Why glyphosate is not the issue with Roundup

A short overview of 30 years of our research

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Roundup and other glyphosate-based herbicides are the most widely used pesticides in the world; their residues are among the main pollutants in surface waters. Their use has increased through the spraying of 80% of edible agricultural GMOs, which also contain high levels of their residues. They are composed of glyphosate (35–40% in general) and adjuvants that are around 1,000 times more toxic than glyphosate alone, and are also endocrine disruptors below toxic thresholds. All endocrine disruptors (ED) are also nervous system disruptors (ND), because they act as "spam" for cell–cell communication, in the sense that they are spurious messages (or molecules) sent to a group of organisms or cells, impeding and slowing down, and in some cases accelerating, the physiological communication system. Therefore, they should be called ENDs (endocrine and nervous system disruptors). From 0.1 ppb in chronic tests *in vivo*, Roundup is highly tumorigenic, provoking hormone-dependent tumours, other hormonal imbalances, and important liver and kidney toxicities. Pesticide adjuvants play the same role in other pesticide formulations. The declared active principles often appear to be by far the least toxic compounds after water in formulations. Unfortunately for public health, they are the only substances tested by companies for regulatory purposes over the long term *in vivo*. Thus, the acceptable daily intakes deduced from these tests are 1000–10000 times too high. In regulatory tests the deleterious effects in rats are compared with historical data on rat pathologies. Analysis of laboratory rodent feeds sourced from five continents reveals that they are so contaminated by pollutants that comparison to these hence inappropriate controls generally masks the chronic pathologies provoked by the pesticides and other chemicals tested. The disputes with industry representatives and lobby groups that arose in the course of this research are also summarized in this short review. Finally, potential methods of improving transparency and advancing scientific knowledge are recommended.

Keywords: adjuvants, endocrine and nervous disruptors, glyphosate-based herbicides, GMOs, pesticides, xenobiotics

1. INTRODUCTION[1]

Have you ever tried to kill a plant with a 2% dilution of a pure glyphosate salt in plain water, the dilution recommended for glyphosate-based herbicides? Pour it on a square metre of your garden or the grounds of your University, if it is not yet banned from those areas. Observe the area over the next few days. It will have the same effect as plain water. Then, on a square metre nearby, pour on a formulation such as Roundup in the same 2% concentration. This time you will see the herbicidal effect. Pour on one of its adjuvants, such as POEA or petroleum distillate, at the same concentration, and you will again see the same broad-spectrum herbicidal activity as for Roundup. Now test human cells, as we did in our research studies described below, with a more dilute concentration of Roundup, at 0.01%. With fresh placental or umbilical cells, or embryonic cell lines, you will observe an embryocidal effect within a few hours. Try the same experiment with sea urchin eggs, oysters, fish tissues and rat testicular cells: similar results have been demonstrated in these and other models. Test the glyphosate salt at the same concentration, and you will see no such toxic effect. Test the mixed adjuvants at similar doses: they will kill everything.

What is the lesson? Glyphosate alone has never been used as a herbicide and has no herbicidal activity at this

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[1] Abbreviations: Bt Bacillus thuringiensis; ED endocrine disruptors; ND nervous system disruptors; END endocrine and nervous system disruptors; GMOs genetically modified organisms; PCB polychlorobiphenyl; POEA polyoxyethylene tallowamine; ppb parts per (US) billion (10^9).

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concentration. At around 5–10% it is more toxic. Roundup (from the Monsanto company) and other glyphosate-based formulations are potent nonselective herbicides. However, they have an embryocidal activity at lower concentrations (see below). In the adult rat, Roundup chronically administrated in water at 0.1 ppb is tumorigenic, an endocrine disruptor, and a liver and kidney toxicant. This was revealed by our two year-long rat feeding study, in which we measured around 100 000 parameters, as explained in this paper. However, according to regulatory authorities analysing Monsanto's long-term experiments, glyphosate has no such side-effects. Glyphosate, like other so-called "active principles" of pesticides, is always tested in isolation by industry to calculate long-term risks and the acceptable daily intake. We will explain how this places public health at risk. Adjuvants are almost always declared as inert and their identity and quantity relative to the total formulation are kept confidential. This also places public health at risk according to our discoveries. In fact, and in spite of the terminology used by industry, health agencies, and many scientists and ecologists, glyphosate is not the issue with Roundup.

2. BACKGROUND

Why did we choose to carry out this research? I began while working on my PhD thesis as an endocrinologist studying hormonal disruption by carcinogens *in vivo* in rats, as well as liver reactions through alpha-fetoprotein synthesis [1–7], not so far from our present work. In the rat, alpha-fetoprotein is a steroid-binding protein and a liver toxicity marker. In my postdoctoral research I studied the roles of steroid-binding proteins as carriers for hormones and xenobiotics, followed by cloning or localizing their genes in the human genome. This enabled the realization that foetuses are exposed to maternal compounds or pollutants that have an efficient maternal–foetal transfer [8–13]. Foetal life is a crucial period of exposure. The steroid regulators and steroid-like compounds such as pesticides have numerous targets: the enzymes necessary for steroid biosynthesis, the nuclear proteins reacting to steroids and steroid binders [14–24]. The aromatase enzyme, for instance, controls an irreversible step in androgen to estrogen conversion, a process involved in sexual differentiation. This happens during foetal life in many species and aromatase is crucial in sexual cycles in the adult, as well as in the development of breast cancer and in other pathologies or physiological activities. Its activity in breast cancer may be inhibited at a pharmacological level (many years of my scientific career were dedicated to researching this topic), or by environmental pollutants [25–44].

3. FIRST DEMONSTRATION OF GREATER TOXICITY OF PESTICIDE ADJUVANTS OVER THE DECLARED ACTIVE PRINCIPLE

To cure some hormone-dependent breast cancers with new, more efficient aromatase inhibitors with fewer side-effects was a difficult challenge [25–30, 33, 41, 42]. We became interested in the origins of breast cancers and other hormone-dependent diseases from the point of view of prevention. As pesticides had been identified in human milk all over the planet, we knew that they were present in the human breast. We investigated the long-term and combined effects of pollutants in tissues—a topic that had been poorly investigated hitherto. It was logical to focus on the effects of the most widely used pesticide in the world, Roundup, as its residues are major pollutants in rivers and surface waters. Moreover, this was a perfect model to study the combined effects of substances intentionally combined to have toxic effects: adjuvants and the so-called "active principle". The latter is known as the active principle only by assertion and not through scientific evidence. We studied Roundup's mammalian toxic effects and its role in endocrine disruption at a time when it was considered as safe as water. Regulatory authorities considered it ridiculous to question its safety. I lost some collaborators because of that perception.

Furthermore, Roundup was becoming the main broad-spectrum herbicide used on agricultural food crop plants. Usage greatly increased with the development of genetically modified organisms (GMOs) for consumption. More than 80% of the genetically engineered soya and maize cultivated in the world, mostly in North and South America, are modified to be rendered tolerant to it; that means these crops can contain high levels of its residues without dying. This allows farmers using industrial practices to kill all other plants in the field by spraying with Roundup. Since glyphosate is apparently not a steroid-like molecule, even if it has some endocrine-disruptive activities, we searched for other compounds, hidden in the Roundup formulation, which could be responsible for the aromatase disruption [45]. By 2005 we had concluded that the adjuvants exercised this toxic effect, even if glyphosate alone was demonstrated to bind the active site of aromatase at higher levels, in a semi-irreversible manner [45].

4. LINK WITH GMO TOXICITY

In parallel, as a molecular endocrinologist and toxicologist, I was called upon to serve on official committees of the French government over a period of nine years, and then for the European Union and various countries, to assess the health risks of GMOs in the diet. In contrast with the major debates on the risks of the technology itself,

notably those of insertional mutagenesis [46], my research group focused on the analysis of blood and urine composition of the animals eating these pesticide-rich plants [47]. We had to take into consideration also the second category of GMOs, which are not engineered to tolerate a herbicide but are modified to synthesize in their cells high levels of insecticidal toxins, like the Bt maize [47]. Hundreds of Bt toxins are synthesized from reconstructed and modified genes originating from the natural insecticidal crystalline toxins produced by some bacteria of the *Bacillus thuringiensis* family. Unfortunately at that time (2007) there was no independent study of the potential toxicity of GMOs in mammals that included blood analyses, in spite of the fact that GM crops had been commercially released ten years previously. The industry even considered their raw data from animal toxicological studies as confidential, in common with data on the adjuvants used in pesticide formulations. We gained access to these raw data after an Appeal Court action in Germany in 2005 [48]. Monsanto then sued the German government for releasing the data that informed our scientific publication [47] (the company lost the court case).

We then demonstrated that the GM industry tested their pesticide-rich plants in rats only for 90 days, with blood, urine and organ analyses, before releasing the GM crops into the diets of many millions of people and animals with the claim of "no risk". Of course, short-term effects were not expected; they would have been immediately visible. For the long-term chronic diseases, according to the prevailing belief at the time, it was not felt to be relevant to raise this question. We described in 2007 [47] signs of hepatorenal toxicity in rats after 90 days of feeding with Bt MON 863 GM maize in tests commissioned by industry for regulatory purposes, after re-examining the industry raw data. For the industry lobby, well represented in health agencies [48] that had recognized these tests as valid for safety all over the world, the real war began. I still ignore it as much as I can; but it does not ignore me in all aspects of my scientific, academic and personal life [48]. In 2011 we won a court case in Paris for defamation. The former head of the French committee (the Biomolecular Engineering Commission, CGB) responsible for assessing GMOs, who was also head of the French Association for Plant Biotechnology (AFBV), which promotes biotechnology, was convicted [48].

Many scientists were in agreement with our view [49] that the initial statistically significant effects observed in these tests cannot be dismissed because of sex specificity, or absence of linear response to dose of the GMO, or because of no obvious correlation with organ lesions. These were the Monsanto arguments [49]. In our view they were clearly invalid in the case of hormonal disruption, which could lead to chronic diseases. However, our critics claimed that the health agencies' opinions provided to their governments, which coincided with the opinions of Monsanto, were in agreement with the opinion of the scientific community—which was often silent because the raw data were confidential. Many scientists, including myself, made it clear that there was no consensus regarding these views [50]. This was ignored by the authorities, but science progressed.

We thus had to extend the feeding experiments in order to test our hypothesis that early statistically significant effects found in GM-fed groups of animals could develop into serious illness. However, we found it impossible at that time to gain access to the seeds, and detailed chronic studies are extremely expensive.

In peer-reviewed papers, we explained the potential risks posed by transgenic salmon (in collaboration with Canadian researchers) [51], and by transgenic Bt aubergine in India [52]. Because of the German court decision, lawyers gave us access to the industry raw data from 90-day animal feeding trials with two other GM crops, Bt MON 810 maize and the Roundup-tolerant NK 603 maize. We found dysregulation of hepatorenal functions in GM-fed groups of animals [53]. In the latter case, around 50 significant effects were recognized by industry [48], but were claimed to lack biological meaning because they were within the range of "historical control data" for the rats, or nonlinear to the dose, or not found in both sexes, or not clearly correlated with lesions observed, as previously explained [49]. We published critiques of the insufficiency of these arguments to declare these GMOs as safe and to authorize their market release [54, 55]. This is why we later chose to study Roundup Ready NK 603 maize, extending industry's 90-day rat feeding study to the relatively long-term period of two years, following the same protocol and using the same rat strain, the Sprague Dawley, which is a standard model for long-term studies, including those on carcinogenicity, conducted by industry and US National Toxicology Program researchers, as well as academic researchers.

We also analysed nineteen 90-day regulatory animal feeding trials with GMOs, all those that were available at the time, and found that the kidneys were particularly disrupted. Effects in these organs comprised 43.5% of all disrupted parameters in males, whereas the liver was more disrupted in females (30.8% of all disrupted parameters) [56]. In our view this was unlikely to have been due to chance; the kidneys are the main detoxification organs and they appeared to be reacting to chronic intoxication by chemicals or other toxic agents present in these pesticide-rich plants.

5. MECHANISMS OF ROUNDUP TOXICITY IN HUMAN CELLS IN COMPARISON TO GLYPHOSATE, AND IN OTHER CASES

In parallel, we confirmed in human umbilical, embryonic, and placental cells that the toxicity from a concentration of 0.01% was due to Roundup adjuvants and not to glyphosate, and that the toxic effect was amplified over time [57, 58]. Mixtures of declared active principles from several pesticides could have synergistic effects in some cases (2 to 5 times) but this was almost negligible in comparison to the synergistically toxic effect of glyphosate with its formulating adjuvants (the formulations are 1000 times more toxic than the isolated active ingredient) [58, 59]. Below the toxic thresholds, the adjuvants (not glyphosate) disrupted aromatase, both oestrogen receptors and androgen receptors [60]. We confirmed endocrine disruptive effects below toxic levels in rat testicular cells [61, 62], and even on testis markers after acute exposure *in vivo* [63].

We worked with an agricultural worker's family using 1.3 tonnes of pesticides a year, including Roundup. They had children with severe developmental problems that resembled developmental failures in experimental animals exposed to some of these pesticides [64]. We demonstrated that after Roundup spraying the father had glyphosate (the easiest biomarker of Roundup to assay) in his urine. More surprisingly, one of his sons, who was not in contact with the farm but at home far from the farm, also had glyphosate in his urine one day after the spraying [65]. In another case report, we studied that after spraying pesticides on an airplane during a pregnancy, the baby had neurodevelopmental defects [66]. We also documented the cardiac effects of Roundup after human exposure and in mammals [67] and in the rabbit ventricular myocardium; glyphosate had no such effects alone [68].

We also wanted to find potential solutions to this omnipresent contamination. In certain conditions, human cells were able to detoxify themselves from Roundup, bisphenol A or atrazine with the administration of specific plant extracts that have been accepted as medicinal drugs [69, 70]. Food microorganisms essential for cheesemaking are also negatively affected by Roundup, but not by glyphosate alone [71].

6. ENDOCRINE DISRUPTORS ARE ALSO NERVOUS DISRUPTORS

We became interested in developing the concept that all these toxins are like sand in our bodies, interfering with the cell–cell communication system, which is essentially electrical (nervous) or chemical (hormonal). They are in fact analogous to spam messages in e-mail systems, in the sense that they are spurious messages (or molecules) sent to a group of organisms or cells, impeding and slowing down or, more rarely, speeding up the physiological communication system [48]. This is why most, if not all, of them are not only endocrine disruptors (ED) but also nervous system disruptors (ND) below toxic levels. They should, therefore, be abbreviated as END (endocrine and nervous system disruptors). We have detailed the actions of pollutants as ED in several reviews, during gestation, development, adult life and in various organs [72–75].

7. *IN VIVO* CHRONIC EFFECTS OF ROUNDUP FROM 0.1 PPB IN WATER AND IN GM FOOD

It became obvious that GMOs containing high levels of Roundup residues could present chronic effects after consumption in food and feed, and that the hypothesis had to be tested. As well, we argued that the effects of Roundup in drinking water at environmentally realistic levels like those present in tap water (the authorized threshold is around 0.1 ppb) should be tested. We published that in reviews, book chapters, and scientific reanalyses, and repeatedly alerted the scientific community and authorities [76–79]. In *in vitro* experiments we found that even Bt toxins in agricultural GMOs could have toxic effects, especially in combination with Roundup residues [80] (a growing proportion of GMOs combine herbicide tolerance and synthesis of modified Bt insecticidal toxins).

With the help of several foundations and through crowdfunding, we finally succeeded in raising the funds for a long-term experiment using 200 rats and measuring over 100 000 parameters. This experiment was unique and had never been carried out before, overall independently of the producer of the two commercial products tested, the Roundup-tolerant GM maize NK 603 and Roundup itself. We first bought the seeds and grew the plants (with difficulty) with the help of an agricultural school in Canada, where, unlike in Europe, cultivation was authorized. Monsanto's own 90-day rat feeding study had provoked around 50 statistically significant effects in 90-day-long feeding trials, but the company had interpreted them as not biologically relevant. We used the closest isogenic non-GM variety as a control, and also used it to make the basic non-GM diets for the rats given Roundup in their drinking water, in doses from 0.1 ppb upwards. We legally imported the plants into France and prepared controlled equilibrated diets, labelled with numbers only. These were used in blinded experiments to avoid influencing the technicians in the laboratory.

After a regular and detailed reviewing process, the journal *Food and Chemical Toxicology* accepted the paper and duly congratulated us [81]. However, within

hours of publication, violent reactions came from plant biologists and others working for health agencies, who demanded that the paper be retracted immediately. According to them, there were not enough rats in the study groups and the Sprague Dawley strain used was too prone to tumours to give reliable results. The research was covered in the media in many countries. A former Monsanto employee complained about the paper to the editorial board of the journal and was then appointed to its editorial board. A few weeks later, the editor of the journal who had dealt with our paper was replaced in favour of the former Monsanto employee, and a process of re-analysis of our raw data began. One year after the paper was published, it was retracted by the journal with the verdict that there was no evidence of fraud and no intentional misinterpretation of data, but the results did not warrant the conclusion of a definitive link between NK 603 maize and cancer. Nevertheless, the journal wanted to keep the copyright of the paper it unilaterally retracted.

Unfortunately for the new committee of the journal, keeping the copyright of the paper after retraction turned out to be an illegal procedure and, moreover, the word "cancer" did not even appear in our paper. We described oestrogen-dependent tumours in the groups treated with Roundup from 0.1 ppb in drinking water and from 11% Roundup-tolerant GM maize NK 603 in food. The tumours were big enough to induce internal haemorrhages and pressures on vital organs, inducing death, even before some of them became cancers. We photographed an adenocarcinoma, but since our study was not a cancer study but followed a chronic toxicology protocol, we fully documented all toxic effects: the kidney and liver toxicities, hormonal disruptions and tumours. We had asked, without success, for the release of the raw data from Monsanto, which had led to authorization of the market release of Roundup and GM NK 603 maize, for comparison with our own work.

After receiving several proposals from journals to republish our study, we chose to republish it in *Environmental Sciences Europe* [82], which has an open-access policy for raw data. More recently, after international condemnation of the retraction, including from a former member of the editorial board of *Food and Chemical Toxicology*, the *Food and Chemical Toxicology* editor who had overseen the first publication of our paper became editor-in-chief and the former Monsanto collaborator no longer appeared on the editorial board. This episode illustrated the vulnerable position of dependent "science" and the economic and political forces that move to defend Roundup and Roundup-contaminated crops [48].

At the scientific peer-reviewed level, we answered the critics of our study with fully documented explanations [83, 84], and detailed the important conflicts of interests of the critics and of *Food and Chemical Toxicology* at that time [85].

8. HOW TOXIC EFFECTS OF ADJUVANTS AND THEIR PESTICIDES ARE HIDDEN: THE ROLE OF HISTORICAL CONTROL DATA IN REGULATORY TESTS

Using mass spectrometry, we identified the adjuvants of pesticides, which are typically declared inert and kept confidential by the manufacturing companies. We tested them in human cell lines independently of glyphosate and published our findings [86]. We concluded that these ethoxylated compounds are the real active principles of Roundup, with glyphosate only finishing the herbicidal work. My hypothesis, which needs to be tested, is that they are composed of an uncharacterized mixture of burned distillates of petroleum, together with residues of animal fat, forming corrosive diluents for pesticides. They could be used as detergents by other companies or mixed with water for the extraction of shale gas.

In a separate study, we compared the toxicity of the declared active principles of nine pesticides, including neonicotinoids, to that of their formulations [87]. All the formulations were (except in one case, in which the formulation declared no adjuvants) considerably more toxic to human cells than the declared active principles alone. Moreover, there is no scientific reason to assume that the declared active principle with respect to plants, insects or fungi would also be the most toxic in the formulation in the case of other organisms such as mammals. There is also no scientific reason to test one of the compounds alone in long-term experiments with mammals and not the whole formulation for regulatory purposes. Acceptable daily intakes derived from this process will be largely wrong because they do not test the whole formulation as marketed and used.

One common criticism of our study on the long-term effects of very low environmental doses of Roundup was the extreme proneness of the Sprague Dawley rat to tumours and other diseases, forming a background from which no specific conclusions could be drawn. We looked at the data, known as historical control data, for this strain of rat, which the chemical industry has compiled since regulations requiring animal testing of chemicals were implemented (going back at least to the 1970s). From the data it was inferred that up to 71% of the animals would spontaneously or naturally (without being deliberately exposed to toxic agents) present mammary tumours and up to 93% would present pituitary tumours; moreover, the kidney function of these animals would frequently be

deficient. This prevents the attribution of observed toxic effects to the products tested and requires the sacrifice of a large number of animals in an attempt to observe statistically significant results in carcinogenicity tests, for example. But often, doubt persists and the product remains on the market.

We wanted to find out whether these diseases originate from genetic or environmental factors. We analysed the dried feed of laboratory animals, using standard methods from accredited laboratories. These animal feeds, sourced from five continents, are generally considered balanced and hygienic. The study was exceptionally wide-ranging; it investigated 13 samples of commonly used laboratory rat feeds for traces of 262 pesticides, 4 heavy metals, 17 dioxins and furans, 18 PCBs and 22 GMOs. The results were overwhelming [88]. All the feeds contained significant concentrations of several of these products, at levels likely to cause serious diseases and disrupt the hormonal and nervous system of the animals. This hides the effects of the products tested. For example, residues of the most widely used pesticide in the world, glyphosate, and its formulations with highly toxic adjuvants (e.g., Roundup—the main glyphosate based-herbicide), were detected in 9 of the 13 diets; eleven of the 13 diets contained GMOs that are grown with large amounts of Roundup.

It should be noted that one of these feeds was used in DuPont's regulatory study on GM Roundup-tolerant oilseed rape. The type of feed given to the control animals in the DuPont study was found [89] to contain significant amounts of Roundup residues, at levels known to cause toxic effects. The study concluded that the oilseed rape in question was safe, yet the study is obviously flawed and we asked for its retraction [89].

9. CONCLUSION: MORE SCIENCE AND MORE TRANSPARENCY ARE NEEDED

A possible new way forward for science and public health is to use the law to force disclosure of "commercially confidential" industry studies. The most important raw data when studying health risks of any chemical *in vivo* are the blood and urine analyses (generally of rats) used to conclude that the products are safe enough to be released onto the market. In 99% of the cases these raw data are obtained once only, in tests commissioned by the companies wishing to release the products, and given to health agencies worldwide (not all request such data). The protocols should be also transparent: for example, number and strain of rats, parameters measured, length of study, and the use of historical control data for *post hoc* comparisons of significant effects, which is a systematic practice in analyses of regulatory tests. Then there will be widespread acknowledgment, for instance, that for 90-day tests with GMOs, no more than 5–10 rats are measured per group by industry; for Roundup and other formulated pesticides, no medium- or long-term tests at all are carried out with the complete formulations.

The scientific community will then understand better how to enter the debate and how to interpret industry toxicity results, which appear to have been overlooked or dismissed by regulatory authorities, for instance to check the statistics of the company. The raw data should be accessible on the Internet; these tests should not qualify as manufacturers' trade secrets. Moreover, long-term *in vivo* tests should be carried out with the relevant products; that is, diluted formulations, and not only the declared active principles, such as glyphosate. This process of reformation will doubtless take many years. Meanwhile, acceptable daily intakes should be divided by 10000 to take into account the toxic effects of untested adjuvants and END effects.

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