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Submission to APVMA to place glyphosate (and all products/formulations containing glyphosate as the active ingredient) under formal reconsideration.

Glyphosate is the most extensively used pesticide in Australia; a broad-spectrum, non-selective, post-emergent systemic herbicide. Exposure to glyphosate is ubiquitous; mostly from food but glyphosate also resides for variable times (4 to 180 days and over 1000 days in cooler climates) in soil and water[1], dependant on ambient temperatures. It is also widely used in home gardens, road side vegetation strips and urban public outdoor areas. It is commonly used on crops and plantations including about 80% of genetically modified crops (crops resistant to glyphosate). It is also commonly used as a pre-harvest desiccant with relatively high levels allowed as residue in food and animal feed, and because it is a systemic herbicide it cannot be completely removed from food by washing, peeling or processing.
Glyphosate was initially marketed as a safe, nontoxic herbicide with minimal environmental impacts. 40 years later, it is now known that these claims cannot be substantiated.

APVMA have stated that "*there are no scientific grounds for placing glyphosate and products containing glyphosate under formal reconsideration*".

We submit that there is no substance to APVMA's assertion and ask that the recent review of glyphosate undertaken by Pesticides Action Network

[1] Mercurio, P., et al., 2014; Glyphosate persistence in seawater. Marine Pollution Bulletin. Vol 85.2.385-390

International (October 2016)[2] and Myers et. al.[3] be examined in detail by APVMA as part of their formal reconsideration.
This submission regarding glyphosate also includes all products/formulations containing glyphosate and contained excipients[4] (72 now banned by the US EPA but still allowed for use in Australia), and all need to be assessed as entities for toxicity both for short and long term exposures, acute and sub lethal toxicity, including adverse effects on immune systems, endocrine systems and those including the genome. (*Agricultural and Veterinary Chemicals Code Act 1994*, Section 4 Part 1, Object of Code, Division 1(b)).

APVMA is required under the *Agricultural and Veterinary Chemicals Code Act 1994* (Section 1A, Implementing the Code, Clause 2) to protect the health and safety of human, animals and the environment.

As such we request that:

- All modes of action of glyphosate are taken into consideration including, but not confined to the following :
    - Substitution by glyphosate (a synthetic amino acid analogue of glycine) for glycine throughout the organism with resultant multiple adverse health effects
    - Chelating effects of essential metals causing deficiencies in the organism.
    - Adverse effects on an organism's beneficial gut microbes[5] and biosynthesis of aromatic amino acids, knowing glyphosate is an antibacterial and was listed as such in 2010.
    - Inhibition of cytochrome P450 enzymes.
    - Endocrine disrupting chemical with adverse effects on hormone systems and cell signalling in the organism.
    - Immune dysregulator and modifier.
    - Oxidative stress inducer[6]
    - Genotoxicity[7]

[2] http://pan-international.org/wp-content/uploads/Glyphosate-monograph.pdf
[3] Myers, J.P., et al., 2016; Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environmental Health 15:19 DOI 10.1186/s12940-016-0117-0
[4] https://www.epa.gov/newsreleases/epa-prohibits-72-inert-ingredients-use-pesticides
[5] Claus, S., Guillou, H., and Ellero-Simatos, S., 2016; The gut microbiota: a major player in the toxicity of environmental pollutants? Nature, npj; Biofilms and Microbiomes 2, (16003). http://www.nature.com/articles/npjbiofilms20163
[6] Webster, T., et al., 2015; Global transcriptomic profiling demonstrates induction of oxidative stress and of compensatory cellular stress responses in brown trout exposed to glyphosate and Roundup. BMC Genomics. 16:32 DOI 10.1186/s12864-015-1254-5.

- Modifier of antibiotic susceptibility[8]

- All known scientific papers and data are used in the reconsideration of glyphosate by the APVMA; with no "cherry picking" of data/ scientific papers/ unpublished industry data relevant to the effects of glyphosate and including all industry data especially that withheld from public scrutiny. The industry data specifically cited by Clausing[9] and Samsel[10,11] relating to tumours and cancers[12] need to be analysed and examined in detail independently and transparently with no bias relating to statistical analysis.

- All industry data needs to be examined and re-analysed. In addition the determination of NOEL and ADI levels for glyphosate and all products and formulations need to be reassessed in view of the emerging contemporary novel mechanisms of action of glyphosate and excipients. This needs to include data for all Australian native flora and fauna.

- Any products/ formulations of glyphosate which use any materials to increase or amplify the actions of glyphosate need to be reviewed along with the reconsideration of glyphosate. For instance the effects of nano –materials and polyoxyethylene tallow amine (POEA) used along with glyphosate needs to be assessed as an actual product and the total effects need full consideration.[13] POEA is a known aquatic toxicant[14]

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[7] Ghisi, N., et al. 2013; Genotoxic effects of the herbicide Roundup in the fish Corydoras paleatus (jenyns 1842) after short-term, environmentally low concentration exposure. Environmental Monitoring and Assessment. Vol 185. 3201-3207.

[8] Kurenbach, B., 2015; Sublethal exposure to commercial formulations of the herbicides dicamba, 2,4-dichlorophenoxyacetic acid, and glyphosate cause changes in antibiotic susceptibility in Escherichia coli and Salmonella enterica serovar Typhimurium. mBio 6(2):e00009-15. Doi:10.1128/mBio.00009-15.

[9] Clausing, P., 2016; Memorandum by Dr. P. Clausing; PAN Germany, as a witness to the Monsanto Tribunal. The Hague, Netherlands, 15-16 October 2016. http://www.pan-germany.org/downlods/Memo_Monsanto-Tribunal_Peter_Clausing_10_2016.pdf

[10] Samsel, A., and Seneff, S., 2016; Glyphosate pathways to modern disease V: Amino acid Analogue of glycine in diverse proteins. Journal of Biological Physics and Chemistry; 16, 9-46.

[11] Samsel, A., and Seneff, S., 2013; Glyphosate's Suppression of Cytochrome P450 Enzymes and Amino Acid Biosynthesis by the Gut Microbiome: Pathways to Modern Diseases. Entropy, *15*, 1-x manuscripts; doi:10.3390/ e140x000x

[12] Lankas, G.R. and Hogan, G.K., 1981; A lifetime feeding study of glyphosate (Roundup Technical) in Rats: Project no 772062. (Unpublished study received Jan 20, 1982 under 524-308; prepared by Bio/dynamics, Inc., submitted by Monsanto Co., Washington D.C.; CDL: 246617-A;246618;246619;246620;246621). MRID 00093879.

[13] Lanctôt, C., Navarro-Martín, L., Robertson, C., Park, B., Jackman, P., Pauli, B.,D. and Trudeau, V.L., 2014; Effects of glyphosate-based herbicides on survival, development, growth and sex ratios of wood frog (Lithobates sylvaticus) tadpoles. II: agriculturally relevant exposures to Roundup WeatherMax® and Vision® under laboratory conditions. Aquat Toxicol. 2014 Sep;154:291-303 doi: 10.1016/j.aquatox.2014.05.025.

and was banned when used with glyphosate in the European Union in July 2016.

- The potential for glyphosate to be a carcinogen needs full review. The following points need to be included in a full reconsideration and used to determine whether in fact there is a safe level of exposure for glyphosate and any products/formulations.
    - The Memorandum by Clausing clearly states information relevant to this reconsideration. Quoting from this referenced article by GMWatch[15] (numbering of references changed here)

> "Clausing explained that the males of all five mouse carcinogenicity studies considered by these authorities to be of an acceptable quality showed a statistically significant increase in the incidence of one or several tumour types.
>
> Three of the five mouse studies exhibited a significant increase in one specific type of cancer, malignant lymphoma, emphasizing the reproducibility of the finding.[16]
>
> Clausing pointed out that these findings alone exceed the criterion for the classification of glyphosate as a 1B carcinogen (substances presumed to have carcinogenic potential for humans, largely based on animal evidence[17] under European legislation.[18]
>
> Europe's pesticide regulation has a "hazard-based cut-off" clause regarding carcinogenicity,[19] meaning that a 1B carcinogen classification for glyphosate would lead to an automatic ban unless exposure was proven to be "negligible". The law does not allow industry and regulators to argue that the doses we are exposed to are below permitted levels and therefore safe."

Clausing's evidence to the Tribunal raises serious concerns and questions about the scientific integrity and competence of The German Federal Institute for Risk Assessment (BfR) and the European Food Safety Authority (EFSA).

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[14] Tush, D., Loftin, K.A., and Meyer, M.T., 2013; Characterization of polyoxyethylene tallow amine surfactants in technical mixtures and glyphosate formulations using ultra-high performance liquid chromatography and triple quadrupole mass spectrometry: Journal of Chromatography A, v. 1319, p. 80-87, doi:10.1016/j.chroma.2013.10.032.

[15] http://gmwatch.org/news/latest-news/17307

[16] Clausing, P., 2016; Memorandum by Dr. P. Clausing; PAN Germany, as a witness to the Monsanto Tribunal. The Hague, Netherlands, 15-16 October 2016. http://www.pan-germany.org/downlods/Memo_Monsanto-Tribunal_Peter_Clausing_10_2016.pdf

[17] CNRS Chemical Risk Prevention Unit (PRC) 2011; Carcinogens, mutagens, reproductive toxicants: European regulatory classification criteria, hazard communication elements. CNRS. http://www.prc.cnrs-gif.fr/IMG/pdf/cmr-criteria-clp.pdf

[18] Regulation EC 1272/2008

[19] Regulation EC No 1107/2009

- Samsel demonstrates clearly that the modes of action of glyphosate can cause many disease states including cancer.[20] The substitution of glycine by the synthetic amino acid and the incorporation of non-coding amino acids in protein synthesis obviate a dose response harm evaluation with regards to glyphosate and products as this approach is inappropriate when investigating changes in protein synthesis. Industry studies show abnormal incorporation of non-coding amino acids in altered +/- mis-folded proteins which are inherently unstable and of altered functionality.
  For more than a decade it has been known that glyphosate in the millimolar range inhibits global transcription. The hatching process of sea urchins is disturbed by millimole exposures to glyphosate. Sea urchins are used as biological models to gain comprehension of the cellular and molecular targets of pollutant exposure.[21]
- It is also been clearly demonstrated that for endocrine disrupting chemicals (EDCs), the most sensitive endpoint can vary depending on the endocrine active compounds present and their pattern and timing of exposure, due to EDCs low dose effects and nonmonotonic dose response curves.[22] Many EDCs have been clearly demonstrated to be associated with induction and the promotion of carcinogenic processes.[23]

- All glyphosate products are contaminated by N-Nitrosoglyphosate (NNG) and NNG is also formed *in vivo* in all animals. NNG is a carcinogen and therefore on this information alone, glyphosate must be placed under formal reconsideration for removal from use and follow the IARC's explanation for their recommendation.[24]

[20] Samsel, A. and Seneff, S., 2016; Glyphosate pathways to modern disease V: Amino acid Analogue of glycine in diverse proteins. Journal of Biological Physics and Chemistry; 16, 9-46.
[21] Marc, J. Le Breton, M., Cormier, P., Morales, J., Bellé, R. and Mulner-Lorillon, O., 2005; A glyphosate-based pesticide impinges on transcription. Toxicol Appl Pharmacol. 15;203(1):1-8.

[22] Schug, T., Johnson, A., Birnbaum, L., Colborn, T., Guillette, L., Crews, D., Collins, T., Soto, A., vomSaal, F., McLachlan, J., Sonnenschein, C. And Heindel, J., 2016; Minireview: Endocrine Disruptors: Past Lessons and Future Directions. Mol Endocrninol,30(8):833-847.
[23] World health organisation, 2012; State of the science of endocrine disrupting chemicals. Geneva, Switzerland.
[24] https://www.iarc.fr/en/media-centre/iarcnews/pdf/Q&A_Glyphosate.pdf

In March 2015, IARC[25],[26] classified glyphosate as "probably carcinogenic to humans" (Group2A), and APVMA have not produced adequate evidence to the contrary.

APVMA needs to behave independently, with integrity and transparency for the Australian public and consumer to yield confidence in their regulatory functions.

APVMA primarily needs to protect public and environmentally health. It was not established to protect business interests ahead of public and environmental safety.

In light of the above, APVMA have no option but to formally reconsider glyphosate.

[25] http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf
[26] http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70134-8/fulltext