

Review of Roundup Herbicide Health Effects as reported by Antoniou et al., (2011)

*A list of potential health impacts as documented in the report:
"Roundup and birth defects Is the public being kept in the dark?"*

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Below is a list of the potential health disorders that have been observed from exposure to the herbicide glyphosate as documented by the report of Antoniou et al., 2011. Below, each potential health disorder is presented separately, along with "quotes" extracted from their report and with the respective citations of refereed publications provided by the authors.

Citation of the report by Antoniou et al.:

Antoniou, M., M.E.E. Mostafa. H.C. Vyvyan, HC. Jennings, C. Leifert Rubens, O. Nodari, C. Robinson, and J. Fagan. 2001. *Roundup and birth defects Is the public being kept in the dark?* Earth Open Source. June 2011. 52 pp.

Available at: <http://www.scribd.com/doc/57277946/RoundupandBirthDefectsv5>

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Index

- 1.0. Summary assessment, pg. 2
- 2.0. Birth defects, pg. 3
- 3.0. Birth-defects, mechanism of action, pg. 4
- 4.0. Birth defects: Epidemiological evidence, pg. 5
- 5.0. Embryonic deaths, death of fetus, pg. 7
- 6.0. Embryonic deaths, death of fetus, pg. 8
- 7.0. Lung, kidney, heart, and skeletal malformations, pg. 9
- 8.0. Skeletal malformations, pg 10
- 9.0. Teratogenic effects: skeletal malformations; craniofacial and mouth deformities, eye abnormalities and bent, curved tails in tadpoles, pg. 11
- 10.0. Endocrine Disruption: Powerful endocrine disruptor and reproductive abnormalities, pg. 12
- 11.0. Endocrine Disruption, Reproductive, developmental, and endocrine disruption effects, pg. 13
- 12.0. Endocrine disruption, pg. 15
- 13.0. Irreversible damage to liver cells, pg. 16
- 14.0. Human cell death, pg. 16
- 15.0. DNA damage: Roundup causes genotoxic (DNA damage) effects, pg. 17

- 16.0. Cancer: Roundup carcinogenic effects, pg. 20
- 17.0. Cancer: Observed salivary gland lesions, carcinogenic?, pg. 22
- 18.0. Nervous system: Roundup causes neurotoxic effects, pg. 22
- 19.0 Conflict of interest: industry bias on safety studies conducted by their own scientists, pg. 24
- 20.0. Conflict of interest: Monsanto, and bias in their response to health safety studies showing potential negative health effects from roundup, pg. 25
- 21.0 NY Courts: Monsanto can't make safety claims about Roundup, pg. 26
- 22.0. Inert ingredients (adjuvants) increase toxicity of Roundup, pg. 27
- 23.0. Roundup remains biologically active in the soil, pg. 27

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1.0. Summary assessment

“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.”

2.0. Birth defects

“Research published in August 2010 showed that the best-selling herbicide Roundup¹ 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.”

2. Paganelli, A., Gnazzo, V. et al. 2010. Glyphosate-based herbicides produce teratogenic effects on vertebrates by impairing retinoic acid signaling. *Chem Res Toxicol* 23(10): 1586–1595.

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[Monsanto and Dow refuted the research from Argentina:](#)

“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.

47. Saltmiras, D., Bus, J. S. et al. 2011. Letter to the editor regarding the article by Paganelli et al. *Chem Res Toxicol* 24(5): 607–608.

48. Carrasco, A. E. 2011. Reply to the letter to the editor regarding our article (Paganelli et al., 2010). *Chem Res Toxicol* 24(5): 610–613.

49. Saltmiras, D., Bus, J. S. et al. 2011. Letter to the editor regarding the article by Paganelli et al. *Chem Res Toxicol* 24(5): 607.

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3.0. Birth defects, mechanism of action

“5.1. How Carrasco’s findings built on previous studies

Carrasco built on the findings of Dallegrove 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 Dallegrove may represent teratogenic effects on late embryonic development. His experiments did not extend the observations to the same late stage of development as Dallegrove’s. However, the malformations he found are compatible with those found by Dallegrove.178”

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170. Sulik, K. K., Cook, C. S. et al. 1988. Teratogens and craniofacial malformations: relationships to cell death. *Development* 103 Suppl: 213-231.
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172. Lopez, S. L., Carrasco, A. E. 1992. Retinoic acid induces changes in the localization of homeobox proteins in the antero-posterior axis of *Xenopus laevis* embryos. *Mech Dev* 36(3): 153–164.
173. Lopez, S. L., Dono, R. et al. 1995. Differential effects of retinoic acid and a retinoid antagonist on the spatial distribution of the homeoprotein Hoxb-7 in vertebrate embryos. *Dev Dyn* 204(4): 457–471.
174. Clotman, F., Van Maele-Fabry, G. et al. 1998. Structural and gene expression abnormalities induced by retinoic acid in the forebrain. *Reprod Toxicol* 12(2): 169–176.
175. Clotman, F., Van Maele-Fabry, G. et al. 1997. Retinoic acid induces a tissue-specific deletion in the expression domain of Otx2. *Neurotoxicol Teratol* 19(3): 163–169.
176. Padmanabhan, R. 1998. Retinoic acid-induced caudal regression syndrome in the mouse foetus. *Reprod Toxicol* 12(2): 139–151.
177. Paganelli, A., Gnazzo, V. et al. 2010. Glyphosate-based herbicides produce teratogenic effects on vertebrates by impairing retinoic acid signaling. *Chem Res Toxicol* 23(10): 1586–1595.
178. Carrasco, A. E. 2010–2011. Personal email communications with the authors.

4.0. Birth defects: Epidemiological evidence

“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 hypothetical 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 than 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."

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179. Amnesty International. 2010. Argentina: Threats deny community access to research. 12 August. <http://bit.ly/cJsqUR>
180. Benitez-Leite, S., Macchi, M.A., Acosta, M. 2009. Malformaciones congénitas asociadas a agrotóxicos. Arch. Pediatr. Urug 80, 237–247.
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<http://www.weedscience.org/Summary/UspeciesMOA.asp?IstMOAID=12&FmHRACGroup=Go>
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5.0. Embryonic deaths, death of fetus

With respect to a study on increased embryonic deaths, the authors quote what German regulators found from a Monsanto study, and provide their own analysis:

“Brooker et al., 1991

Submitter companies: Monsanto/Cheminova⁶⁵

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.”

Reference cited:

65. Rapporteur member state, Germany. 1998. Monograph on Glyphosate. Annex B–5: Toxicology and Metabolism. In: Glyphosate DAR, released by German government agency BVL on CD, Volume 3-1_Glyphosat_05.pdf: p. 45 of the pdf.

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6.0. Embryonic deaths, death of fetus

[Another EU/German regulatory review of a study showing deaths of embryos:](#)

“Anonym. (1981)

Submitter company: Alkaloida73

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.”

References cited:

74. Rapporteur member state, Germany. 1998. Monograph on Glyphosate. Annex B–5: Toxicology and Metabolism. In: Glyphosate DAR, released by German government agency BVL on CD, Volume 3-1_Glyphosat_05.pdf: p. 19 of the pdf.

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76. EU Commission. 1999. Glyphosate: Comments from Pesticides Safety Directorate, York, UK, on EC Review Monographs for Glyphosate and Glyphosate Trimesium, March 24. In:

Glyphosate DAR, released by German government agency BVL on CD,
FullReport_Glyphosat_05.pdf: p. 26 of the pdf.

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7.0. Lung, kidney, heart, and skeletal malformations

Comments by German, UK regulators and by the independent scientists:

“Bhide and Patil (1989)

Submitter companies: Barclay/Luxan68

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 fetuses 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. “

References cited ([EU regulator papers, analysis of industry studies](#)):

69. Rapporteur member state, Germany. 1998. Monograph on Glyphosate. Annex B–5: Toxicology and Metabolism. In: Glyphosate DAR, released by German government agency BVL on CD, Volume 3-1_Glyphosat_05.pdf: p. 19 of the pdf.
70. EU Commission. 1999. Glyphosate: Comments from Pesticides Safety Directorate, York, UK, on EC Review Monographs for Glyphosate and Glyphosate Trimesium, March 24. In: Glyphosate DAR, released by German government agency BVL on CD, FullReport_Glyphosat_05.pdf: p. 26 of the pdf.

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8.0. Skeletal malformations

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

Submitter companies: Monsanto and Cheminova⁷⁷

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 sternbrae (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 sternbrae as a “variation” rather than a malformation is scientifically unjustifiable and at odds with other authorities. Unossified sternbrae in the rat are clearly defined as a skeletal deformity in *The Handbook of Skeletal Toxicology*.⁷⁹

References cited:

78. Rapporteur member state, Germany. 1998. Monograph on Glyphosate. Annex B–5: Toxicology and Metabolism. In: Glyphosate DAR, released by German government agency BVL on CD, Volume 3-1_Glyphosat_05.pdf: p. 13 of the pdf.
79. Krieger, R. I. (ed.). 2001. Handbook of Pesticide Toxicology: Principles. Elsevier Inc.: 1185.

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9.0. Teratogenic effects: skeletal malformations; craniofacial and mouth deformities, eye abnormalities and bent, curved tails in tadpoles

Note, teratogenic= ability to cause malformations/birth defects.

EU regulators indicate there is no evidence of birth-defects but the researchers provide evidence to the contrary:

“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.”

Cited references:

165. BVL, Germany. 2010. Glyphosate – Comments from Germany on the paper by Paganelli, A. et al. (2010): “Glyphosate-based Herbicides Produce Teratogenic Effects on Vertebrates by Impairing Retinoic Acid Signaling”. October 19.

<http://www.powerbase.info/index.php/File:BVL2010.comments.Paganelli.pdf>

166. Dallegrove, E., Mantese, F. D. et al. 2003. The teratogenic potential of the herbicide glyphosate-Roundup in Wistar rats. *Toxicol Lett* 142(1-2): 48.

167. Lajmanovich, R. C., Sandoval, M. T., Peltzer, P. M. 2003. Induction of mortality and malformation in *Scinax nasicus* tadpoles exposed to glyphosate formulations. *Bull. Environ. Contam. Toxicol.* 70, 612–618.

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<http://www.powerbase.info/index.php/File:BVL2010.comments.Paganelli.pdf>

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10.0. Endocrine Disruption: Powerful endocrine disruptor and reproductive abnormalities

“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.”

99. Romano, R. M., Romano, M. A. et al. 2010. Prepubertal exposure to commercial formulation of the herbicide Glyphosate alters testosterone levels and testicular morphology. *Archives of Toxicology* 84(4): 309–317.

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11.0 Endocrine Disruption: Reproductive, developmental, and endocrine disruption effects

“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 fetuses 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).”

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12.0. Endocrine disruption

“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}”

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13.0. Irreversible damage to liver cells

“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”

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14.0. Human cell death

The authors make reference to a review by German regulators (BVL), in reference to research done in Argentina by Carrasco:

“BVL’s response to Carrasco’s study was not a one-off. In 2009, BVL issued a similarly dismissive response²³⁷ 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.”

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15.0. DNA damage: Roundup causes genotoxic (DNA damage) effects

"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

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16.0. Cancer: Roundup carcinogenic effects

“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 skin²⁸⁰
- Epidemiological studies show a link between Roundup/glyphosate exposure and two types of cancer: multiple myeloma²⁸¹ 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}”

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17.0. Cancer: Observed salivary gland lesions, carcinogenic?

“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.”

313. EU Commission. 1999. ECCO 78 Reporting Table. In: Glyphosate DAR, released by German government agency BVL on CD, FullReport_Glyphosat_03.pdf: p. 29 of the pdf.

18.0. Nervous system: Roundup causes neurotoxic effects

“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

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19.0 Conflict of interest: Industry bias on safety studies conducted by their own scientists

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}

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20.0. Conflict of interest: Monsanto, and bias in their response to health safety studies showing potential negative health effects from Roundup

“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.”

21.0 NY Courts: Monsanto can't make safety claims about Roundup

“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.”

Reference cited:

354. Attorney General of the State of New York, Consumer Frauds and Protection Bureau, Environmental Protection Bureau. 1996. In the matter of Monsanto Company, respondent.

Assurance of discontinuance pursuant to executive law § 63(15). New York, NY, Nov. False advertising by Monsanto regarding the safety of Roundup herbicide (glyphosate). <http://www.mindfully.org/Pesticide/Monsanto-v-AGNYnov96.htm>

22.0. Inert ingredients (adjuvants) increase toxicity of Roundup

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.

References cited:

355. Marc, J., Le Breton, M., Cormier, P., Morales, J., Bellé, R., Mulner-Lorillon, O. 2005. A glyphosate-based pesticide impinges on transcription. *Toxicol Appl Pharmacol.* 203(1): 1–8.
356. Benachour, N., Séralini, G. E. 2009. Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells. *Chem Res Toxicol.* 22: 97–105.
357. Benachour, N., Sipahutar, H., Moslemi, S., Gasnier, C., Travert, C., Séralini, G. E. 2007. Time- and dose-dependent effects of Roundup on human embryonic and placental cells. *Arch Environ Contam Toxicol.* 53: 126–133.

23.0. Roundup remains biologically active in the soil

“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.”

References cited:

349. EU Commission. 1999. Glyphosate: Comments from Pesticides Safety Directorate, York, UK, on the EC Monograph – ECCO 76. March 4. In: Glyphosate DAR, released by German government agency BVL on CD, FullReport_Glyphosat_04.pdf: p. 39 of the pdf.

350. Eberbach, P. L., Douglas, L. A. 1983. Persistence of glyphosate in a sandy loam. Soil Biology and Biochemistry 15(4): 485–487.

“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.”

References cited:

351. EU Commission. 1999. Monsanto/Cheminova comments to Monograph (dated 11 Dec 1998). Feb 11. In: Glyphosate DAR, released by German government agency BVL on CD, FullReport_Glyphosat_04.pdf: p. 52 of the pdf.

352. Reddy, K. N., Rimando, A. M. et al. 2004. Aminomethylphosphonic acid, a metabolite of glyphosate, causes injury in glyphosate-treated, glyphosate-resistant soybean. J Agric Food Chem 52(16): 5139–5143.

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