to the public in particular, who may be much less inclined than policymakers to accept even minimal risk?

- Much has been made of the conflicting conclusions between the IARC and EFSA reports, yet scientifically they are not measuring the same thing. How can a science advisor help make clear the differences between determining causal relationships and determining safe exposure to potentially toxic chemicals?

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PHOTO CREDITS

COVER: Chafer Sentry applying glyphosate to stubbles in North Yorkshire on a sunny December day. Credit: Chafer Machinery, CC-BY 2.0 . Source: https://www.flickr.com/photos/chafermachinery/15415567073

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INGSA provides a forum for policy makers, practitioners, academies, and academics to share experience, build capacity and develop theoretical and practical approaches to the use of scientific evidence in informing policy at all levels of government.

INGSA's primary focus is on the place of science in public policy formation, rather than advice on the structure and governance of public science and innovation systems. It operates through:

- Exchanging lessons, evidence and new concepts through conferences, workshops and a website;
- Collaborating with other organisations where there are common or overlapping interests;
- Assisting the development of advisory systems through capacity-building workshops;
- Producing articles and discussion papers based on comparative research into the science and art of scientific advice.

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