



Summary on the Toxicity of Glyphosate

Cancer/Carcinogenicity

IARC: The International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO), classified glyphosate as a "probable human carcinogen", following a thorough analysis performed by 17 independent and world's leading experts from 11 countries using only publicly available studies¹. This conclusion was reached based on "limited evidence of carcinogenicity in humans" and "sufficient evidence" in experimental animals. For humans, IARC took into account evidence from human cancer studies from 3 different countries where 2592 people (workers), in total, had developed Non-Hodgkin lymphoma (NHL; a rare case of cancer) following exposure to glyphosate-based herbicides and from a combined analysis (meta-analysis) of all NHL studies available. The conclusion on experimental animals was based on two experiments where mice had developed malignant tumours as a result of exposure to glyphosate alone, one revealing a rare case of cancer (kidney), which is extremely important in assessing human risk. Furthermore, the experts took into consideration the strong evidence of genotoxicity (DNA damage) and oxidative stress (tissue/cell damage) in humans and laboratory animals following exposure to glyphosate-pesticides and its metabolites.

EFSA peer review and Revised Assessment Report (RAR)ⁱ – BfR (German Health Authority) acting as a Rapporteur Member State for the European Commission: In fact, BfR having access to undisclosed industry studies found not two but five experimental studies were mice fed with glyphosate had developed malignant tumours. But it decided to dismiss the findings as non-significant. Ironically, it then dismissed the mechanistic data on genotoxicity and cell toxicity as non-relevant, because apparently, there were no evidence of carcinogenicity in experimental animals. Furthermore, all results on genotoxicity, cell toxicity or any toxicity in fact due to exposure to glyphosate products were all considered non-relevant because according to the EU rules risk assessment is done only on the active ingredient, despite the fact that people are exposed to the whole products. EFSA in its peer review approved the work of BfR. The analysis of the carcinogenicity potential of glyphosate by the European Authorities has received criticism by the scientific community^{2,3,4,5}.

Endocrine disruption: Glyphosate alone and glyphosate-based products alter the hormone metabolism in different mammalian cell lines^{6,7} and have been reported to reduce the conversion of androgens to oestrogens (resulting in production of more male than female hormones), with formulations causing a stronger effect^{8,9}. In experimental studies with mice, glyphosate-based products also alter the reproductive hormone metabolism and reduce fertility^{10,11,12}. Despite the fact that endocrine disruption can cause serious health effects, very few studies have examined the

ⁱ Before the authorisation of an active substance, the applicant (pesticide industry) submits a dossier with all data requirements (chemical properties, toxicity, environmental fate etc.) to a Member State which acts as a Rapporteur (RMS) for the European Commission. RMS then evaluates the dossier and produces first the Draft Assessment Report (DAR) or the Revised Assessment Report (RAR) in case of re-authorisation.



capacity of glyphosate to alter the hormonal system⁴. Actually, EFSA has requested industry to evaluate the endocrine disruption potential of glyphosate and will publish its opinion in August 2017.

Toxicity of glyphosate on reproduction and development: In the RARⁱ, there are already several incidences of developmental effects of glyphosate in mammals and in many cases below the recommended regulatory limits¹³. Experimental animals exposed to glyphosate have given birth to foetuses with increased heart malformations and abnormalities, absent kidneys, distorted ribs, lungs and skeleton, as well as embryonic deaths. These data were dismissed for unclear reasons that cannot be verified since the studies are not published. However, independent published scientific studies show that pups exposed to glyphosate-based products developed abnormal reproductive organs and had altered hormone levels and mating behaviour^{14,15}. In a Danish farm, 38 live-borne one-day-old piglets had extraordinarily high percentages of abnormalities including serious cranial and skeletal malformations. By switching to non-GM and glyphosate-free feed the farmer instantly observed positive changes in the health of the sow herdⁱⁱ.

Nervous system toxicity: Glyphosate and Glyphosate-based products affect the growth and development of nerve cells¹⁶. Glyphosate has been reported to disrupt the function of brain nerve signalling, brain cell organelles (mitochondria) and cause neuronal cell death all hallmarks of Parkinson disease^{17,18,19}. Exposure to glyphosate products has been associated to ADD/ADHD, Parkinson disease and autism^{20,21,22}.

Plant Toxicity and effects on biodiversity: Glyphosate being a wide-spectrum herbicide, kills all plants and even large trees. No other herbicide is so non-selective. Significant reductions in plant biomass, flower and wild plants have been observed in green areas close to fields treated with glyphosate products²³. This reduction in plant species causes in turn a reduction in terrestrial species that feed on them, including natural insect predators, amphibians, pollinators and birds, resulting in significant ecological impact and biodiversity loss^{24,25,26}.

Ecotoxicity: The ecotoxicity of glyphosate to aquatic and terrestrial organisms is already recognised in RAR and EFSA peer-review, reporting glyphosate toxicity with long-lasting effects. By using prediction models to estimate the environmental exposure and considering that mitigation measures are applied by the farmers, the European Authorities conclude that the risk for non-target organisms is low. But, studies have confirmed that these models often underestimate real environmental exposures, indicating that non-target organisms are at a much higher risk²⁷. Nevertheless, glyphosate causes a wide range of adverse effects in non-target organisms.

Aquatic ecotoxicity: Glyphosate and glyphosate-based herbicides are toxic to microorganisms, and alter plankton and algae communities²⁸. Adverse effects following exposure have been reported in insects²⁹, crustaceans³⁰, molluscs, amphibians³¹ and fish³² and effects include reproductive and developmental abnormalities, DNA damage, immune effects, oxidative stress, decreased capacity to cope with stress, altered feeding and mating behaviour that can threaten their survival. Glyphosate products are usually more toxic to fish than glyphosate alone³³.

Terrestrial ecotoxicity: Glyphosate has adverse effects on some earthworms and arthropods; and a number of beneficial insects useful in biological control, particularly predatory mites, carabid beetles and ladybugs^{23,34}. It can also adversely affect other insects that play an important part in ecological

ⁱⁱ Full story: <u>http://www.gmwatch.org/index.php/articles/gm-reports/13882</u>



balance such as wood louse and field spiders²⁴. Glyphosate use may result in significant population losses of a number of terrestrial species, including birds through habitat and food supply destruction³³.

Anti-bacterial properties and toxicity implications: The anti-microbial activity of glyphosate is known since it was first licensed in 1970s³⁵. It is also toxic to certain soil bacteria of the *Bacillus* and *Pseudomonas* families that have a key role in suppressing specific pathogenic fungi, as well as in making the soil minerals available to plants. Thus, glyphosate alters the microbial community of the soils, which has a direct impact on the health of the crops. Glyphosate also seems to bind to the soil minerals (Manganese, Iron, Copper and Zinc) and blocks their bioavailability to the plants. In fact, glyphosate has been characterised to "significantly increase the severity of various plants diseases, impair plant defence to pathogens and diseases, and immobilize soil and plant nutrients rendering them unavailable for plant use". Due to these effects and weed resistance farmers are obliged to use fungicides and additional herbicides on their crops^{36,37}.

Due to its antibacterial properties glyphosate has been reported to affect the gut microbiota of animals, killing the beneficial bacteria and leaving the pathogenic ones behind³⁷. This has been linked to adverse effects in farm animals, which feed on glyphosate-treated soya and corn feed. Some studies suggest that this particular glyphosate action which affects the gut bacteria may have serious implications to humans ³⁸.

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¹ Guyton KZ, Loomis D, Grosse Y, et al. 2015. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology , 16: 490 – 491.

² Portier, C. J., Armstrong, B. K., Baguley, B. C., Baur, X., Belyaev, I., Bellé, R., ... Zhou, S. F. (2016). Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). Journal of Epidemiology and Community Health. DOI: 10.1136/jech-2015-207005

³ Greiser E, 2016. Expert statement on epidemiological studies which examine the possible correlation between exposure to glyphosate-based herbicides and non-Hodgkin's lymphoma and human fertility disorders in relation to evaluations undertaken by the German Federal Institute for Risk Assessment (BfR) and the European Food Safety Authority (EFSA). University of Bremen https://www.global2000.at/sites/global/files/Human%20evidence_EberhardGreiser.pdf

⁴ Myers JP, Antoniou MN, Blumberg B et al. 2015. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environmental Health 15:19

⁵ Clausing P. Regulatory agencies (BfR, EFSA) used biased arguments to deny the carcinogenicity of glyphosate: Memorandum by Dr Peter Clausing, PAN Germany, as a witness to the Monsanto Tribunal. The Hague, Netherlands, 15-16 October 2016. http://www.pan-germany.org/download/Memo Monsanto-Tribunal Peter Clausing 10 2016.pdf

⁶ Walsh LP, McCormick C, Martin C, Stocco DM. 2000. Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression. Environ Health Perspect 108:769-76.

⁷ Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J. 2013. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol 59:129-36.

⁸ Richard S, Moslemi S, Sipahutar H, Benachour N, Séralini GE, 2005. Differential effects of glyphosate and Roundup on human placental cells and aromatase. Environ Health Perspect 113(6):716-20.

⁹ Defarge N, Takács E, Lozano VL, Mesnage R, Spiroux de Vendômois J, Séralini G-E, Székács A. 2016. Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels. Int J Environ Res Pub Health 13(3):264.

¹⁰ Romano RM, Romano MA, Bernardi MM, Furtado PV, Oliveira CA. 2010. Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology. Arch Toxicol 84:309-17.

¹¹ Romano MA, Romano RM, Santos LD, Wisniewski P, Campos DA, de Souza PB, Viau P, Bernardi MM, Nunes MT, de Oliveira CA, 2012. Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression. Arch Toxicol 86(4):663-73.



¹² Varayoud J, Durando M, Ramos JG, Milesi MM, Ingaramo PI, Muñoz-de-Toro M, Luque EH. 2016. Effects of a glyphosatebased herbicide on the uterus of adult ovariectomized rats. Environ Toxicol [Epub Jul 27th].

¹³ Mesnage R, Defarge N, Spiroux de Vendômois J, Séralini GE, 2015. Potential toxic effects of glyphosate and its commercial formulations below regulatory limits. Food Chem Toxicol 84:133153.

¹⁴ Dallegrave E, Mantese FD, Oliveira RT, Andrade AJM, Dalsenter PR, Langeloh A. 2007. Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. Arch Toxicol 81:665-73.

¹⁵ Guerrero Schimpf M, Milesi MM, Ingaramo PI, Luque EH, Varayoud J. 2016. Neonatal exposure to a glyphosate based herbicide alters the development of the rat uterus. Toxicology pii: S0300-483X(16)30093-2.

¹⁶ Coullery RP, Ferrari ME, Rosso SB. 2016. Neuronal development and axon growth are altered by glyphosate through a WNT noncanonical signaling pathway. Neurotoxicology 52:150-61.

¹⁷ Hernández-Plata I, Giordano M, Díaz-Muñoz M, Rodríguez VM, 2012. The herbicide glyphosate causes behavioral changes and alterations in dopaminergic markers in male Sprague-Dawley rat. Neurotoxicology 46:79-91.

¹⁸ Astiz M, de Alaniz, MJ, Marra CA. 2009b. The impact of simultaneous intoxication with agrochemicals on the antioxidant defense system in rat. Pestic Biochem Physiol 94:93-99.

¹⁹ Negga R, Stuart JA, Machen ML, Salva J, Lizek AJ, Ricahrdson SJ, Osborne AS, Mirallas O, McVey KA, Fitsanakis VA. 2012. Exposure to glyphosate- and/or Mn/Zn-ethylene-bis-dithiocarbamatecontaining pesticides leads to degeneration of γaminobutyric acid and dopamine neurons in Caenorhabditis elegans. Neurotox Res 21:281-90.

²⁰ Garry VF, Harkins ME, Erickson LL, Long-Simpson LK, Holland SE, Burroughs BL. 2002. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Environ Health Perspect 110(s3):441-9.

²¹ Wan N, Lin G. 2016. Parkinson's disease and pesticides exposure: new findings from a comprehensive study in Nebraska, USA. J Rural Health. 32(3):303-13.

²² Nevison CD. 2014. A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors. Environ Health. 5;13-73.

²³ Heard MS, Hawes C, Champion, GT, Clark SJ, Firbank LG, Haughton AJ, Parish AM, Perry JN, Rothery P, Roy DB, Scott RJ, Skellern MP, Squire Gr, Hill MO. 2003b. Weeds in fields with contrasting conventional and genetically modified herbicide-tolerant crops. I Effects on abundance and diversity & II Effects on individual species. Philos Trans R Soc Lond B Biol Sc i358(1439):1833-46.

²⁴ Haughton AJ, Bell JR. Boatman ND, Wilcox A. 2001. The effect of the herbicide glyphosate on non-target spiders: Part II. Indirect effects on Lepthyphantes tenuis in field margins. Pest Manag Sci 57:1037-42.

²⁵ Hawes C, Squire GR, Hallett PD, Watson CA, Young M. 2010. Arable plant communities as indicators of farming practice. Agric Ecosys Environ 138(1-2):17-26.

²⁶ Thies C, Haenke S, Scherber C, Bengtsson J, Bommarco R, Clement LW, Ceryngier P, Dennis C, Emmerson M, Gagic V, Hawro V, Liira J, Weisser WW, Wingvist C, Tscharntke T. 2011. The relationship between agricultural intensification and biological control: experimental tests across Europe. Ecol Appl 21(6):2187-96.

²⁷ Stehle S, Schulz R, 2015. Pesticide authorization in the EU-environment unprotected? Environ Sci Pollut Res 22: 19632.

²⁸ Pérez GL, Torremorell A, Mugni H, Rodríguez P, Solange Vera M, do Nascimento M, Allende L, Bustingorry J, Escaray R, Ferraro M, Izaguirre I, Pizarro H, Bonetto C, Morris DP, Zagarese H. 2007. Effects of the herbicide Roundup on freshwater microbial communities: a mesocosm study. Ecol Appl 17(8):2310-22.

²⁹ Cuhra M. 2015. Glyphosate nontoxicity: the genesis of a scientific fact. J Biol Phy Chem 15:89-96.

³⁰ Avigliano L, Alvarez N, Loughlin CM, Rodríquez EM. 2014. Effects of glyphosate on egg incubation, larvae hatching, and ovarian rematuration in the estuarine crab, Neohelice granulata. EnvironToxicol Chem 33(8):1879-84.

³¹ Paganelli A, Gnazzo V, Acosta H, Lo´pez SL, Carrasco AE. 2010. Glyphosate-based herbicides produce teratogenic effects on vertebrates by impairing retinoic acid signalling. Chem Res Toxicol 23(10):1586-95.

³² Moreno NC, Sofia SH, Martinez CB. 2014. Genotoxic effects of the herbicide Roundup Transorb and its active ingredient glyphosate on the fish Prochilodus lineatus. Environ Toxicol Pharmacol 37(1):448-54.

³³ A review of effects of glyphosate and glyphosate-based herbicides on aquatic and terrestrial organisms is given in Glyphosate Monograph 2016, PAN International <u>http://pan-international.org/wp-content/uploads/Glyphosate-monograph.pdf</u>

³⁴ Schneider MI, Sanchez N, Pineda S, Chi H, Ronco A. 2009. Impact of glyphosate on the development, fertility and demography of Chrysoperla externa (Neuroptera: Chrysopidae): Ecological approach. Chemosphere 76(10):1451-5.

³⁵ Franz, J.E. (1974) Nphosphonomethylglycine Phytotoxicant Compositions. US Patent 3,799,758, Mar. 26, 1974, USPTO, Washington, DC.

³⁶ Reviewed in Sirinathsinghji E., 2012. USDA Scientist Reveals All: Glyphosate Hazards to Crops, Soils, Animals, and Consumers. Prof Don Huber. ISIS Report <u>http://www.i-sis.org.uk/Ueurop. SDA scientist reveals all.php</u>

³⁷ Krüger M, Shehata AA, Schrödl W, Rodloff A, 2013. Glyphosate suppresses the antagonistic effect of Enterococcus spp. on Clostridium botulinum. Anaerobe 20:74–78.

³⁸ Samsel A, Seneff S. Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. Interdiscip. Toxicol. 2013;6(4):159-184. doi:10.2478/intox-2013-0026.