Roundup and birth defects

Is the public being kept in the dark?

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by
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About Earth Open Source

Earth Open Source uses open source collaboration to engage individuals, farmers, communities, corporations, universities, and governments in programmes to achieve breakthrough advances that help nourish humanity, increase equity, support food security, and preserve the Earth.

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Summary

Concerns about the best-selling herbicide Roundup® are running at an all-time high. Scientific research published in 2010 showed that Roundup and the chemical on which it is based, glyphosate, cause birth defects in frog and chicken embryos at dilutions much lower than those used in agricultural and garden spraying. The EU Commission dismissed these findings, based on a rebuttal provided by the German Federal Office for Consumer Protection and Food Safety, BVL. BVL cited unpublished industry studies to back its claim that glyphosate was safe.

The Commission has previously ignored or dismissed many other findings from the independent scientific literature showing that Roundup and glyphosate cause endocrine disruption, damage to DNA, reproductive and developmental toxicity, neurotoxicity, and cancer, as well as birth defects. Many of these effects are found at very low doses, comparable to levels of pesticide residues found in food and the environment.

This issue is of particular concern now that Monsanto and other producers of genetically modified seed are trying to get their glyphosate-tolerant crops approved for cultivation in Europe. If the EU Commission gives its approval, this will lead to a massive increase in the amount of glyphosate sprayed in the fields of EU member states, as has already happened in North and South America. Consequently, people's exposure to glyphosate will increase.

All these concerns could be addressed by an objective review of Roundup and glyphosate in line with the more stringent new EU pesticide regulation due to come into force in June 2011. Just such a review was due to take place in 2012. However, shortly after the Commission was notified of the latest research showing that glyphosate and Roundup cause birth defects, it quietly passed a directive delaying the review of glyphosate and 38 other dangerous pesticides until 2015. This delay is being challenged in a lawsuit brought against the Commission by Pesticides Action Network Europe and Greenpeace.

Delaying the review of glyphosate until 2015 is serious enough. But in reality, the Commission's slowness in preparing the new data requirements for the incoming regulation mean that glyphosate may well not be re-assessed in the light of up-to-date science until 2030. The beneficiary will be the pesticide industry; the victim will be public health.

The need for a review of glyphosate is particularly urgent in the light of the shortcomings of the existing review of the pesticide, on which its current approval rests. In this report, we examine the industry studies and regulatory documents that led to this approval. We show that industry and regulators knew as long ago as the 1980s and 1990s that glyphosate causes malformations – but that this information was not made public. We demonstrate how EU regulators reasoned their way from clear evidence of glyphosate's teratogenicity in industry's own studies (the same studies that BVL claimed show the safety of glyphosate) to a conclusion that minimized these findings in the EU Commission's final review report.

The German government and its agencies played a central role in this process. As the "rapporteur" member state for glyphosate, Germany was responsible for liaising between industry and the EU Commission and reporting the findings of industry studies. We show how Germany played down findings of serious harm in industry studies on glyphosate. It irresponsibly proposed a high "safe" exposure level for the public that ignored important data on glyphosate's teratogenic effects. This level was accepted by the Commission and is now in force.

Taken together, the industry studies and regulatory documents on which the current approval of glyphosate rests reveal that:

- Industry (including Monsanto) has known since the 1980s that glyphosate causes malformations in experimental animals at high doses
- Industry has known since 1993 that these effects could also occur at lower and mid doses
- The German government has known since at least 1998 that glyphosate causes malformations

- The EU Commission's expert scientific review panel knew in 1999 that glyphosate causes malformations
- The EU Commission has known since 2002 that glyphosate causes malformations. This was the year its DG SANCO division published its final review report, laying out the basis for the current approval of glyphosate.

The public, in contrast, has been kept in the dark by industry and regulators about the ability of glyphosate and Roundup to cause malformations. In addition, the work of independent scientists who have drawn attention to the herbicide's teratogenic effects has been ignored, denigrated, or dismissed. These actions on the part of industry and regulators have endangered public health. They have also contributed to the growing division between independent and industry science, which in turn erodes public trust in the regulatory process.

This report provides a comprehensive review of the peer-reviewed scientific literature, documenting the serious health hazards posed by glyphosate and Roundup herbicide formulations. On the basis of this evidence, we call on the Commission to cancel its delay in reviewing glyphosate and to arrange an objective review of the pesticide. The review must take into account the full range of independent scientific literature, as demanded by the new pesticides regulation, and should be started as soon as the new data requirements are in place this year. In the meantime, the Commission should use its powers to withdraw glyphosate and Roundup from the market.

1. Roundup link with birth defects – study

Research published in August 2010 showed that the best-selling herbicide Roundup[1] causes malformations in frog and chicken embryos at doses much lower than those used in agricultural spraying.[2] The malformations found were mostly of the craniofacial and neural crest type, which affect the skull, face, midline, and developing brain and spinal cord.

The research team was led by Professor Andrés Carrasco, lead researcher of the Argentine government research body CONICET. Carrasco was prompted to carry out the study by reports of high rates of birth defects in areas of Argentina dedicated to growing genetically modified Roundup Ready (GM RR) soy.[3] The birth defects seen in humans were of a similar type to those found in Carrasco's study.

GM RR soy is designed to be sprayed with Roundup herbicide, based on the chemical glyphosate. The Roundup Ready gene allows the crop to be sprayed with Roundup herbicide, which kills weeds but allows the crop to survive.

It is also important to note that GM RR soy and other crops are *tolerant* rather than *resistant* to Roundup and glyphosate: that is, they absorb the herbicide and survive. As a result, GM RR crops are a reservoir of potentially high levels of glyphosate, which will then be ingested by animals or people who eat the crops.

The spread of GM RR varieties has led to massive increases in the amount of glyphosate sprayed in soy-producing areas.[4] [5] [6] In Brazil, nearly 90,000 tons of glyphosate-based pesticides in 71 different commercial formulations were sold in 2009.[7] In Argentina, over half the cultivated land is given over to GM soy, which is sprayed with 200 million litres of glyphosate herbicide each year.[8] Spraying is often carried out from the air, causing major problems of drift.

Carrasco said, "From the ecotoxicological point of view, what is happening in Argentina is a massive experiment."[9] It is a cautionary tale of what could happen in any country that adopts glyphosate-tolerant GM crops on a large scale.

1.1. Why should Europeans worry?

The maximum residue limit (MRL) allowed for glyphosate in food and feed products in the EU is 20 mg/kg. Soybeans have been found to contain glyphosate residues at levels up to 17mg/kg.[10] Carrasco found malformations in frog and chicken embryos injected with 2.03 mg/kg glyphosate – ten times lower than the MRL. While an injected dose is not the same as eating food containing glyphosate residues, no attempt has been made to properly investigate how much glyphosate people and animals are ingesting.[11]

Each year, the EU imports around 35 million tons of soy and derivatives,[12] most of which is used for animal feed and biofuels. A loophole in the EU's GM labelling laws allows meat, dairy and eggs produced with GM animal feed to be sold without a GM label. So the GM soy, and residues of the glyphosate with which it is treated, go into the food chain through animal feed and remain hidden from European consumers.

Europeans are also exposed to Roundup in the form of sprays. In Europe, marketing claims that Roundup is safe and readily biodegradable have helped expand its use beyond farmers' fields. Municipal authorities use it for weed control on roadsides and in school grounds, parks, and other public areas. Home gardeners can easily buy it in supermarkets and garden centres.

Given the widespread use of the herbicide and industry plans to introduce glyphosate-tolerant GM crops into Europe, the safety questions over Roundup must be answered objectively and in accordance with the most up-to-date scientific knowledge. However, an opposite process appears to be in train: industry and regulators are minimising concerns in what seems to be an effort to keep the pesticide on the market.

2. EU regulators respond to birth defects study

In September 2010, Carrasco's research was sent to John Dalli, the EU Commissioner for Health and Consumer Policy. The following month, Greek Green MEP Michail Tremopoulos asked Dalli in a parliamentary question what action the Commission planned to take on Monsanto's application for cultivation in the EU of its NK603 glyphosate-tolerant GM maize.

The European Food Safety Authority (EFSA) has already given the go-ahead to NK603. If the Commission gives its approval, NK603 will be the first GM herbicide-tolerant plant to be grown commercially in the EU[13] – and the first to enable the intensive glyphosate spraying that has come under fire in Argentina.[14]

2.1. Glyphosate approval could be reconsidered – Dalli

Dalli's answer to Tremopoulos did not exactly promise action, but it did suggest a willingness to re-assess glyphosate on the basis of the new evidence. Dalli said that the existing approval of glyphosate could be reconsidered and, "depending on the seriousness and urgency of the matter," it could be restricted or even banned. Dalli said he would also consider reviewing the current maximum residue levels (MRLs) allowed in soy.[15]

Dalli said a programme was under discussion for re-examining those pesticides for which the EU approval was soon to expire – "and this programme includes glyphosate".[16] Pesticides approved for use in the EU are reviewed every ten years. Glyphosate was last reviewed in 2002,[17] so the next review would normally be expected in 2012.[18] But Dalli's response to Tremopoulos suggested that in light of the new evidence, more immediate action could be taken.[19]

Dalli asked the German government to examine Carrasco's study and report back on whether it reflected real-life exposure levels. Germany was given this task because it is the "rapporteur" member state for glyphosate, responsible for liaising between the industry applicants for the pesticide's approval, member states, and the EU Commission.

2.2. No reason for concern – Dalli

MEP Tremopoulos followed up with another parliamentary question to Dalli in December,[20] asking if the EU would carry out a new risk assessment of glyphosate, based on the latest scientific evidence. But Dalli had heard back from the German government and was reassured that there was no need. Dalli reported the German authorities' verdict on Carrasco's study:

- The study had been performed under "highly artificial" conditions that did not reflect the real-life use of glyphosate in agriculture or its effects on mammals
- There is a "comprehensive and reliable toxicological database for glyphosate" and the findings of these studies do not throw into doubt its existing approval
- There was no need to ban or restrict the use of the substance.[21]

As discussed below, the basis for these conclusions by the German regulators is highly questionable.

2.3. EU Commission flouts EU law

The glyphosate question has arisen at a crucial moment in EU pesticides regulation. The old Directive 91/414[22] is in the process of being replaced by the new Regulation 1107/2009,[23] which comes into force in June 2011. The new law contains stringent requirements to protect public health and the environment. It has the potential to set the gold standard for pesticide safety assessments internationally, bringing the system more into line with public health interests.

The new pesticide regulation 1107/2009 makes clear that the European Parliament and Council will no longer rely for pesticides approvals on industry-generated "grey literature"[24] and studies that are hidden from the public under commercial confidentiality rules. It states that the "scientific peer-reviewed open literature" must be taken into account from now on in assessing pesticides.[25]

The regulation also solves the problem of old and outdated studies dominating pesticides approvals dossiers. It states that studies from

the open literature published within the last ten years before submission of the dossier must be included in the assessment.[26]

But the EU Commission appears to be doing everything in its power to flout the intent of the new regulation. It is putting massive energy and resources into prolonging the approval of pesticides under the old, less stringent rule, instead of what it should be doing – working on the evaluation of pesticides under the new Regulation 1107/2009. If the Commission gets its way, glyphosate and other dangerous pesticides will avoid the scrutiny of the new regulation for many years.

2.4. Commission delays glyphosate review – until 2015

As it turned out, the Commission did not bring the glyphosate review forward, or even stick to the expected date of 2012. In an astonishing move, it delayed the review of glyphosate until 2015.[27] It then rushed through a new directive, setting the delay into law, on November 10, 2010 – two days before Dalli told Tremopoulos that action might be taken soon on glyphosate.[28] It is unclear whether Dalli misled Tremopoulos, or was unaware of the new directive.

The entire decision-making process on the delay was done behind closed doors with a limited group of national representatives (mainly from the agricultural ministries of member states) and set into law without notifying stakeholders. This process is called "comitology" and is much criticized for being non-transparent, confusing (even to legal experts) and undemocratic.[29]

2.5. Commission too busy to review glyphosate

The German government body dealing with the glyphosate review is BVL, the Federal Office for Consumer Protection and Food Safety. In December 2010, Friends of the Earth Germany (BUND) asked BVL the reason for the delay in the review. BVL replied that the EU Commission and other authorities (including food safety watchdog, the European Food Safety Authority, EFSA) had too heavy a workload and had not finalized the rules for renewing the approval of certain pesticides, including glyphosate.

BVL added that the delay is not confined to glyphosate but also applies to other pesticides.[30] In fact, the list of 39 pesticides for which the review will be delayed includes the highly toxic 2,4-D and diquat.[31]

If BVL meant this statement to reassure, it was mistaken. The fact that not just one but 39 pesticides will get a free regulatory ride for an extra three years is a political scandal. If BVL's explanation is taken at face value, public health is being put at risk because of bureaucratic inefficiency. The beneficiary is the pesticide industry.

The Commission's delay in reviewing the 39 pesticides is being challenged in a lawsuit brought by Pesticides Action Network Europe and Greenpeace.[32]

2.6. Why the delay matters

The delay will have far-reaching consequences because it means glyphosate will be reviewed under the data requirements of the old pesticide Directive 91/414 rather than the new Regulation 1107/2009. The old directive is much less effective than the new regulation because it has lax and outdated data requirements. Data requirements instruct industry which effects to study and which testing methods to use.

The data requirements of the old Directive 91/414 are based on outdated protocols designed decades ago.[33] They ignore new scientific insights and developments. Effects likely to be missed include endocrine disruption, effects on development, effects of added ingredients (adjuvants), effects of combinations of chemicals, and effects on bees. Also likely to be missed are effects found in independent peer reviewed scientific literature, as the old directive does not explicitly say that such studies must be included in industry's dossier. In short, the most rigorous and advanced science is ignored under the data requirements of the old Directive 91/414.

According to Danish MEP Dan Jørgensen, the Commission has been working on the new data requirements for Regulation 1107/2009 since 2002 and has still not completed them.[34] They are scheduled for publication on June 14, 2011.[35]

Once they are published, industry needs at least two years to do the new tests on glyphosate and to liaise with the rapporteur, Germany, and the Commission over its dossier. Industry has to deliver its new dossier for glyphosate by 31 May 2012,[36] and the EU Commission will give its delayed decision in 2015.[37]

Because the Commission has taken so long to prepare the new data requirements, industry will not have enough time to do the tests on glyphosate under the new data requirements. So glyphosate and the 38 other pesticides will be reviewed in 2015 under the old, lax data requirements. Commissioner Dalli confirmed this in a reply to a Parliamentary question from MEP Jørgensen.[38]

The Commission has the option to tighten the 2015 glyphosate review by forcing industry to include studies from the open peer-reviewed scientific literature in its dossier. The new regulation, which stipulates that such literature should be considered, will be in place. Also, EFSA has already published its Guidance on the use of science for the regulation,[39] giving industry time to collect the independent studies before its 2012 dossier submission deadline. However, it is not yet clear whether the Commission has the political will to make industry comply with this aspect of the new regulation.

2.7. The real delay – until 2030?

The EU Commission's delay in reviewing glyphosate and the 38 other pesticides until 2015 is serious enough. But the situation is far worse than it appears. Because glyphosate will go through its 2015 review on the basis of old, lax data requirements, it will likely be approved. The approval period is 15 years. As a result, glyphosate will not in effect face a review under the new, more stringent data requirements until 2030.[40] By then, public policy on glyphosate will be based on evidence generated using research protocols that are decades out of date.[41] It will exclude all evidence from independent studies unless the Commission insists that this be included.

2.8. What's keeping the Commission so busy

A Commission source who spoke on condition of anonymity confirmed that the real cause of the delay in the review of glyphosate and the 38 other pesticides is a process called Resubmission.[42] This was instituted in 2008 after the Commission rejected a number of industry pesticide applications on the grounds that the dossiers were incomplete. Industry disagreed and threatened the Commission with lawsuits. The Commission reached a compromise with industry, offering it a second chance to deliver more complete dossiers while allowing the pesticides to stay on the market for an additional 3–4 years. Resubmission is a fast-track procedure with a limited dossier.

According to Pesticides Action Network Europe, the loophole "turned into a big hole" when industry submitted applications for more than 80 substances, including some "dirty" pesticides that had been regarded as having no chance of approval.[43] PAN said that companies jumped on the train of this fast-track procedure, hoping for a mild evaluation or to put pressure on Commission through member states if their farmers were interested in getting a banned substance back.

The Commission has been bogged down in Resubmission applications ever since. Industry has benefited because the Commission is directing all its resources into prolonging the approval of pesticides under the weak old rule – and ignoring the demands of the new, more stringent regulation.

3. EU regulators "disappear" birth defects

The regulators' response to Carrasco's study suggests that they are in no hurry to take on board the findings of independent science. At Commissioner Dalli's request, the German Federal Office for Consumer Protection and Food Safety, BVL, produced a written response to the study.[44] This was not published but was only sent to the EU Commission.

BVL's statement is anonymous. Though common with such items of grey literature, this

operates against the public interest as no one can be held accountable a decision that could significantly affect public health. There is no way of knowing whether the people who wrote it are even qualified scientists, let alone if they have industry interests.

BVL's conclusion can be summarised as: no action is needed on glyphosate. It tries to isolate Carrasco's study, implying that it is the only one to find problems. BVL cites Germany's 1998 draft assessment report (DAR) on glyphosate, which it says showed "no evidence of teratogenicity" (ability to cause malformations/birth defects).[45]

The DAR is a crucial document underlying glyphosate's current EU approval. It is Germany's summary and report on the dossier of studies submitted by industry in support of glyphosate's approval. Based on this DAR, along with EU member states' comments and a peer review of the dossier by the EU Commission's ECCO scientific panel, the EU Commission's health and consumer division DG SANCO approved glyphosate for 10 years in 2002. DG SANCO's final review report on glyphosate acknowledges developmental abnormalities found in the industry studies but dismisses their importance by saying that they are confined to "maternally toxic doses" (see Section 3.1, below).[46]

BVL's response to Carrasco was followed by a response from industry. Employees of Monsanto and Dow, two major manufacturers of glyphosate herbicides, published a letter in the same journal that published Carrasco's original study.[47] The Monsanto/Dow letter was published back-to-back with Carrasco's response.[48]

Monsanto/Dow take the same line as BVL, claiming:

> Glyphosate does not cause adverse reproductive effects in adult animals or birth defects in offspring of these adults exposed to glyphosate, even at very high doses.[49]

But both BVL's and Monsanto/Dow's claims are misleading, as we show below.

3.1. Industry's own studies show that glyphosate causes malformations

Germany's DAR concludes from the industry dossier of studies, "Glyphosate does not cause teratogenicity". But Germany immediately goes on to qualify its conclusion, saying that higher doses of glyphosate caused "reduced ossification and a higher incidence of skeletal and/or visceral [internal organ] anomalies" in rats and rabbit foetuses.[50] In reality, at odds with Germany's reassuring conclusion, the details of the DAR contain convincing evidence of glyphosate's teratogenicity.

Germany adds that in the industry studies, glyphosate given at high doses reduced the number of viable foetuses produced by rats and rabbits.[51] Decreased numbers of viable foetuses are often consistent with increased incidence of malformations, as many mal-developed foetuses are spontaneously aborted.

The skeletal "anomalies" found in these early industry studies are consistent with Carrasco's findings. But Germany dismisses them on the claimed grounds that the doses at which the effects were found were so high as to be toxic to the mothers (maternally toxic doses).

Germany here makes an assumption common among regulatory authorities – that foetal abnormalities found at maternally toxic doses are irrelevant to human risk assessment. The reasoning is that poisoning of the mother with any substance can affect the development of the foetus and lead to birth defects and therefore such malformations may not be a direct effect of the chemical in question on the foetus. So malformations in foetuses found at dose levels that are considered toxic to the mother are dismissed as irrelevant and the substance under examination is not classed as a developmental toxin or teratogen.

But this assumption is debated in the independent scientific literature. Paumgartten (2010) says that in cases of maternal toxicity, it is not possible to know whether an effect on the embryo is only due to maternal poisoning or due to a direct action of the chemical at doses that also adversely affect the mother. In the latter case, the chemical would be a developmental toxin.[52]

Even industry is actively discussing the relationship between maternal toxicity and birth defects. It was the subject of a recent workshop held by the industry-funded group, the

International Life Sciences Institute.[53]

As yet there is no scientific consensus around the issue. The confusion is made worse by the poor design of standard industry chronic toxicity tests, which use so few animals that unrealistically high doses of the chemical have to be used in an attempt to obtain statistical significance in non-lethal effects.[54] In fact, the doses for chronic two-year toxicity tests are derived from, and are only slightly below, the acute poisoning dose. So poisoning effects are common in such tests, which often miss more subtle effects.[55]

Thus, virtually all chronic tests commissioned by industry have an escape clause: "Perhaps the dose was so high it poisoned the animals." This escape clause is frequently used by the rapporteur Germany in its DAR on glyphosate.

Germany's dismissal of the malformations found in industry studies on grounds of maternal toxicity is thrown into doubt by the findings of an independent study. Dallegrave (2007) examined the reproductive effects of Roundup on male and female offspring of Wistar rats treated with 50, 150 or 450 mg/kg of Roundup during pregnancy and lactation. The study found that these doses of Roundup did not induce maternal toxicity but did induce adverse reproductive effects on male offspring. Findings include a decrease in sperm number and daily sperm production during adulthood, an increase in the percentage of abnormal sperms, a dose-related decrease in the serum testosterone level at puberty, and signs of sperm cell degeneration during both periods. The study showed that Roundup is a reproductive toxin at non-maternally toxic doses.[56]

Even if we confine the argument to evidence generated by industry studies, Germany's argument that glyphosate's teratogenicity is confined to high, maternally toxic doses is untrue. The industry studies also found malformations at lower doses. This is made clear by Germany's own summaries of the industry studies in the DAR and by the comments of the UK's Pesticides Safety Directorate (PSD).

Our edited versions of Germany's summaries of industry studies are presented below, along with the UK PSD's comments and our own.

How are pesticides assessed for risk in the EU?

Risk assessment of pesticides in the EU is a long and complex process:

- Industry submits a dossier of studies in support of its application for approval of a pesticide. The studies should fulfil the data requirements of the regulation in force.
- The rapporteur member state reviews the industry dossier and compiles a draft assessment report (DAR).
- The EU member states are invited to comment on the industry dossier and DAR.
- A scientific panel of the EU Commission – formerly the ECCO Panel, now EFSA's Panel on Plant Protection Products and their Residues (PPR Panel) – reviews the industry dossier and DAR, and writes an Opinion.
- The EU Commission's Health and Consumer Protection Directorate General (DG SANCO) compiles a review report, summarising the evidence on the pesticide.
- A committee made up of representatives of DG SANCO and the member states, known as the Standing Committee on the Food Chain and Animal Health (SCFCAH) – Phytopharmaceuticals, meets to discuss the pesticide.
- DG SANCO makes a proposal at a meeting of the SCFCAH to approve, reject, or conditionally approve the pesticide for certain uses.
- If a large majority of SCFCAH members reject DG SANCO's proposal, DG SANCO can change it or find a compromise.
- The SCFCAH votes on whether to accept DG SANCO's proposal.
- In the event that a qualified majority vote is not achieved, the proposal passes to the European Council for a final decision.

The documents on which the current EU approval of glyphosate is based, including Germany's 1998 DAR on glyphosate and comments of member states, are not readily available to the public or seemingly even to the EU Commission's regulators, DG SANCO. DG SANCO told the authors of this report that it was unable to supply the DAR and referred the request to the German government office BVL, which only supplied it after a delay of several weeks. Even then, BVL withheld part of the DAR. In contrast, DG SANCO's 2002 review report on glyphosate is publicly available.

Suresh (1993)

Submitter company: Feinchemie[57]

Germany's summary: This study on the teratogenicity of glyphosate in rabbits found that the total number of foetuses with major visceral anomalies was high in all treatment groups, including the low-dose level of 20 mg/kg, and was significantly increased at the 500 mg/kg (highest dose) level. The percentage of foetuses with dilated heart was significantly elevated at all dose levels. Skeletal variations, anomalies and malformations were found but there was no clear dose-response pattern. There was a dose-related increase in the occurrence of an extra 13th rib in all the glyphosate-treated groups and in the highest dose group this was statistically significant.

The NOEL (no observable effect level, the highest dose tested that did not produce an adverse effect) for maternal toxicity was 20 mg/kg bw/d [body weight]/day, based on the fact that possibly treatment-related deaths occurred in the higher dose groups. With regard to visceral malformations, the study's author concluded that the NOEL was less than the lowest dose of 20 mg/kg bw/d.[58]

UK's comment: "The increased incidences of abnormalities … are of concern, particularly the heart effects which are also reported in other rabbit studies with glyphosate… The interpretation of this finding must rely on comparison with historical control data. If the typical incidence [of malformations] is approximately 5 fetuses per group then there is no concern. However if this is a very rare finding in control animals and the concurrent controls for this study are typical then there are concerns regarding the potential fetotoxicity of this source of glyphosate."[59]

Our comment: With regard to this study, even industry is telling Germany that glyphosate is toxic at 20 mg/kg bw/d, if not lower. Germany however explains away the findings on the grounds that the actual number of foetuses with dilated heart was small, that there was no increase in foetuses with heart dilation in the mid-dose over the low-dose group, that almost no other soft organ malformations occurred, and that the consequences of this heart malformation are "equivocal". Together, those arguments lead them to conclude that the low dose of 20 mg/kg bw/d and even the mid dose of 100 mg/kg bw/d were NOELs.

An objective evaluation of this study would conclude that the low dose of 20 mg/kg bw/d is not the NOEL, or, as it is usually called today, the NOAEL (no observed adverse effect level). In this study, 20 mg/kg is the LOAEL – the lowest level at which an adverse effect was found. Statistically significant teratogenic effects were found at this dose. As no NOEL was found in this study, Germany should have demanded that further tests be done to establish the NOEL, with the highest dose set at 20 mg/kg bw/d and lower doses added to try to establish a true NOEL.

Germany's comment that the number of foetuses with abnormalities was small merely identifies a shortcoming of industry studies. Larger numbers of test subjects are always preferable. If the number of animals used in the study is small, any effect will only be seen in small numbers of animals.

Germany's dismissal of the heart malformations on the grounds that no other types of soft organ malformations were found is not consistent with the current state of knowledge in developmental biology. Many toxic agents target a specific organ (known as "organ specific" effects) or have one specific effect. In light of this, Germany has no basis for arguing that the heart malformations are not important because malformations were not observed in other tissues. Also, Germany's argument that the heart dilation malformation has unknown consequences and can therefore be dismissed is scientifically and clinically indefensible.

Germany's expectation of a proportional dose-response pattern in skeletal malformations is also not supported by current knowledge of developmental biology. There is no evidence in the scientific literature demonstrating that toxicity must always be proportional to dose, increasing as the dose increases. Toxicologists now recognize that dose-response relationships can be complex, especially when the endocrine system is involved. Toxic effects can be found at low doses but not at higher doses, and different toxic effects can be found at different doses.[60 61 62 63]

Industry toxicologists ignore these scientifically established facts. They only test unrealistically

high doses and extrapolate effects to low doses, wrongly assuming a linear dose-response relationship. They also wrongly assume that there is a threshold dose below which there is no toxicity. In short, they fail to gather data from almost every area of the dose-response graph.

Germany has wrongly dismissed the hard data in this study, which clearly indicate the toxicity of glyphosate.

Germany repeatedly tries to explain away the finding of malformations in industry studies by referring to historical control data instead of focusing on comparison of the experimental and control groups within the study under consideration. When a study shows clear differences between experimental and control groups, instead of concluding that the study demonstrates the toxicity of glyphosate, Germany compares the experimental group to control data from other sources. Such control data will have wide variability, the range of which will overlap with the values reported for the glyphosate-treated groups in the study under consideration. Based on this overlap, Germany concludes that there is no evidence of toxicity, since the experimental results are within the range of normal variability. This conclusion is not valid, because the variability within the control data gathered by Germany is artificially large, due to the fact that the studies from which those data are drawn have been done under a range of conditions.

Germany's practices might be overlooked if the effects found were marginal and if other studies with similar findings did not exist. But neither condition applies to these industry studies on glyphosate, which consistently show malformations. Significantly, the independent studies cited in this report do not rely on "historical control data" to explain away findings.

It is clear from the UK's PSD's comment on the teratogenicity studies that it had not seen the historical control data and so was not prepared to discount the possibility that glyphosate was teratogenic and toxic to foetuses.[64]

Brooker et al., 1991

Submitter companies: Monsanto/Cheminova[65]

Germany's summary: This study looked at the effects of glyphosate on pregnancy in rabbits, at doses of 50, 150, and 450 mg/kg bw/d. It found a significant increase in embryonic deaths in all the glyphosate-treated groups compared with controls. However, a comparison with historical control data showed that the incidence in the control group was untypically low. Also, a clear dose-response relationship was not shown. On the other hand, an increase in late embryonic deaths at the top dose level (450 mg/kg bw/day) was also found in another study on rabbits.

There was concern about the more frequent occurrence of foetuses with heart malformations in the high dose group, but the incidence was in the range of historical background data. However, anomalies of the heart have been described in other rabbit teratogenicity studies with glyphosate, too. Thus, a possible effect on the occurrence of visceral anomalies remains equivocal.[66]

UK's comment: "The increased levels of embryonic death/post-implantational loss at all dose levels are of concern, as are the reports of heart defects… a more robust argument should be presented before these findings can be dismissed."[67]

Our comment: Again, Germany uses historical control data and an inappropriate model for toxicity dose-response to explain away malformations of the heart in a glyphosate-exposed group. Again, by taking this position, Germany appears to be acting against the public interest by ignoring or dismissing findings of glyphosate-induced teratogenicity and foetotoxicity.

Bhide and Patil (1989)

Submitter companies: Barclay/Luxan[68]

Germany's summary: This study examined teratological effects of glyphosate in rabbits at doses of 125, 250, and 500 mg/kg bw/d. At the high dose, two females aborted. There was no evidence of foetotoxic and teratogenic effects up to and including the mid-dose group. But the high-dose group had a decreased number of viable foetuses per litter and the number of non-viable implants (non-development and death of embryo) increased. The number of visceral and skeletal

malformations was increased in the high-dose group.[69]

The study's authors do not mention whether a statistical analysis was performed.

UK's comment: "Another study with equivocal evidence of heart defects."[70]

Our comment: The data shows that dose-dependent increases in lung and kidney malformations were found *across all glyphosate-exposed groups*. Increased heart malformations were found in all exposed groups. Increased skeletal (rudimentary 14th rib) malformations were found in the mid-dose and high-dose groups.

Germany incorrectly claims that the teratogenic NOAEL is the mid dose of 250 mg/kg bw/d. In reality, there are evident increases in most of the defects, even at the lowest dose of 125 mg/kg bw/d. The authors of this study do not provide an analysis of statistical significance and groups of only 15 animals were used, making statistical significance difficult to establish. But it is more accurate to say the mid dose, possibly even the low 125 mg/kg dose, is the LOAEL. Testing the effects of lower, realistic doses requires far larger animal groups if an increase in toxicity compared with the unexposed control group is to be reliably detected.[71 72]

At the very least, this study should have been repeated with a larger sample size and lower doses. Effects should have been examined thoroughly by allowing full gestation and pup development.

Anonym. (1981)

Submitter company: Alkaloida[73]

Germany's summary: This oral feeding study examined teratological effects of glyphosate in rats and rabbits. Vital details were either not recorded or poorly described, so the study was only considered as supplementary information. No malformations were recorded, but there were more foetal deaths at the two upper dose levels (50.7 and 255.3 mg/kg bw/d).[74] It is difficult to understand why an increase in foetal deaths would occur at doses far below those at which foetal effects were found in the gavage [force-feeding via stomach tube] studies. Thus it is doubtful whether this effect is related to glyphosate.[75]

UK's comment: "Though this study is questioned [by the rapporteur, Germany] for showing evidence of fetotoxicity at lower doses than other studies, the study by Brooker (see above) may also indicate fetotoxicity at 50 mg/kg bw/d."[76]

Our comment: Germany here again appears to show a bias towards considering low-dose findings as non-treatment-related and irrelevant – seemingly because it cannot accept that oral feeding may result in different exposures and effects than gavage. But the UK's PSD points out that another study supports this study's findings.

Tasker, E.J. and Rodwell, D.E. (1980)

Submitter companies: Monsanto and Cheminova[77]

Germany's summary: This teratogenicity study in rats found a higher number of foetuses with malformations at the highest dose level (3500 mg/kg bw/d), but this was within the range of historical control data and was not considered to be due to glyphosate treatment. Specifically, there were more foetuses with unossified sternebrae (bones of the sternum/breastbone) in the high-dose group. While this effect was considered to be due to the glyphosate treatment, it is "rather a developmental variation than a malformation."[78]

UK's comment: The UK PSD does not comment on this study.

Our comments: Germany once again resorts to historical control data in order to conclude that there is lack of evidence of teratogenicity. Given the findings of malformations from glyphosate treatment in several other studies, this is unjustifiable.

Germany's decision to redefine unossified sternebrae as a "variation" rather than a malformation is scientifically unjustifiable and at odds with other authorities. Unossified sternebrae in the rat are clearly defined as a skeletal deformity in *The Handbook of Skeletal Toxicology*.[79]

3.2. Glyphosate's "pattern" of teratogenicity dimissed by EU expert panel

The UK PSD's overall conclusion supports the teratogenicity of glyphosate: "Taken in isolation, none of the findings in these rabbit teratology studies would be clearly of concern. *However, overall there is an indication of a pattern*."[80]

The PSD ended by asking Germany to make

available the historical control data. It is unclear whether the PSD ever saw this data or, if it did, how it responded. Certainly, the data has not been placed in the public domain for scrutiny by independent scientists.

The teratogenicity question then passed to the EU Commission's ECCO scientific review panel. The panel noted "the incidence of heart malformations", but dismissed them on the grounds that they were "within the range of the historical control data".[81] It is unclear whether the ECCO Panel saw the historical control data or merely accepted Germany's conclusion. No details are given of the previous studies from which the historical control data were derived or how the figures were analyzed. The experimental animal species, experimental design, identity of the researchers and laboratories, and purity of the substance tested, are unknown. There are significant variations between different formulations of glyphosate: glyphosate produced in the 1970s will not be the same as formulations produced in later decades. But none of these variables can be checked because the historical control data does not appear to be in the public domain.

The historical control data that enabled the ECCO Panel to dismiss glyphosate's teratogenicity must be added to the large pile of grey literature supporting pesticide approvals that cannot be evaluated by the public or independent experts.

The use of historical rather than concurrent controls adds variables to an experiment that aims to control variables, obscures the teratogenic effects of glyphosate, and biases any conclusion. This is why the use of historical control data is controversial.[82 83] The practice should not be allowed in evaluating animal toxicological and other studies for pesticide approvals.

Valid control groups for an experiment are animals of the same strain and age, in the same environment, which are studied at the same time as the exposed (experimental) animals. In addition, the manner in which the animals are examined and evaluated, and the data recorded, must be the same. "Historical control data" fail to meet these criteria. It appears that they are being used as a smokescreen to hide glyphosate's teratogenic effects.

Clearly, only after findings emerged showing glyphosate's teratogenicity did Germany and the ECCO Panel introduce the artifice of historical control data as a way of calling into question the scientifically-proper controls. In this way, the differences between exposed and unexposed animals were buried in the variability within the historical control data.

If such practices were uncovered in an independent scientific study, they could be considered scientific fraud. In this case, we do not even know who perpetrated this act, which has placed public health at risk.

Taking all these industry studies together, there is enough evidence to require regulators to apply the precautionary principle and withdraw glyphosate from the market.

3.3. Industry and regulators failed to disclose glyphosate's teratogenicity

The evidence discussed above shows how EU regulators reasoned their way from evidence of glyphosate's teratogenicity in industry's own studies to a dismissal of these effects in DG SANCO's 2002 final review report.[84]

Taken together, the industry studies and regulatory documents on which the current approval of glyphosate rests reveal that:

- Industry (including Monsanto) has known since the 1980s that glyphosate causes malformations in experimental animals at high doses
- Industry has known since 1993 that these effects could also occur at low and mid doses
- The German government has known that glyphosate causes malformations since at least 1998, the year it submitted its DAR on glyphosate to the EU Commission
- The EU Commission's expert scientific review panel has known since 1999 that glyphosate causes malformations
- The EU Commission has known since 2002 that glyphosate causes malformations. This was the year its DG SANCO division published its final review report, laying out the basis for the current approval of glyphosate.

The public, on the other hand, has been kept

in the dark by industry and regulators about the ability of glyphosate and Roundup to cause malformations. In addition, the work of independent scientists who have drawn attention to the herbicide's teratogenic effects has been ignored, dismissed, or denigrated.

3.4. Germany set misleading "safe" level for glyphosate

The central purpose of any pesticide risk assessment is to establish the Acceptable Daily Intake (ADI), a level of exposure that is deemed safe for humans over a long period. The ADI is calculated from the industry tests in the dossier. The level that should be used to set the ADI is the highest dose at which no adverse effect is observed (NOAEL), which is also lower than the lowest dose that is toxic (LOAEL). This level should be selected from "the most appropriate study in the most sensitive species", as the glyphosate rapporteur Germany notes.[85]

Germany set the ADI for glyphosate at 0.3 mg/kg bw/d.[86] This ADI was accepted by the European Commission in its final review report.[87]

However, we argue that this is incorrect. Germany indulges in some creative manipulation of data to arrive at this level. It begins by excluding certain studies from the ADI process:

- Germany excludes mid-term studies on the grounds that only long-term studies should be used to set safe chronic exposure levels.[88] This enables it to avoid using the rabbit teratogenicity studies, which were mid-term.
- Germany claims that the most sensitive species for chronic exposure is the rat. This gives it another reason to exclude the inconvenient rabbit teratogenicity studies, which found significant adverse effects at lower doses than the rat studies.

Based on this biased selection of data, Germany cites as its starting point for working out the ADI a LOAEL of 60 mg/kg bw/d from a two-year rat study by Suresh (1996), which found significant toxicity at that level.[89] This is said to be the lowest dose at which toxicity was observed. Germany then identifies the highest NOAEL below that level: 31 mg/kg bw/d, in a study by Lankas (1981). It implies that this is the figure from which it calculates its ADI (though also, confusingly, denies that it bases the ADI on any single study).[90] The ADI is derived by dividing this figure by 100, to allow a safety margin. Applying this 100-fold safety factor, Germany arrives at an ADI of 0.3 mg/kg bw/d.

However, we argue that Germany should have begun the ADI process using the LOAEL of 20 mg/kg from the 1993 Suresh rabbit teratogenicity study, which is *three times lower than Germany's chosen LOAEL of 60 mg/kg bw/d*.[91 92]

To sum up the difference between these two studies:

- The study Germany uses to set the ADI: Suresh's 1996 chronic toxicity study on rats found statistically significant toxicity at 60 mg/kg bw/d (the LOAEL).
- The study Germany ignores in setting the ADI: Suresh's 1993 teratogenicity study on rabbits found statistically significant toxicity at 20 mg/kg bw/d (the LOAEL).

Germany relegates the inconvenient 1993 Suresh study to setting the acceptable operator (applicators') exposure level (AOEL). It argues that it is a mid-term rather than long-term experiment and therefore more suitable to setting an applicators' exposure level.[93]

We believe that Germany's reasoning would not stand up to independent scientific scrutiny. Germany's failure to take into consideration the worrying rabbit teratogenicity studies means that its ADI ignores the problem of the teratogenic effects of glyphosate – as shown even in weak industry studies.

In our view, the Suresh 1993 LOAEL of 20 mg/kg bw/d should be the starting point for the ADI and for the applicators' AOEL. The 1993 Suresh study from which this LOAEL is derived found no NOAEL (no observed adverse effect level). In other words, even the lowest dose produced adverse effects.[94 95] So Germany should have insisted on further tests to establish the NOAEL, using 20 mg/kg as the highest dose.

If this LOAEL of 20 mg/kg were used, then, following the same procedure as Germany, the highest NOAEL below this dose from Germany's approved list of studies is 10 mg/kg.[96] Applying the 100-fold safety factor, this would give a more

objectively accurate ADI of 0.1 mg/kg bw/d, one-third of the ADI suggested by Germany.

Interestingly, one of the industry applicants, Feinchemie, suggests a far lower ADI than Germany or us: 0.05 mg/kg bw/d. This is five times lower than the ADI suggested by Germany and accepted by the Commission. Feinchemie bases its suggested ADI on its 2-year rat study, which found a NOAEL of 5.5 mg/kg bw/d.[97]

Feinchemie's suggested ADI is consistent with the NOAEL of the 1996 Suresh study, which Germany used to derive the LOAEL but ignored to set the ADI. The NOAEL of that study was 6.3 mg/kg bw/d, which would give an ADI of 0.06 mg/kg bw/d, close to Feinchemie's proposed ADI of 0.05 mg/kg bw/d.

It is ironic that industry asked for stricter – and more scientifically justifiable – safety standards than the rapporteur, Germany. In contrast with Feinchemie's proposed low ADI, however, Monsanto asked for an ADI of 1.75 mg/kg bw/d, the highest of all the industry-suggested ADIs.[98]

3.5. What the ADI should be – according to independent studies

If a manufacturer of glyphosate says the ADI should be five times lower than the one suggested by Germany and accepted by the Commission, what do independent studies say it should be?

Two high-quality mammalian toxicity studies show that glyphosate's LOAEL should be even lower than that proposed by Feinchemie (which in turn was lower than that proposed by Germany):

- A study on rats showed that a Roundup formulation was a potent endocrine disruptor and caused disturbances in reproductive development when the exposure was performed during the puberty period. Adverse effects, including delayed puberty and reduced testosterone production, were found at all dose levels, including the LOAEL of 5 mg/kg. The dose-response relationship was clear.[99] One of the critical failures of regulatory toxicity tests is to ignore important developmental windows such as puberty. This study helps to fill that knowledge gap.
- A 75-day study on rats showed that Glyphosate-Biocarb (a Brazilian formulation) caused damage to liver cells in a dose-response manner, including at the LOAEL of 4.87 mg/kg. According to the authors, the findings suggest that the damage to liver cells was "irreversible".[100]

Both studies use a species (rats) and an exposure route (oral) approved by EU regulators and industry.

No dose below these two LOAELs was tested in these studies, so the true NOAEL is lower – by how much, no one knows. But the NOAEL could reasonably be assumed to be 2.5 mg/kg bw/d. Applying the usual 100-fold safety margin results in a scientifically defensible ADI of 0.025 mg/kg bw/d. This is over ten times lower than the Germany's ADI, which is currently in force. The MRL (safe level in food) should be correspondingly revised downward.

Of course, all assumptions need to be tested, and not even independent science has explored the full picture of Roundup and glyphosate's toxicity. Studies should be carried out immediately to determine the true NOAEL and ADI for glyphosate and Roundup, using the most comprehensive, up-to-date scientific knowledge. These studies would involve:

- testing for more effects
- using lower, more realistic doses that will allow accurate determination of the NOAEL
- using larger numbers of animals to ensure sufficient statistical power to reliably detect effects from realistic doses
- dosing during vulnerable developmental windows
- extending study time-frames to allow mid- and long-term effects to show up, instead of killing the test animals before disease has a chance to develop. Industry test animals are killed at the human equivalent of about 60 years old, so many effects of the chemical tested are missed.[101]

In addition, research should be done that determines glyphosate levels in food and feed imported into the EU. Finally, based on independent (not industry) data from North and South America, an assessment should be carried out of the increase in glyphosate use, and therefore exposure, that would be expected to occur if glyphosate-tolerant GM crops were allowed to be grown in the EU.

This science-based assessment of glyphosate and Roundup will allow the EU to establish a credible policy that protects EU citizens. Until that assessment is complete, the EU should apply the precautionary principle and withdraw glyphosate herbicides from sale in the EU.

3.6. Does current risk assessment protect the public?

The current system of pesticide risk assessment in the EU is not transparent or easy to understand. Those who make the effort to study it will see that it is open to manipulation and abuse. In risk assessment, it is the details that count. The conclusions that are drawn depend heavily on how data is selected – what is included and what is left out. This is clear from the above discussion of the approach Germany used in justifying its incorrect conclusion that glyphosate does not have teratogenic or foetotoxic effects. Particularly revealing was Germany's exclusion of the rabbit teratogenicity studies in setting the ADI for glyphosate.

Industry also has room for manoeuvre in discussions of how toxins behave in the human body. For example, industry uses broad arguments to claim that toxins are broken down in the liver, or do not cross the placental barrier in pregnant women. Even cases of clear harm can be minimized. An anonymous scientist critic said, "There are many tricks that are used. If all insects in a field are killed for a full year, this is not a problem, because they will come back next year. A regulator told me that with the current system of risk assessment you could get any chemical approved, including DDT."

Even the underlying assumption of risk assessment, that there is a "safe" level below which a toxic pesticide is not toxic, is questionable. Many compounds accumulate in the body. Some toxins, particularly endocrine disrupting chemicals, are more potent at low doses than higher doses. People and species vary in their susceptibility to toxins and individuals at different stages in development and maturation and at different stages of biological cycles. Even the latest independent science has only begun to explore the true effects of chemicals on vulnerable groups such as developing foetuses, infants and children, the elderly, and immune-compromised people.

In addition, the industry tests carried out for risk assessments mostly look for a narrow range of gross effects. These include tissue and structural changes, such as malformations and tumours, which tend to occur at the high doses that industry tests use. But these tests often miss functional changes (effects on how the body's organs and systems function), which tend to be seen at lower doses and more closely reflect effects from real-life human exposures. These functional changes are important because they can lead to more severe and difficult-to-reverse disease conditions. In other words, they perform a signalling role in predicting serious health problems. Independent scientific literature, which is not tied to OECD test designs, has been more effective than industry science in finding these functional effects – but it has hitherto been virtually ignored in pesticide risk assessments.

Other aspects that have not been adequately examined in existing risk assessments are the impact of the individual's existing body burden of toxins and synergistic effects that are not seen when the compounds are tested in isolation.

For these reasons and more, some scientists and policy-makers advocate reforming the risk assessment of pesticides – for example, by increasing the use of hazard analysis. Hazard analysis stipulates that if a pesticide has certain hazardous qualities, it should automatically be rejected ("hazard cut-off"). This differs from the current risk assessment approach, which assumes that even when a hazard exists, the risk can be managed. The new pesticide regulation 1107/2009 contains some "hazard cut-off" criteria. For example, a pesticide cannot be approved if it is carcinogenic, mutagenic, a reproductive toxin, persistent in the environment, bioaccumulative, or an endocrine disruptor (apart from specific uses, such as in closed systems).

These are positive developments. But industry, together with the German Federal Institute for Risk Assessment (BfR), which is involved in the registration of pesticides in Germany, is lobbying to prevent the new system of hazard analysis and

cut-off criteria gaining a foothold in Europe and to keep the existing system of risk assessment.[102 103] For the sake of public health, it is vital that they do not succeed.

4. The problem of industry bias in testing

Regulatory approvals of pesticides are based almost exclusively on industry's own studies. The conflicts of interest inherent in this system were pointed out by Andrés Carrasco in his original research study. The German government agency BVL replied to this criticism by defending the reliability of industry studies. BVL says industry studies on other substances have sometimes found developmental effects and "it is not likely that developmental effects would have not been reported for glyphosate but for other substances". BVL adds that many different companies provided their own toxicological data from tests they had commissioned from different laboratories, and all found "absence of teratogenicity".

It is interesting that the BVL makes this bold and categorical statement, despite the fact that industry studies in the dossier that the BVL reviewed did find evidence of teratogenicity.

Even if the industry tests had shown no malformations, this would not be proof of glyphosate's safety. Every time industry studies are compared with those from the independent scientific literature, the same verdict is reached: industry tests are biased towards conclusions of safety. The best known example is tobacco industry studies, which successfully delayed regulation for decades by manufacturing doubt and controversy about the effects of smoking and passive smoking.[104] More recently, studies sponsored by the pharmaceutical and mobile phone industry have been shown to be more likely to portray their products in a favourable light than non-industry-funded studies.[105 106 107] A review of studies on genetically modified crops and foods showed that the existence of either financial or professional conflict of interest was associated with study outcomes that cast products in a favorable light.[108]

Fewer comparisons of industry vs. independent studies have been performed for chemicals (including pesticides), but in four such reviews the same relationship is found: industry sponsorship is more likely to find favorable results, while the independent literature finds both safety and risk.[109 110 111 112]

The Monsanto/Dow employees follow BVL in defending industry studies. In their response to Carrasco, they write: "Multiple high quality toxicological studies and expert review panels consistently agree glyphosate is not a teratogen or reproductive toxicant." They say the industry-funded studies that Carrasco calls untrustworthy "have been exhaustively reviewed by multiple government scientific regulators, often comprised of academic expert scientists and all of which have strongly supported the conclusions put forth in those studies."[113] Monsanto/Dow names the "Regulatory authorities and independent experts who have documented this position" as WHO/FAO, US EPA, the European Commission, and Williams (2000).

But Monsanto/Dow's cited authorities for its position do not stand up to scrutiny:

- The European Commission's 2002 review of glyphosate claims that developmental effects are confined to "maternally toxic doses". But this claim is examined and discredited above.
- The WHO report on glyphosate (1994)[114] mainly cites industry studies. For example, 180 studies were generated by Monsanto, of which over 150 were not published or subjected to peer review. Other unpublished technical reports provided as references in the same document include 17 reports from Agrichem, five from Luxan BV, and five from Rhone Poulenc – all producers and/or marketers of pesticides.[115]
- Williams co-authored his paper on glyphosate's safety with Ian C. Munro.[116] Munro is executive vice president of the chemical industry consulting firm Cantox,[117] which states that its mission is "protect client interests while helping our clients achieve milestones and bring

products to market".[118] The Williams paper was published in the controversial chemical industry-sponsored journal Regulatory Toxicology and Pharmacology (RTP). RTP was one of several industry-linked organizations that were investigated by a US Congressional Committee in 2008 over their role in the FDA's decision allowing the toxic chemical bisphenol A in infant formula and other foods.[119] [120] [121] All this would matter less if Williams had cited credible sources in his claims for glyphosate's reproductive and developmental safety. But he cites unpublished industry studies, such as Schroeder (1981), Reyna (1990), and Tasker (1980). As these studies are from the industry dossier submitted for glyphosate's approval, it is strange that Williams fails to mention the other studies from the same dossier that we examine above – Suresh (1993), Brooker (1991), and Bhide and Patil (1989) – which found that glyphosate was teratogenic.

In sum, Monsanto/Dow relies for its claims of glyphosate's safety on carefully selected industry sources and cooperative regulators who only consider industry studies.

4.1. Good Laboratory Practice: A shield for industry?

In its response to Carrasco, Monsanto/Dow praises the "high quality" industry tests that it claims show the safety of glyphosate on the grounds that they were conducted under Good Laboratory Practice (GLP) rules.

GLP specifies the organisational process and the conditions under which industry studies for the regulatory purposes are planned, performed, monitored, recorded and reported. GLP is a management system. It is not a hallmark – much less a guarantee – of "good science".

GLP was initiated by the US Food and Drug Administration in 1978 in an attempt to end the serious problem of fraud in industry testing of pesticides, chemicals, and pharmaceutical drugs for regulatory assessment.[122] In 1983, the US Environmental Protection Agency (EPA) established similar guidelines for pesticide toxicology studies and in 1989, extended them to cover studies submitted for pesticide approvals.[123]

The move to GLP standards was prompted by a high-profile case of fraud involving a company called Industrial Bio-Test Laboratories (IBT), which brought into question 15% of the pesticides approved for use in the US.[124] [125] However, the implementation of GLP failed to prevent a second major case of fraud, this time at Craven Labs, which was discovered in the 1990s.[126]

Interestingly, both the IBT and Craven Labs fraud cases involved toxicological and residue tests of Roundup for regulatory purposes by laboratories under contract to Monsanto. Monsanto says it later repeated the tests under GLP rules,[127] though this is hardly reassuring given that the Craven Labs fraud occurred after GLP rules were in place.[128] Clearly, GLP neither prevents fraud, nor assures high quality science.

The GLP guidelines are set by the OECD (Organisation for Economic Cooperation and Development), a body dedicated not to public health but to promoting international trade and economic development. OECD guidelines prescribe the choice of experimental animal, number of animals, exposure times, and doses.[129] The aim was to establish a set of standardized tests that would be acceptable in all WTO member countries (WTO having come to an agreement with OECD). This facilitates international trade because all countries involved agree to the same testing requirements.[130] [131]

Though the aims of GLP were laudable, they have been used to create a regulatory system that excludes open peer reviewed scientific literature. One critic called GLP a "shield" that industry uses to protect itself from inconvenient findings in the independent scientific literature.[132] Regulatory bodies across the world – including the EU Commission's DG SANCO and the European Food Safety Authority (EFSA) – collude in this process by designating industry's GLP-compliant toxicity studies as the highest quality data. They rely almost exclusively on these industry-sponsored studies for pesticide and chemical assessments, rejecting studies from the open peer reviewed scientific literature because they are not conducted under GLP rules.[133] [134]

Thus, Monsanto/Dow is able to dismiss

Carrasco's research and other independent studies showing harm from glyphosate/Roundup by saying that the testing systems are "unvalidated" and the studies "inappropriate and irrelevant for human health risk assessment purposes".[135] In other words, they are not GLP.

The tyranny of GLP over regulatory processes has been heavily criticised in a paper co-authored by 30 scientists. The authors point out that GLP "specifies nothing about the quality of the research design, the skills of the technicians, the sensitivity of the assays, or whether the methods employed are current or out-of-date".[136] Indeed, the dismissive attitude of the EU Commission – and of pesticide regulators worldwide – to high-quality independent studies that find harm from pesticides raises the question: why do governments fund scientific research if they ignore its findings in almost every risk assessment?

Another review criticizes GLP toxicity studies for using outdated protocols, some of which "have failed to modernise for nearly 100 years": "Very high doses are used (to assure statistical significance, due to insensitivity of the assays), but such near-poisoning levels may have little to do with what happens to organisms that are exposed to real world doses... and which go untested.... Test animals are killed before old age, masking most developing diseases. In short, GLP tests use protocols that cannot find toxicity."[137]

Government pesticide and chemical regulators use data from industry OECD-compliant tests to determine the claimed safe level or NOAEL (no observed adverse effect level, the level at which the effect being looked for is not found). But Tweedale (2011) compared the NOAELs from industry and independent tests on dozens of chemicals and found that in every case, independent studies detected important toxic effects at levels well below those that industry studies claimed to be safe. Yet regulators ignore the independent data and take note only of the industry data because they comply with OECD GLP criteria.[138]

In addition, OECD tests set rigid and scientifically incorrect criteria regarding dose-response in toxicological tests. These criteria fail to take into account the fact that endocrine disrupting and other effects are often stronger at low dose than at high dose. Their assumption that there is a safe dose below which no significant toxicity occurs has been challenged by findings in the independent scientific literature.[139]

OECD has still not come to terms with low-dose effects or complex dose-response relationships. One critical scientist who spoke on condition of anonymity said, "It will probably take OECD 10–15 years to come up with a complete set of tests to take endocrine disruption into account – which by then will be outdated again. On endocrine disruption, only a few standardized tests are available at the moment and there is no overall strategy to decide which substances should be subjected to which tests."[140 141 142]

The EU Commission said in 2009 that it expects its range of tests on endocrine disrupting effects of pesticides to be ready in 2013.[143] The US Environmental Protection Agency is ahead of the EU Commission and OECD and already has a strategy and a list of substances for endocrine disruption screening. These include glyphosate.[144 145 146]

Even if we take Monsanto/Dow's elevation of GLP studies at face value, its argument does not stand up, as many of the studies in the industry dossier on glyphosate are not GLP. They are so old that they pre-date the introduction of GLP. The industry studies cited by Williams to back his claim that glyphosate is not a reproductive toxin include non-GLP studies by Schroeder (1981) and Tasker (1980).[147]

4.2. EFSA undermines democratic decision to end tyranny of GLP

Science has separated into two diverging pathways – industry GLP science, which is often used to claim safety for a risky product, and independent science, which is usually not conducted according to GLP rules, and which often shows harm. The new EU pesticide regulation has the potential to end the tyranny of GLP by insisting on the use of peer-reviewed independent scientific studies in pesticide assessments.

However, the new regulation obliges industry to do its own scientific literature search in preparing a pesticide dossier. The risk inherent

in giving industry control of the search could be removed by forcing it to do a complete and non-selective search. But the European Food Safety Authority (EFSA) has undermined the intent of the new democratically established regulation by issuing a Guidance on the use of peer-reviewed science in pesticide assessment.[148] The Guidance actively encourages industry to select only those studies it finds convenient to include in the dossier, through the following means.

Industry evaluates reliability of studies

The Guidance advises industry how to evaluate the reliability of, and thus how to select, studies for possible inclusion in its dossier. The first source that EFSA recommends industry to consult is a paper by a BASF employee, Klimisch (1997),[149] published in the industry-sponsored journal Regulatory Toxicology and Pharmacology.[150] Klimisch gives a list of "categories of reliability" by which to assess the suitability of a scientific study for inclusion in the regulatory dossier. His most reliable category 1 ("reliable without restriction"), consists of studies conducted according to GLP rules. Klimisch relegates independent studies, which do not follow GLP/OECD rules, to categories 2 and 3, "reliable with restrictions" and "not reliable", respectively.[151]

Industry can carry out selective searches

EFSA's Guidance encourages industry to choose search terms that would provide only a narrow-focused search of the literature by, for example, specifying the type of test design.[152] This works against the public interest, as a search for "mutagenicity AND GLP" would find industry-generated studies but exclude independent studies. If an independent study found mutagenicity by a non-GLP test, it would not turn up in the search.

Industry defines what is a "relevant" study

EFSA's Guidance encourages industry to select out studies on the basis that they are not "relevant" to human risk assessment. EFSA defines "relevant" species for toxicological studies as mammals, preferably rats, mice, and dogs. This would exclude studies such as Carrasco's, which was on frogs and chickens – even though the developmental mechanisms in humans are similar.[153]

EFSA defines "relevant" exposure routes as oral, dermal, or inhalation.[154] This would exclude many independent studies, which use injection or culture as the exposure route. Among the research findings excluded through this definition would be Carrasco's study and much of the research on glyphosate and Roundup conducted by Professor Gilles-Eric Séralini's team. However, the question of relevance of different exposure routes is by no means settled, and EFSA's exclusion of certain exposure routes as irrelevant is premature at best (see Section 6, below).

Through its Guidance, EFSA has given industry licence to dismiss independent scientific studies – and regulators an excuse to continue to ignore them in risk assessments of pesticides.

4.3. Case study in the misuse of GLP: bisphenol A

The problem of the tyranny of GLP over regulators is exemplified by the case of the chemical bisphenol A (BPA), a plastics ingredient widely used in food packaging.

Hundreds of peer reviewed, published – and non-GLP – studies show significant effects of BPA at low doses, with over 30 showing significant effects below the predicted "safe" dose. The evidence that BPA poses a danger to public health is strong. It has been found in human blood and tissues, including in human foetal blood, at levels higher than those causing adverse effects in mice. An epidemiological study shows that that BPA is related to ovarian disease in women.[155]

But industry studies on BPA have reached diametrically opposite conclusions. While 94 of 104 (90%) government-funded published studies on bisphenol A reported significant effects at low doses, no industry-funded studies (0 of 11) report significant effects at the same doses. A 2005 review of studies on BPA found that source of funding is highly correlated with positive or negative findings.[156]

A 2009 review blamed regulatory fixation on GLP for the BPA débacle. The authors criticized the US Food and Drug Administration and

the European Food Safety Authority (EFSA) for deeming two industry-funded studies that adhered to GLP to be superior to hundreds of independent non-GLP studies funded by the US National Institutes of Health (NIH) and similar agencies in other countries.[157]
The authors stated:

> It is of great concern that the US and EU regulatory communities are willing to accept these industry-funded, antiquated, and flawed studies as proof of the safety of BPA while rejecting as invalid for regulatory purposes the findings from a very large number of academic and government investigators using 21st-century scientific approaches. The basis for these decisions by US and EU regulatory agencies should be thoroughly investigated.[158]

The authors pointed out that there is simply no data from GLP studies on many of the toxic effects observed in independent studies on BPA, such as some adverse effects on the female reproductive system. This is because those effects have not yet made their way into the outdated regulatory testing system. In other words, the reason the effects are not found in GLP studies is not because the chemical is safe, but because those effects are not looked for. The authors added that there is a large literature on neurotoxic effects and behavioral abnormalities caused by low doses of BPA which are not capable of being detected by current GLP studies conducted for regulatory purposes because of their outdated methodologies.

The authors argued that the chemical industry-sponsored GLP studies on which the agencies based their decisions are incapable of detecting low-dose endocrine-disrupting effects of BPA and other hormonally active chemicals. They stated that the FDA and EFSA "mistakenly assumed that GLP yields valid and reliable scientific findings (i.e., 'good science')."[159]

The authors stated that the main factors determining the reliability of scientific findings are independent replication and use of the most sensitive and up-to-date tests – neither of which is an expectation of GLP. They concluded:

> We are not suggesting that GLP should be abandoned as a requirement for industry-funded studies. We object, however, to regulatory agencies implying that GLP indicates that industry-funded GLP research is somehow superior to NIH-funded studies that are not conducted using GLP.[160]

The EFSA continues to rely for its risk assessment of BPA on the few industry studies adhering to Good Laboratory Practice (GLP) guidelines that found no adverse effects. Based on these studies, EFSA refuses to take decisive action restricting its use.[161] [162] The EU Commission announced in November 2010 that it would ban BPA from babies' bottles but would not extend the ban to materials such as the linings of food and drinks cans as there was no scientific evidence to support such a move.[163] [164]

The regulatory prejudice against open scientific literature and in favour of OECD- and GLP-standardized studies has forced the public to live with many more years of exposure to potentially dangerous levels of BPA.

The case of bisphenol A parallels that of glyphosate. Many studies from the independent scientific literature indicate that glyphosate and Roundup cause harm to human and animal health and the environment at low, realistic doses. Yet EFSA and the Commission continue to rely on a few outdated and flawed industry studies as proof of the herbicide's safety.

5. Evidence of teratogenicity in independent studies

In its response to Carrasco's findings of malformations in frog and chicken embryos exposed to glyphosate and Roundup, the German government agency BVL says: "There is a huge and reliable database for developmental toxicity of glyphosate and no evidence of teratogenicity has been obtained."[165] It is fair to assume that BVL's "huge and reliable database" stretches beyond the industry studies to include the independent scientific literature. This interpretation is confirmed by the fact that BVL cites Dallegrave's studies (2003, 2007) on the reproductive and

developmental toxicity of Roundup on rats, which BVL claims showed "no craniofacial [of the skull and face] malformations".

But this is untrue. The 2003 Dallegrave study cited by BVL does show craniofacial malformations from Roundup. Dallegrave found that sublethal oral doses of Roundup cause craniofacial ossification defects, loss of caudal vertebrae, and misshapen atlas and other cervical and thoracic vertebrae in rats. The author did not use the word "craniofacial" but described the nature of the malformations, which included the craniofacial type: "incomplete skull ossification and enlarged fontanel". The effects were statistically significant and dose-dependent, strengthening the conclusion that they were caused by the glyphosate formulations.[166]

Another study, not cited by BVL, found that glyphosate formulations cause craniofacial and mouth deformities, eye abnormalities and bent, curved tails in tadpoles.[167]

Both these studies are part of what BVL calls the "huge and reliable database" on glyphosate. Both show evidence of teratogenicity.[168] Therefore, BVL must publicly retract its claims of "no craniofacial malformations" in Dallegrave's 2003 study and of "no evidence of teratogenicity" in the scientific literature. In dismissing these findings, BVL and the EU Commission are ignoring data that is publicly available in the peer-reviewed literature.

5.1. How Carrasco's findings built on previous studies

Carrasco built on the findings of Dallegrave in that he identified the mechanism for the teratogenic activity of Roundup/glyphosate. Such malformations in humans and animals are known to be linked with an excess of retinoic acid (RA), an oxidized form of vitamin A.[169] [170] [171] [172] [173] [174] [175] [176] The link between RA and malformations is the reason why pregnant women are advised not to take vitamin A supplements. Carrasco found that glyphosate increased RA activity in frog embryos and that this was the mechanism through which the malformations occurred.[177]

Carrasco says that the malformations of the vertebrae found by Dallegrave may represent teratogenic effects on late embryonic development. His experiments did not extend the observations to the same late stage of development as Dallegrave's. However, the malformations he found are compatible with those found by Dallegrave.[178]

5.2. Epidemiological evidence on glyphosate and birth defects

In response to Carrasco's study, BVL claims: "There is no epidemiological evidence in humans that glyphosate (herbicides) might be teratogenic" and "There is no clear-cut link to a hypothetic increase in malformations in regions with extensive use of plant protection products [pesticides, including herbicides] in South America."

It is true that the authorities in South America have not carried out systematic epidemiological studies in areas where glyphosate spraying is widespread. Even so, enough evidence exists to show that the rapid escalation in the rates of birth defects coinciding with the expansion of GM soy and glyphosate spraying is far from "hypothetic":

- Amnesty International reported that since Carrasco's research findings were announced, "Activists, lawyers and health workers ... have started to conduct their own studies, registering cases of foetal malformations and increased cancer rates in local hospitals."[179]
- An epidemiological study in Paraguay found that women who were exposed during pregnancy to herbicides were more likely then unexposed women to deliver offspring with birth defects of a similar type to those that Carrasco found in his experiments.[180] BVL dismisses this study on the grounds that it is small and does not mention glyphosate. BVL fails to mention that the study was carried out in an area of Paraguay (Itapua) devoted to GM soy monocultures sprayed with glyphosate and agrochemical mixtures. Itapua was home to Silvino Talavera, an 11-year-old boy who died in 2003 from agrochemical poisoning after being sprayed. Glyphosate was one of three agrochemicals found in his blood.[181] These were the facts that gave rise to public demand

for the epidemiological study that BVL so lightly dismisses.

- A report commissioned by the provincial government of Chaco, Argentina, analyzed health statistics in the town of La Leonesa and other areas where soy and rice crops are heavily sprayed. The report found that the rate of birth defects increased nearly fourfold over the entire state of Chaco in only a decade, coinciding with the expansion of the agricultural frontier into the province and the corresponding rise in agrochemical use. The report mentioned glyphosate as one of several agrochemicals that were causing problems. It noted that complaints from sprayed residents centred on "transgenic crops, which require aerial and ground spraying (dusting) with agrochemicals".[182]
- BVL dismisses newspaper reports of birth defects and other severe health problems in sprayed areas by saying "To our knowledge, there is no scientific confirmation of these reports so far". BVL fails to mention that some of these newspaper reports mention local epidemiological studies conducted by doctors and scientists showing an escalation in birth defects.[183] [184] Carrasco also refers to clinical observations in his study.[185] The fact that these small studies have not been translated into English or published in a scientific journal is no excuse for BVL to pretend that they do not exist. This is particularly true as BVL's report on Carrasco's study relies for its assurances of glyphosate's safety on unpublished, non-peer-reviewed industry studies.
- In March 2010, just months after the release of Carrasco's findings, a court in Santa Fe province in Argentina banned the spraying of glyphosate and other agrochemicals near populated areas. The court found that farmers "have been indiscriminately using agrochemicals such as glyphosate, applied in open violation of existing laws [causing] severe damage to the environment and to the health and quality of life of the residents". While the decision is limited to the area around San Jorge, other courts are likely to follow suit if residents seek similar court action.[186]
- An epidemiological study in Ontario, Canada found high levels of premature births and miscarriages in female members of farming families that used pesticides, including glyphosate.[187]

None of these cases provides unequivocal evidence that glyphosate is the culprit in causing the harm, since other agrochemicals are used in the areas concerned. This is especially so since the spread of glyphosate-resistant weeds accompanying the spread of GM Roundup Ready crops has forced farmers to use other agrochemicals, such as 2,4-D, in addition to glyphosate.[188] [189] [190] [191] [192] [193]

However, this type of uncertainty is true of all epidemiological studies, which do not show causation but only point to an association. That is why epidemiological studies need to be supported with toxicological studies on a single substance, such as Carrasco's research. His work, along with that of other independent researchers, confirms that Roundup/glyphosate is a reproductive and developmental toxin.

6. Exposure routes an escape for industry and regulators

The German agency BVL tries to dismiss Carrasco's study on the grounds that the exposure routes used (injection and culturing the embryos in solution) are unrealistic and do not reflect real-life conditions of human exposure to glyphosate. In real life, BVL says, pregnant women would be exposed to glyphosate through the skin (dermal) or by inhalation.

Increasingly, industry and its allies in government challenge the findings of independent toxicological studies on the basis that they used injection or some other exposure route that industry argues is unrealistic.[194] [195] Industry prefers oral, dermal, or inhalation exposure routes, on the claimed grounds that they better reflect real-life exposure routes for humans.

As a bonus for industry, these exposure routes can be used to argue for lax allowable daily intake levels, based on the assumption that by the time the chemical has travelled through the protective barriers of the body, such as skin and mucous membranes, and the liver, which helps to break down toxins, very little of the chemical actually reaches the body tissues. Injection, in contrast, allows the substance to bypass these protective barriers. In industry's view, this results in unrealistically high concentrations reaching the tissues. Rejecting injection as an exposure route also allows industry and regulators to exclude many independent studies with inconvenient findings from pesticide risk assessment. A more useful response would be to utilize the signalling role of independent studies and repeat them, substituting the preferred exposure route.

This is the approach recommended by Carrasco, who says that any doubts regarding the realism of his exposure routes could be cleared up by repeating Dallegrave's 2003 study,[196] using inhalation as the exposure route. This would reflect real-life conditions of humans exposed to glyphosate spraying in Argentina, where around 80% of exposure is by inhalation.[197] Dallegrave found skeletal malformations in the foetuses of rats fed orally with high doses of Roundup.[198]

Carrasco suggests that the effects reported by Dallegrave would have been even more striking if treatment had begun on the fifth day of pregnancy, rather than the sixth, as the relevant structures have already begun to form by the fifth day. Beginning treatment on the sixth day is slightly too late to maximize the effects of glyphosate.[199] This is also a shortcoming of the industry teratogenicity tests in the DAR, most of which begin dosing on the sixth or seventh day.[200]

Interestingly, recent study findings suggest that cherry-picking exposure routes may not offer industry much protection. Two recent studies, one on glyphosate, have come up with surprising findings when different exposure routes were tested in the same animal:

- A study on the controversial chemical bisphenol A (BPA) funded by the US government's National Institute of Environmental Health Sciences (NIEHS) tested the effects on rats of the chemical through two different exposure routes, injection and oral dosing. The study was commissioned in response to industry-generated criticism that the injection route of exposure was not relevant to humans, as it would lead to unrealistically high levels of active BPA in the blood. The results showed that while injection showed a seven-fold increased level over oral dosing in the first 30 minutes, after two hours the level of active BPA in the blood was similar for both exposure routes. It is important to note here that the concentration of a chemical found in blood is only an average indicator of its presence in the body and does not provide evidence about its distribution to tissues, where toxic effects occur. Interestingly, in this experiment, both exposure routes resulted in the same pre-cancerous toxic effects on the prostate, seven months after exposure. The study concluded that route of exposure is not as critical as had been thought and therefore, the injection exposure route should be acceptable for human risk assessment.[201 202]
- A study examined the rate at which glyphosate entered the body of rats and what happened to it once it was in the body. Two exposure routes were compared: oral dosage and injection. The study found that injection resulted in a considerable diffusion of glyphosate into the tissues. When given orally, glyphosate was more slowly absorbed but also took longer to clear from blood than when given by injection. Some of this glyphosate was broken down into AMPA (glyphosate's main metabolite/ breakdown product). Because glyphosate and AMPA were cleared from blood more slowly after oral dosing, they could be distributed to body tissues to exert systemic toxic effects.[203]

These findings suggest that industry's insistence on oral, dermal, and inhalation routes is based on incorrect assumptions about what happens to toxins inside the body. While received doses may vary according to different exposure routes, this should be tested and not taken on faith.

Nevertheless, as we have seen above (Section 4.2), EFSA recently incorporated industry's

preference for these exposure routes into a Guidance document on the use of science in industry dossiers under the new pesticide regulation 1107/2009.[204] At one stroke, EFSA gave industry permission to exclude from its dossier any study that does not use oral, dermal, or inhalation exposure routes – without any requirement to further investigate the findings by repeating the study with an "approved" exposure route. This will exclude the findings of many independent scientists, including Carrasco, from the risk assessment.

7. The question of doses

BVL says the fact that Carrasco found malformations from concentrations of Roundup and glyphosate below levels used in agriculture is irrelevant to human risk assessment. It says comparison with internal doses received by exposed humans would be more relevant but still cannot tell us what really matters – the doses received by the developing human foetus in the uterus.

However, BVL must know it is asking for the impossible, since it would be considered unethical to perform toxicological experiments on human foetuses to ascertain the doses of glyphosate they receive – and the new EU pesticide regulation forbids human experimentation.

Nevertheless, Carrasco points out that it would be easy to check whether people exposed to Roundup/glyphosate spraying accumulate glyphosate in their blood. If they do, the glyphosate could circulate and expose multiple tissues in the body to different concentrations of the chemical, producing different effects.[205] One study that measured pesticide residues in the blood of pregnant and non-pregnant women found glyphosate residues in the blood of 5% of non-pregnant women.[206] A study on rabbits suggests that glyphosate may accumulate in body tissues, based on its damaging effects on the sperm six weeks after exposure.[207] [208]

7.1. Did Carrasco use inappropriately high doses?

In its response to Carrasco, Monsanto/Dow argues that Carrasco used "inappropriately high" and "unrealistic" doses.[209] These doses, Monsanto/Dow says, are far higher than the already high doses used in other experiments that have been shown not to cause malformations.

Monsanto/Dow first addresses the frog embryo injection experiments. It says that Carrasco's team

> exposed two-cell frog embryos via direct injections of 360 pg and 500 pg glyphosate acid per cell, bypassing the developing amphibian protective gel coat. Assuming a cell diameter of 1mm to determine spherical volume, the cellular doses are approximately 690 to 950 µg/L within each treated cell.[210]

But this is not an inappropriately high dose. This is made clear by some simple calculations based on Monsanto/Dow's own paper. The Monsanto/Dow authors state elsewhere in their paper that a 400 mg/kg dose of glyphosate, delivered through feeding, results in a blood concentration of 4.6 µg/ml. Animal studies typically use between 50 and 500 mg/kg bw/d doses. Making a linear extrapolation (as the authors themselves do for other purposes), a 50 mg/kg dose should result in a blood concentration of 0.575 µg/ml, or 575 µg/L. Therefore the range of blood concentrations achieved in animal studies would be in the range of 575 to 5750 µg/L. Clearly, the concentrations achieved in the frog embryos (690 to 950 µg/L) are comparable to the blood concentrations achieved in animal feeding studies. So the Monsanto/Dow authors' claim that these are unreasonably high concentrations is not warranted.

Above-lethal doses?

Turning to Carrasco's frog embryo incubation experiments, Monsanto/Dow says that the concentrations used were 9–15 times greater than the acute LC50 value for frog embryos of the same species (LC50 is the concentration needed to kill 50% of experimental animals).[211] Monsanto/Dow

cites as its authority for this argument a study by Edginton and colleagues (2004).[212]

But Monsanto/Dow is not comparing like with like. Carrasco points out that Edginton's team used a different glyphosate formulation, which could have different effects and a different LC50 value.[213] Edginton's team stated that the surfactant POEA was the major toxic component of the formulation, so the two experiments are not comparable: it is not known to what extent the toxic effects were due to the POEA. POEA is known to have a synergistic effect with glyphosate, enhancing its toxicity.[214] Carrasco adds that the LC50 value is not relevant to an examination of what happens to the surviving embryos over time.

Moreover, Carrasco says that the doses he used were extremely low. Even the injection doses were far below what has been accepted as lethal.[215] Carrasco reports that treatments at 1/5000 to 1/3000 dilutions of glyphosate herbicide resulted in extremely low mortality of frog embryos, nowhere near the 50% mortality that would be expected at the true LC50.[216] Thus the Monsanto/Dow authors' claim that the effects observed by Carrasco were acute toxicity effects from inappropriately high doses is not supported.

Carrasco's argument is confirmed by the study of Dallegrave (2003), which found similar malformations at sublethal doses.[217] Monsanto/Dow avoids this issue by not even mentioning Dallegrave's study in its response to Carrasco.

The chicken egg experimental doses

Monsanto/Dow says that Carrasco's experiments with fertilized chicken eggs used an "unrealistic" exposure route by "opening a window in the shell and directly dosing 20 µL of 1/3500 and 1/4500 dilutions of glyphosate formulated product (2.0 and 1.6 µg/chicken embryo)." The implication is that due to this choice of exposure route, the doses that the embryos were exposed to were unrealistically high.

But this is untrue. Using the Monsanto/Dow authors' own estimate that 20µL of a 1/4500 dilution of glyphosate formulated product translates into about 2 µg glyphosate injected into the egg, and assuming that the volume of an egg is about 35 mL, the actual concentration of glyphosate within the egg would be about 57 µg/L. This is much lower than the blood concentrations of glyphosate that would be expected in animal toxicity studies (575 to 5750 µg/L, see above), according to Monsanto/Dow's own calculation methods.

Inappropriate comparison with rat study

As evidence for its argument that Carrasco's doses were unrealistically high, Monsanto/Dow cites a study on the fate of glyphosate orally fed to rats. The study found that a 400 mg/kg oral dose of glyphosate resulted in a maximum blood concentration of 4.6 µg/mL.[218] Monsanto/Dow extrapolates from this study to calculate that the dose necessary to produce a blood concentration in rats of 72 µg/mL (as in the low dose of 72000 µg/L in Carrasco's frog embryo culture experiments) would be over 6200 mg/kg bw (72 µg/mL / 4.6 µg/mL x 400 mg/kg bw = 6261 mg/kg bw).

Thus, Monsanto/Dow calculates that the *in vitro* concentration used by Carrasco's team was equivalent to a glyphosate oral dose to rats of 6261 mg/kg bw. Monsanto/Dow says:

> This dose is over an order of magnitude greater than the already high doses of glyphosate shown not to cause developmental or reproductive effects in rats and rabbits (NOAELs), which are used for risk assessment purposes by some regulatory authorities to establish safe human allowable daily intakes (ADIs).[219]

But the comparison made here is not appropriate. It is not justified to assume that an experimental model designed to track the fate of orally administered glyphosate in rats can be used to predict frog embryo uptake of glyphosate from the culture solution. Monsanto/Dow incorrectly attempts to make a parallel between the cells of the rat, bathed in blood containing 4.6 µg/mL of glyphosate, and a frog embryo bathed in a medium containing 72 µg/mL glyphosate, and says that the concentration used for the frog embryos is huge and physiologically inappropriate compared to that used in the rats.

This conclusion depends on the assumption that glyphosate crosses the membrane of the rat cells and the outer membrane of the frog embryo with equal ease. However, these two membranes are very different in structure and function. The frog embryo membrane is the embryo's sole defense against every physical and chemical challenge that it might encounter and must therefore be very protective, while the cells of the rat are defended by many different protective mechanisms, which operate before a challenge ever reaches the individual cells of the rat. This makes it unnecessary for the cellular membrane of rat cells to possess the protective function and structure of the frog embryo membrane.

Thus we would expect that exposing rat cells to blood containing a concentration of 4.6 µg/mL glyphosate would result in a much higher concentration of glyphosate within the rat cells than would be the case if a frog embryo were exposed to that concentration, and that it would be reasonable to expect that a significantly higher concentration of glyphosate, for instance, 72 µg/mL, would be required to achieve a concentration of glyphosate within the frog embryo that would be equivalent to the concentration achieved within the rat cells when exposed to blood containing 4.6 µg/mL of glyphosate.

Thus Monsanto's claim that the concentration used by Carrasco is extremely high and is equivalent to an oral dose of 6261 mg/kg bw is a gross overestimation.

The evidence that the concentrations of glyphosate used in the frog embryo studies were appropriate is Carrasco's observation that mortality of the embryos was very low, yet dose-dependent effects of glyphosate were observed.

Monsanto/Dow claims that "high doses of glyphosate" have been "shown not to cause developmental or reproductive effects in rats and rabbits" in studies used by regulatory authorities to set the acceptable daily intake or ADI. But this is false, as we have shown above (see Section 3). These industry studies did show teratogenic effects of glyphosate, even at low doses. The ADI set by Germany ignores these effects and is incorrect.

Body burdens of glyphosate

Monsanto/Dow dismisses the concerns raised by Carrasco and colleagues about the risk to people living close to fields where glyphosate herbicides are sprayed. Monsanto/Dow uses findings from the Farm Family Exposure Study (FFES)[220] as evidence that the doses used in Carrasco's work and his claim of a link between pesticide exposure and birth defects in Argentina are unrealistic.

The FFES measures urinary glyphosate concentrations for farmers, their spouses, and their children. The study concludes, reassuringly, that the maximum systemic dose to spouses in the FFES was 0.04 µg/kg body weight, with more than 95% of the spouse exposures below the limit of detection.

But the FFES authors themselves acknowledge that the results of their US-based study depend on the method of glyphosate application, the procedures used by the farmers, and the care with which those procedures are carried out. The circumstances in Argentina differ from those in the US on all these counts. Much of the glyphosate application is conducted by aerial spraying and reports from Argentina suggest that little care is taken of impacts on the environment or human health. On this basis, it is not justified to use the FFES as the basis for evaluating Carrasco's work.

The authors of the FFES acknowledge that the nature of the study may well have motivated participating farmers to take extra care in their work and that therefore this study may not reflect real world conditions, even in the US. It should also be remembered that the FFES was sponsored by the pesticide industry, as were other studies that Monsanto/Dow cite to back up their claims of the safety of glyphosate. Sponsors, as stated in the paper, were Bayer, Dow, DuPont, FMC, Monsanto, Syngenta, and the American Chemistry Council. The lead author, Acquavella, was an employee of Monsanto. A second author was an employee of the industry consulting firm Exponent.

For all these reasons, we suggest that the FFES is likely to paint a picture that is not "real-world", but highly idealized. As stated by Mage in his critique of the FFES, a study that randomly and

frequently assesses glyphosate burdens in farmers and their families over a long period of time would provide a more realistic assessment of exposure.[221]

This is borne out by results of another study, which is relevant to this discussion but is not mentioned by the Monsanto/Dow authors. In a study investigating pesticide exposure in farm and non-farm families in Iowa, Curwin (2007) found that 75% of farmers, 67% of wives, and 81% of farmers' children were carrying urinary burdens of more than 900 ppb of glyphosate (0.9 mg/kg bw). In contrast, the FFES reported average daily urinary burdens of glyphosate ranging from 1 to 6.4 ppb on different days of the study for farmers, and with averages close to zero ppb for wives and children (less than 25% of subjects were reported to have any detectable urinary glyphosate burden).

Regarding the FFES, we conclude that, as has been found time and time again, industry-sponsored studies generate results that are unrealistic, when compared with independent studies such as Curwin's.

We also conclude from all the evidence above that Carrasco's doses were realistic and that they add to the existing body of industry and independent studies showing that glyphosate is teratogenic.

8. The choice of experimental animals

BVL says in its response to Carrasco that while developmental mechanisms in frogs and chicken embryos are similar to those of humans, they respond differently to toxins because frogs and chickens lack the protection of a placental barrier – their embryos develop outside the mother's body. BVL says humans and other mammals, in contrast, have a placental barrier that lends some protection against toxins passing from the mother's blood supply to that of the foetus. Therefore, BVL says, findings in frog and chicken embryos cannot be extrapolated to humans and doses of glyphosate reaching the human foetus are unknown.

However, BVL fails to acknowledge research showing that a significant percentage of glyphosate crosses the human placental barrier and enters the foetal compartment.[222] BVL must produce data to back up its implication that the human placental barrier provides protection against glyphosate exposures.

In addition, Dallegrave's 2003 study found skeletal malformations in rats treated with Roundup.[223] Rats are mammals, so BVL cannot dismiss this study on grounds of the wrong choice of experimental animal. But BVL finds another reason to dismiss Dallegrave's study, wrongly claiming that it found no craniofacial malformations (see Section 5, above).

9. South America's responsibility?

BVL implies that the problems with glyphosate raised by Carrasco's research are South America's responsibility. It says, "Even if there were indications for an increase in malformations because of extensive exposure to pesticides in South America, the state authorities in these countries would be responsible to initiate more in-depth investigations. Taking into account the very different application conditions and the uncertainties with regard to the plant protection products and human exposure, such findings would not automatically give rise to concern about the safety of glyphosate-based herbicides in Europe."

It is true that application conditions and exposures in Europe would be different from those in South America. But BVL and the Commission have made no attempt to define how they would differ, especially in the light of the possible cultivation of glyphosate-tolerant crops in the EU. BVL's statement is inadequate, for the following reasons.

Toxicological findings are not confined within national boundaries

In its discussion of possible effects of Roundup/glyphosate on humans, BVL avoids mentioning

the toxicological findings on Roundup and glyphosate. Some of these, such as those of Séralini's team, found effects in human cells and are relevant to humans. While BVL disingenuously confines its discussion of effects on humans to South America, toxicological findings in human cells, and findings in mammals such as in Dallegrave's studies, apply to all countries where Roundup/glyphosate is used.

Also, glyphosate-tolerant crops carrying glyphosate residues enter the European food chain via animal feed and soy products eaten by humans. The Commission must investigate current and potential future exposures and their relationship to findings in the independent scientific literature.

The political climate in South America is problematic

Some South American economies have become highly dependent on the GM soy/glyphosate agricultural model, so central and regional government authorities are reluctant to challenge it. The Argentine government has come to rely on export taxes on soybeans, which reached 35 per cent in 2010.[224]

In Argentina, after Carrasco announced his findings, a group of environmental lawyers launched a lawsuit petitioning the government to ban glyphosate. But Guillermo Cal, executive director of CASAFE (Argentina's crop protection trade association), said a ban would mean "we couldn't do agriculture in Argentina".[225]

Argentine scientists and experts who have produced evidence of problems with the GM soy/glyphosate model report harassment and censorship.[226] [227] [228] But even in these difficult conditions, they and their international colleagues have collectively produced more than enough evidence to indicate that there are serious problems with the GM soy/glyphosate agricultural model.

Europe has a moral responsibility to its supplier countries

As much of the glyphosate-tolerant soy sprayed with glyphosate herbicides in South America is imported to feed European livestock, Europe is to some extent responsible for the situation in South America. The principle of moral responsibility for human rights abuses in supplier countries has been accepted since eighteenth-century debates about the slave trade.

Europe is considering adopting the GM crops/glyphosate farming model

Applications are in the approvals pipeline for the cultivation in Europe of several glyphosate-tolerant GM maize varieties, including Monsanto's NK603[230] and MON89034 x MON88017.[231] If glyphosate-tolerant crops are approved for cultivation in the EU, then the South American experience with GM soy and glyphosate could be replicated in Europe. BVL's attempt to draw a curtain over the South American experience is irresponsible because it ignores the potential impact of this carcinogen and teratogen on European farmers, their families, and the public.

POEA: Case study in regulatory weakness

BVL's only decisive recommendation in its response to Carrasco is that more toxicity tests should be conducted on the effects on aquatic organisms of the Roundup adjuvant or added ingredient, POEA (polyethoxylated tallow amine). POEA is added to glyphosate herbicides as a surfactant or wetting agent, to enable the glyphosate to penetrate the plant. Unfortunately, POEA is highly toxic to human cells as well as increasing the toxicity of glyphosate by allowing it to penetrate the cells more easily.[232]

While action on POEA would be welcome, focusing only on this substance distracts from Carrasco's finding that pure glyphosate is a developmental and reproductive toxin.[233]

The case of POEA shows the weakness of EU regulators in dealing with industry. The German government recommended as long ago as 1999 that POEA should be phased out in the EU. Monsanto disagreed.[234] Eleven years later in 2010, the German government was still asking for action on POEA – and still being ignored by industry and EU regulators.[235] It has resorted to taking its own measures to restrict the use of POEA within Germany.

10. Science divided

Carrasco notes in his reply to Monsanto/Dow that discussion of toxics risk assessment has separated into two diverging strands:

> Rather than pointing out shortcomings of our research, the [Monsanto/Dow] letter illustrates the increasing difficulty in dialogues between those with a vested interest in product sales and independent researchers who wish simply to understand whether the said products are safe.[236]

It is to be expected that industry should look after its own interests. But it is inexcusable for the public body BVL to follow Monsanto/Dow in what seems to be a desperate attempt to dismiss any possibility of Roundup/glyphosate's teratogenicity rather than ordering further investigations to clear up uncertainties. However, the existing body of evidence on Roundup/glyphosate is more than sufficient to justify that BVL advise the EU Commission to invoke the precautionary principle and conduct an immediate review of the herbicide.

11. Another worrying study on Roundup dismissed

BVL's response to Carrasco's study was not a one-off. In 2009, BVL issued a similarly dismissive response[237] to a study by Benachour and Séralini, which found that Roundup caused total cell death in human umbilical, embryonic, and placental cells within 24 hours.[238] In these experiments, Roundup obtained from the market was diluted by 100,000 times – far below the concentrations used when the chemical is sprayed on GM RR crops.

The researchers tested Roundup formulations, as well as pure glyphosate, AMPA (glyphosate's main breakdown product), and the adjuvant POEA. They concluded that the presence of adjuvants increases the permeability of human cells to Roundup and amplifies the toxicity of glyphosate:

> The proprietary mixtures available on the market could cause cell damage and even death around residual levels to be expected, especially in food and feed derived from R (Roundup) formulation-treated crops.[239]

BVL's response to this complex and worrying study was as brief as it was inadequate. Passing over the findings on the toxicity of glyphosate and AMPA, BVL only admitted that POEA ("tallow amines") was a problem. It said it had asked manufacturers of glyphosate herbicides to replace tallow amines with less problematic ingredients within two years. That was the sum of BVL's recommendations.

In choosing to focus solely on the adjuvant POEA, BVL simply ignored all the harmful effects that the researchers found with the Roundup formulations as a whole, their active ingredient glyphosate, and glyphosate's main breakdown product, AMPA. So Roundup continues to be marketed without restriction and people continue to be put at risk.

12. What's wrong with the current approval of glyphosate?

Glyphosate's current approval in the EU is based on the 2002 review, carried out under the old pesticides regulation 91/414.[240] The 2002 review assesses glyphosate, the glyphosate derivative herbicide glyphosate trimesium, and the glyphosate metabolite (breakdown product) AMPA.

The review exemplifies the general failings of the old pesticides approvals system:

- Insulation from independent peer reviewed scientific findings
- Old, outdated, and badly informed claims for glyphosate's safety go unchallenged

- Virtually exclusive reliance on industry studies for the safety assessment, with the inherent conflicts of interest
- Reliance on studies with old and outdated protocols
- Reliance on dubious and outdated assumptions
- Lack of transparency
- Failure to test the complete glyphosate formulations as they are sold.

A detailed breakdown of these factors follows.

12.1 Open peer reviewed scientific literature is denied

There is broad agreement in the scientific community that peer reviewed publication is the best currently available method to ensure reliable scientific data.

There are undoubted flaws with the peer review process – including publication bias, where certain types of results are more likely to be published than others,[241 242 243] and pressure being placed on journal editors not to publish, or to retract, certain findings.[244 245 246] Some journals have been generated or "captured" by industry and use industry-connected peer reviewers.[247]

In spite of these problems, the strength of the peer review process is that studies in the open literature can be evaluated by independent experts. Their findings can be confirmed, built upon, or contradicted by further studies.

The public, too, has been educated to respect the peer review process and to expect scientific claims to be validated in this way. The part-industry-funded UK-based group Sense About Science, which calls itself "an independent charitable trust promoting good science and evidence in public debates"[248] and promotes the safety of controversial technologies like genetically modified foods,[249] set up an entire project to convince the public that peer review is "an essential arbiter of scientific quality".[250] In its guide for the public on peer review, *I Don't Know What to Believe*, Sense About Science says:

> Unpublished research is no help to anyone. Scientists can't repeat or use it and as a society we can't base decisions about our public safety – or our family's health for example – on work that has a high chance of being flawed.[251]

Given such influential messages, it would shock the public to realize that in the pesticide approvals process, peer reviewed open literature is not normally considered. The studies on which the 2002 EU review of glyphosate is based, as is the norm with pesticides, were generated and submitted by industry.[252] The conclusions about the health hazards of glyphosate in the 2002 EU review are strikingly at variance with the findings from the independent scientific literature, as the analysis below shows.

Genotoxicity

The 2002 review flatly states that glyphosate and glyphosate trimesium are "not genotoxic" (causing damage to DNA). It is difficult to understand how this conclusion could be reached, given that even industry studies from the 1980s found that Roundup caused chromosome aberrations and gene mutations in mice lymphoid cells.[253 254]

In addition, a number of studies showing that glyphosate and Roundup are genotoxic existed in the peer reviewed literature even at the time of the 2002 review. Findings include:

- Roundup increases the frequency of gender-linked lethal recessive mutations in fruit flies (these mutations are normally only seen in males).[255]
- Roundup increases the frequency of DNA adducts (the binding to genetic material of reactive molecules that lead to mutations) in the liver and kidneys of mice at all three doses tested. The response was dose-dependent.[256]
- Roundup causes increased frequency of sister chromatid exchanges in human lymphocytes (white blood cells), even at the lowest dose tested.[257]
- Mice injected with glyphosate and Roundup show increased frequency of chromosome damage and increased DNA damage in bone marrow, liver, and kidney.[258]

Numerous additional recent studies confirm genotoxicity:

- Roundup damages the DNA in the blood cells of European eels at environmentally relevant concentrations.[259]
- Roundup has adverse effects on the cells of various organs in fish exposed at sublethal

concentrations of 5–15 ppm (a typical concentration in a post-application site). Effects include hyperplasia (increased proliferation of cells) and increased activity of metabolic enzymes.[260]

- Glyphosate-based herbicides cause increased frequency of DNA strand breaks and cell nucleus abnormalities indicative of mutagenic stress in goldfish at low doses (5–15 ppm).[261]
- Glyphosate-based herbicides cause DNA damage and endocrine disruption in human cells at levels up to 800 times lower than glyphosate residue levels allowed in some GM crops used for animal feed in the United States.[262]
- Glyphosate-based herbicides inhibit RNA transcription and delay hatching in sea urchin embryos at a concentration well below that recommended for commercial spray application. The Roundup surfactant polyoxyethylene amine (POEA) is highly toxic to the embryos when tested alone and so could contribute to the inhibition of hatching.[263]
- Glyphosate-based herbicides and glyphosate's main metabolite (environmental breakdown product), AMPA, alter cell cycle checkpoints in sea urchin embryos by interfering with the physiological DNA repair machinery. Such cell cycle dysfunction is seen from the first cell division in the sea urchin embryos.[264 265 266 267] The failure of cell cycle checkpoints is known to lead to genomic instability and the possible development of cancer in humans. Studies on glyphosate and AMPA suggest that the irreversible damage that they cause to DNA may increase the risk of cancer.[268 269]
- An epidemiological study in Ecuador found a higher degree of DNA damage in people living in an area that was aerially sprayed with glyphosate compared with those living 80 kilometres away.[270]

AMPA, glyphosate's main breakdown product (metabolite), is also genotoxic in isolation. The 2002 review, on the basis of the industry studies, calls AMPA "less toxic than the parent compound".[271] The ECCO Panel states, "AMPA is not of toxicological significance."[272] However, an independent study found that AMPA is genotoxic, damaging DNA in human cells at very low doses and in mice at a dose of 200–400mg/kg.[273]

Carcinogenicity

The 2002 review claims "no evidence" of carcinogenicity for glyphosate and glyphosate trimesium. But glyphosate was known to have carcinogenic effects long before the 2002 review.

Two long-term studies on rats were conducted in 1979–1981 and 1988–1990.[274] The rats received 3, 10 and 32 mg/kg of glyphosate per day in the first study and 100, 410 and 1060 mg/kg per day in the second. The first study found a significant increase in tumours in the testes of rats fed glyphosate, but the same effect was not found in the second test using the higher doses. On this basis, glyphosate was excluded from the carcinogenic category.[275 276]

This move was based on outdated and incorrect assumptions about toxicology. It used to be thought that toxic effects increased in proportion to dose, and that there is a safe level of a chemical, below which toxic effects are not found. But toxicologists now know that these assumptions are not always true. Some chemicals have more potent effects (notably endocrine effects) at low doses than higher doses.[277] In some cases, no safe threshold can be found.[278 279] However, regulators have not revised their conclusions on glyphosate based on up-to-date scientific knowledge.

Studies from the independent literature also show that Roundup and glyphosate have carcinogenic effects:

- Glyphosate induces cancer in mouse skin[280]
- Epidemiological studies show a link between Roundup/glyphosate exposure and two types of cancer: multiple myeloma[281] and non-Hodgkin's lymphoma.[282 283 284]
- Other studies (mentioned under Genotoxicity, above) show that Roundup, glyphosate, and its metabolite AMPA cause changes to cells and DNA that are known to lead to cancer.[285 286 287 288 289 290]

Neurotoxicity

The 2002 review of glyphosate claims "no relevant effects" in tests for delayed neurotoxicity. But glyphosate is an organophosphate, a class of

chemicals known to have neurotoxic effects, so claims of "no relevant" neurotoxic effects demand a strong and transparent evidence base to back them up.

In fact, studies from the open literature have found neurotoxic effects of glyphosate:

- An epidemiological study carried out in Minnesota, USA found that the children of pesticide applicators exposed to glyphosate had an increased incidence of neurobehavioral disorders.[291]
- In an acute poisoning incident, a man who accidentally sprayed himself with glyphosate developed the neurological disorder Parkinsonism.[292]
- A toxicological study on rats found that glyphosate depletes the neurotransmitters serotonin (serotonin is associated with feelings of well-being and is known as the "happiness hormone") and dopamine.[293]
- Glyphosate causes a loss of mitochondrial transmembrane potential (a hallmark of cellular injuries) in rat brain cells.[294]
- Glyphosate and Roundup act synergistically with the organophosphate insecticide diazinon in neuroblastoma (nerve cancer) cells. Glyphosate and Roundup become more neurotoxic when the cells have been pre-exposed to diazinon. Roundup is more toxic than glyphosate and produces effects at a concentration as low as 10 ppb, which is equivalent to a glyphosate concentration of 0.5 nM. Unusual dose-response relationships are found with both glyphosate and Roundup, which the authors say merit further investigation as they indicate that the relationship between concentration and toxicity at low concentrations may not be entirely predictable.[295]

Reproductive and developmental toxicity and endocrine disruption

The 2002 review notes that studies on glyphosate and glyphosate trimesium found reduced pup weight and decrease in litter size and pup body weight gain, but says these effects are confined to high, "parentally toxic doses". The review adds that effects include lower number of viable foetuses and reduced foetal weight, retarded ossification (bone formation), and higher incidence of skeletal and/or visceral (internal organ) anomalies. Effects of glyphosate trimesium include increased post-implantation losses (miscarriage), reduced foetal weight, and increased incidence of rib "variations" at maternally toxic doses.

The 2002 review gives a developmental NOAEL (the highest level at which the effect being looked for is not found) of 300 mg/kg bw/d for glyphosate and 40 mg/kg bw/d for glyphosate trimesium. However, studies from the open literature have found adverse reproductive and developmental effects, in some cases at much lower levels. While we have discussed some of these studies in the above sections, we provide a comprehensive summary as follows:

- Glyphosate herbicide alters hormone levels in female catfish and decreases egg viability. The study concludes that the presence of glyphosate in water is harmful to catfish reproduction.[296]
- Roundup disrupts production of the steroid hormone progesterone in mouse cells by disrupting expression of a regulatory protein.[297]
- Roundup causes decreased sperm numbers and increased abnormal sperms in rats.[298]
- A commercial formulation of glyphosate was found to be a potent endocrine disruptor in rats, causing disturbances in their reproductive development after they were exposed during puberty.[299]
- In human cells, glyphosate-based herbicides prevent the action of androgens, the masculinising hormones, at levels up to 800 times lower than glyphosate residue levels allowed in some GM crops used for animal feed in the United States. DNA damage is found in human cells treated with glyphosate-based herbicides at these levels. Glyphosate-based herbicides also disrupt the action and formation of estrogens, the feminizing hormones.[300] This in vitro study found the first toxic effects of glyphosate-based herbicide at 5 ppm, and the first endocrine disrupting actions at

0.5 ppm – 800 times less than the 400 ppm level authorized by the US Environmental Protection Agency (EPA) in some animal feeds.[301 302]

- Glyphosate acts synergistically with estrogen, disrupting estrogen-regulated gene expression in human cells.[303]
- Glyphosate is toxic to human placental cells and this effect increases in the presence of Roundup adjuvants. Roundup acts as an endocrine disruptor, inhibiting an enzyme responsible for estrogen production. The authors conclude that Roundup could cause reproductive problems in humans at levels below those used in agriculture.[304] The authors suggest that their results could explain epidemiological findings of increased premature births and miscarriages in female members of farming families using glyphosate.[305 306]
- Glyphosate and Roundup damage human embryonic cells and placental cells, in concentrations well below those recommended for agricultural use. The study's authors conclude that Roundup may interfere with human reproduction and embryonic development.[307]
- The foetuses of rats fed orally with high doses of Roundup had increased incidence of skeletal malformations.[308]
- Roundup causes malformations in frog and chicken embryos at doses much lower than those used in agricultural spraying.[309] Malformations were of the craniofacial and neural tube type (of the skull, face, and developing brain and spinal cord).

Conclusion of open peer-reviewed literature on health effects

Both the existing pesticides regulation, 91/414, and the new regulation, 1107/2009, require that a pesticide should not have any harmful effect on human or animal health.[310 311] The new regulation is stricter, since "vulnerable groups" must be considered in the human health assessment and known "cumulative and synergistic effects" of the pesticide must be addressed.[312] Clearly, glyphosate herbicides do not even meet the requirements of the old regulation, so their approval should be reviewed immediately with a view to restricting or banning their use.

12.2. Outdated and badly informed claims go unchallenged

The discussion between industry, the rapporteur Germany, member states, and the ECCO Panel that led to the 2002 review includes numerous old, outdated, and badly informed claims for the safety of glyphosate and its breakdown product AMPA. Many of these claims have been superseded or discredited by independent studies – but they passed through the review process unchallenged and have remained in place in the regulatory system ever since. Similarly, concerns are raised but not followed up.

Anyone who is informed about the current state of knowledge on glyphosate cannot fail to be alarmed by these claims and uninvestigated concerns. There are too many to cover fully in this report, but a few examples follow.

Unresolved concerns about salivary gland lesions

Concerns about repeated findings of salivary gland lesions in experimental animals treated with glyphosate are expressed throughout the DAR materials and mentioned in the 2002 final review report. However, nobody seems to know what the lesions mean, and no attempt is made to find out. A comment by the ECCO Panel is typical:

> Histological effects were observed in salivary glands in the 6 and 12 month dog study, however, since these lesions were considered without functional consequence or long term effects they were not considered to be adverse.[313]

The regulators should have insisted that these experiments be continued for a longer period, so that the true consequences of these lesions were revealed. Salivary gland lesions can be pre-cancerous.

Failure to consider endocrine disruption

The ECCO Panel says, "Various literature

references suggest that glyphosate is an endocrine disruptor." Again, the panel has no idea what to make of these findings: "The group recognised that there was no guidance available regarding how such information should be used so it was agreed that the rapporteur should consult the Chairperson of the mammalian toxicology meeting at the BBA [German Federal Ministry for Food, Agriculture and Consumer Protection] to see if this is a concern."[314] The final review report of 2002 does not mention endocrine disruption – sufficient reason in itself why the current approval of glyphosate is inadequate. However, independent studies show that glyphosate herbicides are endocrine disruptors.[315 316 317]

Failure to consider the impact of glyphosate-resistant weeds

The DAR and 2002 review report were compiled before the problem of glyphosate-resistant weeds became widespread. Monsanto claims in the DAR materials that it has tested over 500 samples and found that only two locations in Australia were affected. The plant involved was an annual rye grass.[318] The UK Pesticides Safety Directorate (PSD) comments, "It is likely that resistance is low, although there have been two further reports of possible cases in America and Asia."[319] Since the EU Commission's 2002 approval of glyphosate, a large number of independent studies and media reports have documented the extensive and serious problems caused by glyphosate-resistant superweeds, especially in North and South America.[320 321 322 323 324 325 326 327 328 329 330 331 332 333 334] Glyphosate's current approval does not take this into consideration and a critical re-assessment is urgently needed.

In addition, the risk assessment should consider the inevitable shift in herbicide use after glyphosate-resistant weed populations become widespread. The published studies and articles cited above show that weeds evolve resistance to glyphosate within 2–6 years of cultivation of genetically modified (GM) Roundup Ready crops. This is less time than the approval period of a pesticide in the EU – formerly ten years, now 15 years. Once resistant weed populations are established, farmers have to resort to other potentially even more toxic herbicides, including 2,4-D, to try to control glyphosate-resistant weeds.[335 336 337 338]

The chemical companies Dow, DuPont, Bayer, BASF, and Syngenta have responded to the superweeds problem by "engineering crop varieties that will enable farmers to spray on the tough old weedkillers freely, instead of having to apply them surgically in order to spare crops", according to a report in the Wall Street Journal.[339] Bayer has patented a GM soybean with tolerance to the herbicide glufosinate ammonium.[340] Studies show that glufosinate ammonium is a neurotoxin[341] and causes birth defects in mice.[342] Monsanto plans to release a dicamba-resistant GM soybean in 2013.[343] These developments are relevant to Europe as Romania is lobbying the EU for permission to cultivate GM soy.[344]

A new generation of herbicide-resistant crops is being engineered with stacked traits to tolerate multiple herbicides.[345] But weed scientists have commented that these new GM crops will only buy growers a little more time until weeds evolve resistance to other herbicides.[346] In fact, weed species resistant to dicamba and 2,4-D already exist.[347 348]

The existing approval of glyphosate fails to take into consideration the chemical treadmill resulting from the emergence of glyphosate-resistant weeds – and the consequences to human health and the environment. While a full consideration of this issue is beyond the scope of this report, it needs to be addressed in the risk assessment of glyphosate as it is a hazard inherent in the use of the herbicide.

Incorrect claim about biological availability of glyphosate

The UK Pesticides Safety Directorate (PSD) notes that the issue of a waiting period between glyphosate spraying and re-entry into fields in order to protect humans, livestock, and plants, is not properly dealt with in Germany's DAR. However, the PSD immediately dismisses this concern:

> This should not be an issue for glyphosate as it is not usually biologically available once it contacts soil.[349]

But this claim was not true even at the time of the DAR. A 1983 study showed that glyphosate persists in sandy loam soil and is not inactivated in the 120 days prior to planting. Plants growing in the glyphosate-treated soil showed decreased nitrogen fixation, root nodule numbers and root weights – indicating that glyphosate was biologically available and toxic to plants 120 days after application.[350]

A new risk assessment should address the issue of the re-entry period.

Incorrect claim about biological activity of AMPA

Monsanto says AMPA's long persistence in soil is of no "regulatory concern" because "AMPA is biologically inactive".[351] But a 2004 study showed that AMPA causes injury to glyphosate-tolerant and non-glyphosate-tolerant soybeans. Findings are the same when the AMPA is deliberately applied and when it forms from the breakdown of applied glyphosate. The study concludes that soybean injury to glyphosate-tolerant soybeans from glyphosate is due to AMPA formed from glyphosate degradation.[352] Therefore AMPA is biologically active.

It is clear that the documents on which the existing approval of glyphosate is based are out of date and out of touch with current scientific knowledge and farmer experience.

12.3. Industry tests have conflicts of interest

There are clear conflicts of interest in the 2002 review of glyphosate in that the companies that commissioned the tests and submitted the data also market the product. The fact that this is the norm in pesticides approvals does not make it acceptable. The main data submitters were Monsanto, Cheminova, Feinchemie, and Syngenta (formerly Zeneca).[353] These companies manufacture and/or sell glyphosate herbicide. Monsanto, Syngenta, and Dow AgroScience (another data submitter) also sell GM glyphosate-tolerant seeds.

12.4. Industry tests are old and use outdated protocols

Anyone who is familiar with the rapid evolution of scientific knowledge relating to glyphosate over the past decade would be shocked to see that its current approval depends mostly on studies dating from the 1990s – some from as far back as the 1970s and 1980s.

In the 1990s glyphosate was still frequently claimed to be safe and environmentally friendly. Few independent studies were in existence to contradict these claims. Even so, by 1996, independent science had moved on to such an extent that a New York court ruled that Monsanto was no longer allowed to claim that Roundup was "safe, non-toxic, harmless or free from risk", or as biodegradable.[354] During the 2000s, a battery of independent scientific studies showed serious toxic effects from Roundup and glyphosate. None of this knowledge has made its way through to the regulatory system.

12.5. The approvals system is not transparent

In theory, the industry dossier of studies on a pesticide and the regulators' discussions and justifications for their final decision are in the public domain. In practice, it is not so straightforward. The authors of this report had difficulty obtaining the materials. When they were finally obtained, a part of Germany's DAR was withheld. The materials were confusingly presented and difficult to interpret. In the DAR itself, justifications for important decisions are not recorded in detail.

Data protection is claimed for many of the industry studies in the 2002 review of glyphosate on grounds of commercial confidentiality. This is standard practice, ostensibly because it prevents data from getting into the hands of competitor companies. Unfortunately, it also prevents the public and independent scientists from evaluating the data. So tests of unknown quality and unknown reliability are used to allow pesticides onto the market.

There is also no transparent system in place for considering independent scientific data that

comes to light after the approval, as is clear from the case of Carrasco's study.

12.6. The complete formulations as they are sold were not tested

The existing review of glyphosate fails to take into account the complete formulations as they are currently sold. Glyphosate herbicides contain adjuvants (added ingredients) which are themselves toxic and which can act synergistically with glyphosate to increase its toxicity. Studies show that Roundup is more toxic than glyphosate alone because the adjuvants enable the glyphosate to penetrate human cells more easily.[355 356 357] These problems are addressed in the new pesticides regulation 1107/2009, which takes into account the toxicity of the formulation as sold. This alone is reason enough to require that glyphosate herbicides be reviewed under the new regulation without delay.

13. Conclusions and recommendations

The existing approval of glyphosate and Roundup is out of date and scientifically unsupportable. The safety assessment began badly, with a dossier of outdated industry-sponsored tests, and was progressively weakened at each stage:

- The German government produced a draft assessment report (DAR) that minimized the harm shown even in inadequate industry studies and set a dangerously high ADI for glyphosate.
- Germany's DAR was in turn whitewashed by the EU's scientific review ECCO Panel.
- Finally, the EU Commission's DG SANCO accepted these misleading reports in its 2002 review, minimizing the reproductive and developmental effects of glyphosate.

Together, these bodies must share responsibility for making claims about the safety of glyphosate that were contradicted even by the scientific knowledge current at the time. Now that scientific knowledge has moved on, glyphosate and Roundup formulations must be reviewed urgently, taking into consideration all independent scientific evidence.

The new pesticides regulation, if implemented objectively and in timely fashion, would likely result in a ban on glyphosate herbicides. But the Commission and EFSA have abnegated their responsibility to the public in allowing glyphosate a free regulatory ride until 2015, with the possibility of no review under up-to-date data requirements until 2030. Their actions flout a democratically established law and put public health at risk.

13.1. Recommendations on Roundup and glyphosate

In the interests of protecting public health, we call upon the Commission to implement the following measures on Roundup and glyphosate:

- Order an immediate withdrawal of Roundup and glyphosate until a new review can be carried out, based on the full range of up-to-date tests.
- Assess all adverse effects of Roundup and glyphosate found in the open peer reviewed scientific literature.
- Base industry tests on the findings in open literature, not only on generalized data requirements. For example, the experiments of Dallegrave should be repeated with modifications.
- Ensure that regulators look critically at the applications for GM Roundup Ready crops that are in the EU approvals pipeline instead of repeating outdated and misleading assurances about the safety of glyphosate and Roundup.

13.2. Recommendations on pesticides regulation

On pesticides regulation in general, we call upon the Commission to:

- Hold an urgent debate with the full range of stakeholders on the question: What is the point of independent science when regulators ignore it in every assessment of a pesticide? Billions of pounds of taxpayers' money go into public sector research. In our view, this type of

research, when peer reviewed and published, represents the most reliable, independent, and up-to-date knowledge on pesticides. But it appears that the Commission and regulatory bodies and agencies disagree with this view. Currently, independent scientists are wasting their time and energy as far as regulation is concerned. The Commission and other regulatory bodies must publicly explain their attitude to independent science.

- Ensure that all studies from the open scientific literature are considered in the risk assessment. Industry and the rapporteur state must not be allowed to "cherry-pick" acceptable studies on the grounds of exposure route, length of study, choice of experimental animal, etc. If there are genuine questions about the methodology of a study finding adverse effects, regulators must order it to be repeated with the desired modifications.
- Publish all industry studies on the internet as a matter of principle.
- Pay independent scientists who are actively researching and publishing in the field to review industry studies and studies from the open literature on the pesticide under review.
- Ensure that the risk assessment is based on the lowest NOAEL found in any study.
- Ensure that "reviews" or comments on studies from the open literature are written by named experts who are accountable for their views.
- Replace the current system, in which industry directly pays contract labs to carry out regulatory studies on pesticides, with a system in which industry pays into a central fund for the studies and the regulators contract out the work to independent researchers.
- Get industry out of the pesticides regulatory process. Industry should provide the pesticide and its basic compositional information – but leave the testing and evaluation (including the peer-reviewed scientific literature search) to regulators and independent scientists.
- Introduce mandatory disclosure of minutes and conclusions of meetings between EU Commission/EFSA and all stakeholders, including industry-affiliated bodies like the International Life Sciences Institute.
- Ensure that all meetings between EFSA and industry or industry-affiliated bodies such as the International Life Sciences Institute (ILSI) are open to the full range of stakeholders, including NGOs and representatives of the general public.
- Ensure full transparency of the decision-making procedure, from the initial submission of the dossier by industry to the final decision made on the pesticide.

Our examination of the evidence leads us to the conclusion that the current approval of glyphosate and Roundup is deeply flawed and unreliable. What is more, we have learned from experts familiar with pesticide assessments and approvals that the case of glyphosate is not unusual. They say that the approvals of numerous pesticides rest on data and risk assessments that are just as scientifically flawed, if not more so. This is all the more reason why the Commission must urgently review glyphosate and other pesticides according to the most rigorous and up-to-date standards.

13.3. Recommendations to the public

Until the pesticide assessment process is fundamentally reformed, we recommend to the public that they do not rely on the messages of governments or industry about pesticide safety. Instead, they should take measures to protect themselves against the harmful effects of Roundup/glyphosate and other pesticides. These include:

- Avoiding using and exposing themselves to pesticides, insofar as they have choice in the matter.
- Lobbying local authorities, farmers, and other pesticide users to disclose what they are spraying and when.
- Lobbying local authorities and other "cosmetic" users of Roundup/glyphosate and other pesticides to switch to less toxic methods of weed and pest control.
- Writing to garden centres, supermarkets, and other stores asking them not to sell Roundup/glyphosate and other pesticides.
- Supporting citizen "truth-in-labelling" schemes to inform consumers about the true risks of pesticides through accurate product labelling.

Note on citations of Germany's DAR on glyphosate

In the interests of transparency and so that readers can check the accuracy of our statements, we have uploaded onto the Internet those parts of Germany's draft assessment report (DAR) on glyphosate that we cite in the text of our report. Please note that page numbers in the references below refer to the page numbers of the pdf document, not the page numbers printed on the original documents that make up the DAR.

Our citations of the DAR begin as follows:

> Rapporteur member state, Germany. 1998. Monograph on Glyphosate. Released by the German Federal Agency for Consumer Protection and Food Safety, BVL.

Then each citation specifies a pdf file within the DAR. The URLs for each pdf file we have uploaded are as follows:

- Volume1_Glyphosat_02.pdf: http://www.scribd.com/doc/57155781
- Volume 2, Part A, Annex A: List of Tests and Studies: http://www.scribd.com/doc/57156365
- Volume 3-1_Glyphosat_05.pdf: http://www.scribd.com/doc/57155616
- Volume 3-1_Glyphosate_04.pdf: http://www.scribd.com/doc/57155694
- FullReport_Glyphosat_03.pdf: http://www.scribd.com/doc/57155540
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in food production, animal toxicological testing appears to be indispensable for the foreseeable future. And if animals are to be used in toxicological testing, it is vital that their lives are not wasted – in other words, that the results are as reliable as possible.

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Appendix: Potential for reform in pesticide use

A new EU regulation (2009/128) on the sustainable use of pesticides[358] has the potential to bring positive reforms to pesticide practices in the EU. EU member states will have to come up with a National Action Plan aimed at reducing "risks and impacts of pesticide use on human health and the environment and at encouraging the development and introduction of integrated pest management and of alternative approaches or techniques in order to reduce dependency on the use of pesticides". Among other measures, member states will have to:

- Set up programmes to monitor the effects of pesticide spraying on the health of exposed groups of people
- Minimize the use of pesticides in parks, school grounds, and public areas
- Require sellers of pesticides (including retailers who sell to the public) to provide buyers with information about the risks of the pesticide, as well as information on less toxic alternatives
- Require pesticide users to progressively reduce dependence on pesticides and to favour less toxic methods of weed and pest management.

The new regulation allows member states to set up systems to inform local people before pesticide spraying takes place, but this provision is voluntary. We argue that it should be mandatory and should order disclosure of the names of substances sprayed and the names and contact details of the parties who commission and carry out the spraying. Pesticide applicators must no longer be allowed to hide such information based on claims of commercial confidentiality.

While the new regulation contains many positive developments, much depends on how it is implemented. For example, even the old pesticide law has strict wording stipulating that a pesticide can only be approved if it has "no harmful effect on human or animal health or on groundwater" when correctly used, but this has never been properly implemented.[359]