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Review of IARC Monograph 112 (Glyphosate): Tier 1

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FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the Agvet Codes scheduled to the Agricultural and Veterinary Chemicals Code Act 1994.

The APVMA has legislated powers to reconsider the approval of an active constituent, registration of a chemical product or approval of a label at any time after it has been registered. The reconsideration process is outlined in sections 29 to 34 of Part 2, Division 4 of the Agvet Code.

A reconsideration may be initiated when new research or evidence has raised concerns about the use or safety of a particular chemical, a product containing that chemical, or its label. The reconsideration process includes a call for information from a variety of sources, a review of that information and, following public consultation, a decision about the future use of the chemical or product. The information and technical data required by the APVMA to review the safety of both new and existing chemical products must be generated according to scientific principles. The APVMA conducts science and evidence-based risk analysis with respect to the matters of concern, analysing all the relevant information and data available.

When the APVMA receives or is made aware of a significant new piece of information that questions the safety (to animals, humans or the environment) or efficacy of a registered chemical, the APVMA conducts a scoping exercise to determine whether a formal reconsideration of that chemical and/or products containing that chemical should be initiated.

The APVMA made the decision to consider glyphosate for review in 2015 due to human toxicology concerns, following the reclassification of glyphosate as ‘probably carcinogenic’ by the International Agency for Research on Cancer (IARC) in 2015. This document outlines the first step in the nomination assessment process for glyphosate and is based on a draft report provided to the APVMA by the Office of Chemical Safety in October 2015.

The APVMA makes its reports available to the regulatory agencies of other countries as part of bilateral agreements. The APVMA recommends that countries receiving these reports will not utilise them for registration purposes unless they have access to the raw data from the relevant applicant.

1 INTRODUCTION

The World Health Organization's (WHO) International Agency for Research on Cancer (IARC) released a summary of Monograph 112 (Diazinon, Glyphosate, Malathion, Parathion and tetrachlorvinphos) on the 20 March 2015[1]. The full glyphosate monograph was released on 29 July 2015 (referred to in this document as the monograph).

IARC has classified glyphosate as a Category 2A 'probably carcinogenic to humans'. This classification was based on:

- limited evidence of carcinogenicity in humans
- sufficient evidence of carcinogenicity in animals
- strong evidence that glyphosate can operate through two key characteristics of human carcinogens and that these can be operative in humans—genotoxicity and oxidative stress.

The APVMA requested the Office of Chemical Safety (OCS) undertake a preliminary scoping assessment of the monograph (nominated as Tier 1) to ascertain the relevance of the carcinogenicity classification and any implications this may have to the registration of glyphosate and glyphosate formulations in Australia. In particular, as part of this preliminary review, the OCS was requested to identify any relevant data not previously evaluated by Australia.

1.1 Glyphosate

Glyphosate [*N*-(phosphonomethyl) glycine] is an aminophosphonic analogue of glycine, which is a naturally occurring amino acid. Glyphosate is a broad-spectrum, non-selective, post-emergent, systemic herbicide that kills or suppresses all plant types and can be used as a plant-growth regulator/desiccator at lower dose rates. Herbicide products that contain glyphosate are commonly used to control annual and perennial broadleaf and grassy weeds in various agricultural and non-agricultural settings. Glyphosate binds strongly to soil particles and is readily metabolised by soil microorganisms, thus when applied post-emergence, glyphosate demonstrates no pre-emergence or residual activity.

Glyphosate is approved for use in Australia to control various annual and perennial broadleaf, grassy and woody weeds, trees and brush and is used in a variety of different situations. Glyphosate is applied by ground boom, knapsack/handgun, gas/splatter gun, wiper equipment, controlled droplet application equipment, aerial spraying, aerosol spray, ready to use spray bottle and ready to use gel dispenser.

[1] www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

1.2 Australian position on glyphosate

Currently, the OCS considers glyphosate to have no carcinogenicity potential in humans and to be non-genotoxic[2]. All human health risk assessments undertaken by the OCS are consistent in conveying this hazard characterisation.

Safe Work Australia is responsible for classification of hazardous chemicals under the Work Health and Safety Regulations and lists glyphosate as *Xi: R41* (Irritant: risk of serious eye damage) on the Hazardous Substances Information System (HSIS).

1.3 International position on glyphosate

A summary of the international scientific positions on glyphosate are outlined below:

- the Food and Agriculture Organisation of the United Nations (FAO)/WHO Joint Meeting on Pesticide Residues (JMPR, 2004[3]/2011)—glyphosate (and metabolites) is not carcinogenic nor genotoxic in humans[4]
- European Union (EU) including the European Food Safety Authority (EFSA) and the German Federal Institute for Risk Assessment (BfR) (18 December 2013[5])—in an unpublished report on glyphosate, concluded that it is not carcinogenic nor genotoxic. The report also notes that published data suggests a higher toxicity of certain formulations as compared to glyphosate alone[6]
- the United States Environmental Protection Agency (US EPA[7], 26 June 1991)—glyphosate is classified as Group E (evidence of non-carcinogenicity for humans) due to inadequate evidence in animals
- Health Canada[8] (13 April 2015)—products containing glyphosate do not present unacceptable risks to human health (or the environment) when used according to the proposed label directions. However, as part of the Proposed Re-evaluation Decision PRVD2015–01, new risk reduction measures were proposed including:
    - to protect workers entering treated sites a restricted-entry interval of 12 hours is proposed for agricultural uses

[2] D14–2054023 dated 25.8.2014

[3] www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/report2004jmpr.pdf

[4] On 9–13 May 2016, the JMPR concluded their re-assessment of glyphosate, which was in agreement with earlier assessments that glyphosate was unlikely to pose a carcinogenicity risk to humans from exposure through the diet and is unlikely to be genotoxic at anticipated dietary exposures: www.fao.org/3/a-i5693e.pdf

[5] dar.efsa.europa.eu/dar-web/provision

[6] The final report, including an addendum was published on 12 November 2015: www.efsa.europa.eu/en/efsajournal/pub/4302

[7] nepis.epa.gov/Exe/ZyPDF.cgi/901A0500.PDF?Dockey=901A0500.PDF

[8] www.hc-sc.gc.ca/cps-spc/pest/part/consultations/_prvd2015-01/prvd2015-01-eng.php

  - to protect bystanders, a statement indicating to apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal is required.
- National Toxicological Program (NTP[9], as at 17 September 2015) of the United States Department of Health and Human Services—glyphosate is not genotoxic.

Recently, in response to the monograph, the JMPR Core Assessment Group on Pesticides Expert task force on Diazinon, Glyphosate and Malathion[10] (11 September 2015), recommended to JMPR that a full re-evaluation be undertaken based on the significant differences between databases relied on by JMPR and IARC.

1.4 Reference list and key study review

The monograph for glyphosate referenced 264 published papers.

The reference list was examined by OCS and the publicly available papers were sourced. Based on the abstracts, references were designated as either:

- relevant for the carcinogenicity classification for humans and requiring further analysis
- not relevant to the classification and excluded
- requiring further review to ascertain relevance.

The criteria for these designations are outlined in Appendix A.

1.5 Reference list and key study review results and discussion

Following analysis of the abstracts, the 264 references were categorised as follows:

- 174 references were excluded from requiring further review (Table 3)—A majority of these studies were excluded due to investigation of non-standard species or methodology for evaluating human toxicity (eg fish). Generally, the species selected for a toxicology study should be relevant to human biology and should produce all of the metabolites formed in humans (IPCS 2009). Thus, studies conducted in non-mammalian species are often not considered to accurately reflect the biological effect of a chemical in humans. Many of these studies were relevant for assessing the environmental impact of glyphosate exposure
- 19 references were considered relevant to the carcinogenicity classification for glyphosate and require further in-depth review (Table 1)
- 71 references were considered to require further review to determine relevance to the carcinogenicity classification (Table 2).

[9] ntp.niehs.nih.gov/testing/status/agents/ts-m88067.html

[10] www.who.int/foodsafety/areas_work/chemical-risks/main_findings_and_recommendations.pdf

It was noted by the OCS that the monograph relied on cancer epidemiology studies based on exposure to commercial formulations (for example Round-Up®) as opposed to exposure to glyphosate *per se*. On review of the abstracts, these studies did not identify the product formulation used or the type of application (both pertinent to potential exposure estimation). These studies were largely reliant on data collected in the Agricultural Health Study (AHS) based solely in North America, with few studies available to confirm outcomes. It should be noted that the OCS has not evaluated the acceptability of the data collection method(s) in the AHS (ie if the survey questions aimed at estimating 'exposure' were suitably robust for regulatory purposes).

It was also noted by the OCS that the abstracts of the key studies investigating genotoxic potential and oxidative stress markers use product formulations rather than from glyphosate *per se*[11]. A number of studies indicate a clear difference in results between glyphosate and glyphosate formulations (including adjuvants used during application).

1.6 Recommendations to the APVMA

Based on this Tier 1 preliminary review and the criteria outlined in Appendix A, the OCS recommends a review of the studies listed in Appendix B, with a review of the EU position for the key studies listed in Appendix C. Review of the studies listed in Appendix B will be undertaken as per Tier 2 of the OCS scoping document.

The OCS notes parallel reviews of the IARC Monograph are being planned or are in progress by international agencies including JMPR[12] and the European Chemicals Agency (ECHA)[13]. Therefore, the OCS recommends that rather than undertaking a full review in isolation of these agencies (approximately 90 studies), the APVMA make use of these assessments.

[11] This was also noted in the re-registration report by EU.

[12] www.who.int/foodsafety/en/

[13] echa.europa.eu/registry-of-submitted-harmonised-classification-and-labelling-intentions/-/substance-rev/13201/term

2 TIER 2 WORKPLAN

To support APVMA's role in the development of an Australian position regarding the carcinogenicity classification of glyphosate, the OCS proposes that the Tier 2 workplan be further sub-divided into 2 parts. Part 1 involves reviewing the 19 studies identified in this Tier 1 assessment as relevant to the carcinogenicity classification for glyphosate (Appendix B; Table 1). The completion of Part 1 will provide additional data to facilitate the development of an evidence-based Australian position regarding the carcinogenicity of glyphosate.

The OCS notes that international reviews will also be undertaken using the monograph reference list. The OCS recommends that as Part 2 of the Tier 2 assessment, the studies listed in Appendix C (Table 3) should be further reviewed to determine their relevance to the carcinogenicity classification of glyphosate. These studies will also provide insight into the carcinogenicity and genotoxic potential of glyphosate formulations, which may be toxicologically dissimilar to glyphosate technical. However, as the list of key studies outlined in Appendices B and C is extensive, an integrated international approach to evaluation of these studies is preferable to facilitate an Australian position. Thus, in light of the conclusions of international assessments, Part 2 of the proposed Tier 2 assessment may not be required.

APPENDICES

APPENDIX A—SELECTION CRITERIA FOR CRITICAL STUDIES

Exclusion criteria

Studies relating to the following were excluded from requiring further consideration (Appendix D, Table 5):

- studies previously reviewed by the OCS
- studies undertaken using animal models or cell lines not relevant for assessing human toxicity; eg fish, frogs, bovine
- studies investigating endpoints not relevant to a carcinogenicity classification; eg endocrine disruption, reproduction, immune function, neurotoxicity
- environmental fate and residue studies
- studies involving determination of glyphosate in air, soil, water or *in vivo*
- market/industry summary publications
- case studies regarding glyphosate poisoning
- occupational exposure measurement studies
- inclusion criteria

Definite

Studies considered relevant and requiring further review (Appendix B, Table 1):

- Studies not previously reviewed by the OCS or EU; and
    - studies that used glyphosate technical
    - studies that investigated carcinogenicity, genotoxicity or oxidative stress
    - studies that used appropriate test animal models or cell lines; eg mouse, rat, human lymphocytes.
- Studies reviewed by the EU and considered relevant and requiring further review (Appendix C, Table 3):

Possible

Studies requiring further evaluation to determine relevance (Appendix B, Table 2):

- studies not previously reviewed by the OCS or EU; and
    - studies that used a formulation of glyphosate
    - studies that were unclear as to the formulation or combination of active ingredients used
    - studies that do not fit the exclusion or definitive inclusion criteria.
- studies reviewed by the EU, requiring further evaluation to determine relevance (Appendix C, Table 3)

APPENDIX B—LIST OF KEY STUDIES REQUIRING FURTHER REVIEW (REFERENCED IN THE IARC MONOGRAPH 112)

Table 1 lists the studies that the OCS recommends for review. These studies were selected according to the criteria outlined in Appendix A.

Table 1 List of studies relevant to the carcinogenicity classification of glyphosate that require evaluation

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
Alvarez-Moya, C, Silva, MR, Valdez Ramírez, CV, Gallardo, DG, Sánchez, RL, Aguirre, AC, & Velasco, AF	2014	genotoxicity	glyphosate isopropylamine	human (lymphocyte cell line)	Comparison of the in vivo and in vitro genotoxicity of glyphosate isopropylamine salt in three different organisms. Genetics and molecular biology, 37(1), 105-110	Comet assay; glyphosate isopropylamine; human lymphocytes; positive results	www.scielo.br/scielo.php?pid=S1415-47572014000100016&script=sci_arttext
*Astiz, M, de Alaniz, MJ & Marra, CA	2009a	oxidative stress	glyphosate	rat (unknown strain)	Effect of pesticides on cell survival in liver and brain rat tissues. Ecotoxicology and environmental safety,72(7), 2025-2032	Liver and brain rat cell survival; MOA for oxidative stress seen in previous study	www.sciencedirect.com/science/article/pii/S0147651309001018
*Bolognesi, C, Bonatti, S, Degan, P, Gallerani, E, Peluso, M, Rabboni, R, Roggieri, P & Abbondandolo, A	1997	genotoxicity	glyphosate and Roundup	swiss CD-1 mice; human (lymphocyte cell line)	Genotoxic activity of glyphosate and its technical formulation Roundup. Journal of Agricultural and food chemistry, 45(5), 1957–1962	Uses roundup and glyphosate alone; positive results seen in both	pubs.acs.org/doi/abs/10.1021/jf9606518

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
Chan, P & Mahler, J	1992	genotoxicity	glyphosate	F344/N rats and B6C3F1 mice	NTP technical report on the toxicity studies of Glyphosate (CAS No. 1071-83-6) Administered In Dosed Feed To F344/N Rats And B6C3F1 Mice. Toxicity report series, 16, 1–D3	Effects in rats and mice; no mutagenicity in salmonella; negative for LLNA	europepmc.org/abstract/med/12209170
*Chaufan, G, Coalova, I & Rios de Molina Mdel, C	2014	oxidative stress	glyphosate, AMPA and glyphosate formulation	human (HepG2 cell line)	Glyphosate Commercial Formulation Causes Cytotoxicity, Oxidative Effects, and Apoptosis on Human Cells Differences With its Active Ingredient. International journal of toxicology, 33(1), 29–38	Shows formulation increases ROS and has toxic effects not seen in glyphosate alone	ijt.sagepub.com/content/33/1/29.short
*Elie-Caille, C, Heu, C, Guyon, C & Nicod, L	2010	oxidative stress	glyphosate	human keratinocyte (HaCaT cell line)	Morphological damages of a glyphosate-treated human keratinocyte cell line revealed by a micro-to nanoscale microscopic investigation. Cell biology and toxicology, 26(4), 331-339	Shows the timeline of membrane damage and ROS production in human keratinocytes	www.ncbi.nlm.nih.gov/pubmed/20043237
*Gasnier, C, Dumont, C, Benachour, N, Clair, E, Chagnon, MC & Seralini, GE	2009	genotoxicity	glyphosate and glyphosate formulations	human (HepG2 cell line)	Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. Toxicology, 262(3), 184–191	Shows effects are dependent on formulation not glyphosate concentration	www.sciencedirect.com/science/article/pii/S0300483X09003047

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
*Gehin, A, Guillaume, YC, Millet, J, Guyon, C & Nicod, L	2005	oxidative stress	glyphosate and round-up	human keratinocyte (HaCaT cell line)	Vitamins C and E reverse effect of herbicide-induced toxicity on human epidermal cells HaCaT: a biochemometric approach. International journal of pharmaceutics,288(2), 219–226	Shows effects are due to formulation; uses human keratinocyte cell line	www.sciencedirect.com/science/article/pii/S0378517304005733
Greim, H, Saltmiras, D, Mostert, V & Strupp, C	2015	carcinogenicity/ epidemiology	glyphosate and glyphosate formulations	human, rat, mouse	Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Critical reviews in toxicology, 45(3), 185–208	Shows no carcinogenic effect	www.tandfonline.com/doi/abs/10.3109/10408444.2014.1003423#.Vf9hMvk0VcY
JMPR	2006	classification			Glyphosate. Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food –2004: toxicological evaluations, Geneva, Switzerland	No evidence of carcinogenicity in rats or mice; no genotoxic potential	apps.who.int/iris/bitstream/10665/43624/1/9241665203_eng.pdf?ua=1
*Kier, LD & Kirkland, DJ	2013	genotoxicity	glyphosate and glyphosate formulations	in vitro and in vivo	Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Critical reviews in toxicology,43(4), 283–315	Review of genotoxicity testing for glyphosate and formulations	www.ncbi.nlm.nih.gov/pubmed/23480780

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
*Kwiatkowska, M, Huras, B & Bukowska, B	2014	oxidative stress	glyphosate, glyphosate metabolites and glyphosate impurities	human (erythrocyte cell line)	The effect of metabolites and impurities of glyphosate on human erythrocytes (in vitro). Pesticide biochemistry and physiology, 109, 34–43	Uses human erythrocytes; shows that ROS and damage only occurs at levels seen in acute poisoning	www.sciencedirect.com/science/article/pii/S0048357514000200
*Li, AP & Long, TJ	1998	genotoxicity	glyphosate	in vitro and in vivo	An evaluation of the genotoxic potential of glyphosate. Toxicological Sciences, 10(3), 537–546	Multiple genotoxicity tests; shows no genotoxic potential	toxsci.oxfordjournals.org/content/10/3/537.short
*Manas, F, Peralta, L, Raviolo, J, Ovando, HG, Weyers, A, Ugnia, L, Cid, MG, Larripa, I & Gorla, N	2009a	genotoxicity	glyphosate	human (Hep-2 cell line); mouse micronucleus	Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests. Environmental Toxicology and Pharmacology, 28(1), 37– 41	Shows positive genotoxicity results in Hep-2 cells and micronucleus mouse test at 400 mg/kg	www.sciencedirect.com/science/article/pii/S1382668909000258
*Mladinic, M, Berend, S, Vrdoljak, AL, Kopjar, N, Radic, B & Zeljezic, D	2009a	genotoxicity	glyphosate	human (lymphocyte cell line)	Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro. Environmental and molecular mutagenesis, 50(9), 800– 807	Shows no clear dose dependent effect	onlinelibrary.wiley.com/doi/10.1002/em.20495/abstract
*Mladinic, M, Perkovic, P & Zeljezic, D	2009b	genotoxicity	glyphosate	human (lymphocyte cell line)	Characterization of chromatin instabilities induced by glyphosate, terbuthylazine and	Cytome FISH assay; shows no hazardous effect	www.sciencedirect.com/science/article/pii/S0378427409002616

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
					carbofuran using cytome FISH assay. Toxicology letters, 189(2), 130–137	on DNA at low concentrations	
*Monroy, CM, Cortes, AC, Sicard, DM & de Restrepo, HG	2005	genotoxicity	glyphosate	human (GM38 and fibrosarcoma HT1080 cell lines)	Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate.Biomedica, 25(3), 335–345.	Suggests MOA not limited to plants	www.scielo.org.co/scielo.php?pid=S0120-41572005000300009&script=sci_arttext&tlng=pt
Prasad, S, Srivastava, S, Singh, M & Shukla, Y	2009	genotoxicity	glyphosate	swiss albino mice	Clastogenic effects of glyphosate in bone marrow cells of Swiss albino mice. Journal of toxicology, 2009	Shows positive clastogenic and cytotoxic effects in mouse bone marrow	www.hindawi.com/journals/jt/2009/308985/abs/
*Rank, J, Jensen, AG, Skov, B, Pedersen, LH & Jensen, K	1993	genotoxicity	glyphosate isopropylamine salt and Roundup	in vitro and in vivo	Genotoxicity testing of the herbicide Roundup and its active ingredient glyphosate isopropylamine using the mouse bone marrow micronucleus test, Salmonella mutagenicity test, and Allium anaphase-telophase test. Mutation Research/Genetic Toxicology, 300(1), 29–36	Shows negative effects for glyphosate in three genotoxicity tests	www.sciencedirect.com/science/article/pii/0165121893901362

*Considered by EFSA (2015)

APPENDIX C—LIST OF KEY STUDIES REQUIRING FURTHER ASSESSMENT TO DETERMINE RELEVANCE (REFERENCED IN THE IARC MONOGRAPH 112)

Table 2 lists the studies that the OCS recommends for further assessment to determine their relevance to the carcinogenicity classification of glyphosate. These studies were selected according to the criteria outlined in Appendix A.

Table 2: List of studies recommended by the OCS for further assessment to determine if relevant to carcinogenicity classification of glyphosate

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	Website
*Alavanja, MC, Samanic, C, Dosemeci, M, Lubin, J, Tarone, R, Lynch, CF, Knott, C, Thomas, K, Hoppin, JA, Barker, J, Coble, J, Sandler, DP & Blair, A.	2003	Carcinogenicity/ epidemiology	unknown formulation	human	Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. American Journal of Epidemiology,157(9), 800–814	No direct reference to glyphosate in abstract, increased risk to 'other pesticides' only seen in subjects with a FHx of prostate cancer	aje.oxfordjournals.org/content/157/9/800.short
*Astiz, M, de Alaniz, MJ, & Marra, CA.	2009b	oxidative stress	glyphosate	rat	Antioxidant defense system in rats simultaneously intoxicated with agrochemicals. Environmental toxicology and pharmacology, 28(3), 465– 473	Glyphosate administered alone and in combo with other a.i.'s; unclear if results are for combo; in vivo rat model	www.sciencedirect.com/science/article/pii/S1382668909001392
Astiz, M, Hurtado de Catalfo, GE., García, MN, Galletti, SM, Errecalde, AL, de Alaniz, MJ, & Marra, CA.	2013	oxidative stress	glyphosate	wistar rat	Pesticide-induced decrease in rat testicular steroidogenesis is differentially prevented by lipoate and tocopherol. Ecotoxicology and	Oxidative stress seen in testicular cells; investigates antioxidant treatment after administration;	www.sciencedirect.com/science/article/pii/S0147651313000389

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	Website
					environmental safety, 91, 129–138	unclear if administered in combo	
Benachour, N, & Séralini, GE.	2009	MOA	Roundup	human (umbilical, embryonic, placental cell lines)	Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells.Chemical research in toxicology, 22(1), 97–105	Uses glyphosate formulations, investigates metabolites	pubs.acs.org/doi/abs/10.1021/tx800218n
Benachour, N, Sipahutar, H, Moslemi, S, Gasnier, C, Travert, C, & Séralini, GE.	2007	MOA	Roundup (bioforce)	human (embryonic and placental cell lines)	Time-and dose-dependent effects of roundup on human embryonic and placental cells. Archives of Environmental Contamination and Toxicology, 53(1), 126– 133	Uses glyphosate formulations, investigates toxicity and endocrine-disruption	link.springer.com/article/10.1007/s00244-006-0154-8
*Bolognesi, C, Carrasquilla, G, Volpi, S, Solomon, KR, & Marshall, EJP.	2009	genotoxicity/ epidemiology	glyphosate + cosmo-flux	human	Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate.Journal of Toxicology and Environmental Health, Part A, 72(15–16), 986–997	Columbian aerial spray program; uses formulation as exposure to glyphosate; measurement of binucleated lymphocytes with micronuclei as DNA damage	www.tandfonline.com/doi/abs/10.1080/15287390902929741#.Ve0iNfk0VcY
Brewster, DW, Warren, J, & Hopkjns, WE.	1991	metabolism	glyphosate	SD rat	Metabolism of glyphosate in Sprague-Dawley rats: tissue distribution, identification, and quantitation of glyphosate-derived materials following	Tissue distribution study, shows no persistence in	toxsci.oxfordjournals.org/content/17/1/43.short

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	Website
					a single oral dose.Toxicological Sciences, 17(1), 43–51	body after single oral dose	
Brown, LM, Burmeister, LF, Everett, GD, & Blair, A.	1993	carcinogenicity/epidemiology	unknown formulation	human	Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes & Control, 4(2), 153–156	No direct reference to glyphosate or roundup; shows little evidence of association between pesticides and multiple myeloma	link.springer.com/article/10.1007/BF00053156
Cattani, D, Cavalli, VLDLO, Rieg, CEH, Domingues, JT, Dal-Cim, T, Tasca, CI, & Zamoner, A.	2014	oxidative stress	Roundup	rat	Mechanisms underlying the neurotoxicity induced by glyphosate-based herbicide in immature rat hippocampus: Involvement of glutamate excitotoxicity. Toxicology, 320, 34–45	Uses formulation; neurotoxic effects on rat hippocampus	www.sciencedirect.com/science/article/pii/S0300483X14000493
Çavuşoğlu, K, Yapar, K, Oruç, E, & Yalçın, E.	2011	oxidative stress	Roundup	SA mouse	Protective effect of Ginkgo biloba L. leaf extract against glyphosate toxicity in Swiss albino mice.Journal of medicinal food, 14(10), 1263–1272	Uses formulation; i.p. to mice; studies the effect of Ginkgo against effects seen	online.liebertpub.com/doi/abs/10.1089/jmf.2010.0202
Chruscielska, K, Brzezinski, J, Kita, K, Kalhorn, D, Kita, I, Graffstein, B, & Korzeniowski, P.	2000	toxicity			Glyphosate. Evaluation of chronic activity and possible far-reaching effects. Part 1. Studies on chronic toxicity. Pestycydy, 3	Chronic toxicity study review	

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	Website
Coalova, I, de Molina, MDCR, & Chaufan, G.	2014	oxidative stress	atanor + impacto (adjuvant)	human (Hep-2 cell line)	Influence of the spray adjuvant on the toxicity effects of a glyphosate formulation. Toxicology in Vitro,28(7), 1306–1311	Uses formulation and adjuvant on Hep-2 cell line; shows toxicity and ROS	www.sciencedirect.com/science/article/pii/S0887233314001295
Cocco, P, Satta, G, Dubois, S, Pili, C, Pilleri, M, Zucca, M, 't Mannetje AM, Becker, N, Benavente, Y, de Sanjose, S, Foretova, L, Staines, A, Maynadie, M, Nieters, A, Brennan, P, Miligi L, Enna, MG & Boffetta, P.	2012	carcinogenicity/epidemiology	unknown formulation	human	Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occupational and environmental medicine, oemed—2012	No direct reference to glyphosate; based on pesticide exposure determined via survey	oem.bmj.com/content/early/2012/10/31/oemed-2012-100845.short
Culbreth, ME, Harrill, JA, Freudenrich, TM, Mundy, WR, & Shafer, TJ.	2012	MOA	glyphosate	human; mouse	Comparison of chemical-induced changes in proliferation and apoptosis in human and mouse neuroprogenitor cells. Neurotoxicology, 33(6), 1499–1510	Apoptosis induced by glyphosate, neurodevelopmental study; uses human and mouse neural cells	www.sciencedirect.com/science/article/pii/S0161813X12001271
Dennis, LK, Lynch, CF, Sandler, DP, & Alavanja, MC.	2010	carcinogenicity/epidemiology	unknown formulation	human	Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Environmental Health	Uses formulation; no results relating to glyphosate	www.ladep.es/ficheros/documentos/10(35).pdf

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	Website
					Perspectives, 118(6), 812– 817		
*De Roos, A, Zahm, SH, Cantor, KP, Weisenburger, DD, Holmes, FF, Burmeister, LF, & Blair, A.	2003	carcinogenicity/epidemiology	unknown formulation	human	Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.Occupational and Environmental Medicine, 60(9), e11-e11.	Uses formulation; shows positive trend with NHL	oem.bmj.com/content/60/9/e11.short
*Dimitrov, BD, Gadeva, PG, Benova, DK, & Bineva, MV.	2006	genotoxicity	Roundup	mouse (bone marrow)	Comparative genotoxicity of the herbicides Roundup, Stomp and Reglone in plant and mammalian test systems. Mutagenesis, 21(6), 375–382	Comparative study using glyphosate formulation; negative results	mutage.oxfordjournals.org/content/21/6/375.short
*Engel, LS, Hill, DA, Hoppin, JA, Lubin, JH, Lynch, CF, Pierce, J, Samanic, C, Sandler, DP, Blair, A & Alavanja, MC.	2005	carcinogenicity/epidemiology	unknown formulation	human	Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. American Journal of Epidemiology, 161(2), 121–135	Uses formulation; glyphosate not directly referenced in the abstract; no clear association with breast cancer	aje.oxfordjournals.org/content/161/2/121.short
*Eriksson, M, Hardell, L, Carlberg, M, & Åkerman, M.	2008	carcinogenicity/epidemiology	unknown formulation	human	Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. International Journal of Cancer, 123(7), 1657–1663	Uses formulation; results were not adjusted for multiple exposures; shows increased risk of NHL for glyphosate	onlinelibrary.wiley.com/doi/10.1002/ijc.23589/pdf

*Considered by EFSA (2015)

APPENDIX D—LIST OF REFERENCED STUDIES IN THE IARC MONOGRAPH NOT RECOMMENDED FOR EVALUATION BY THE OCS

The following table outlines the references in the IARC Monograph 112 that are not considered to require further evaluation and the reasons for exclusion.

Table 3: List of excluded studies based on criteria outlined in Appendix A

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Abraxis	2005			Plate kit	No	No
Acquavella	2004			Biomonitoring	No	No
Akcha	2012	genotoxicity		Not a relevant human model—oyster	No	No
Alavanja	1996	n/a	Yes	Outline of agricultural health study	No	No
Alvarez-Moya	2011	genotoxicity		Not a relevant human model	No	No
Andreotti	2009	carcinogenicity		No direct reference to glyphosate	No	Yes
Aris	2011			Maternal and foetal exposure to pesticides associated with GM foods	No	No
Band	2011	carcinogenicity		No direct reference to glyphosate, reference to malathion	No	Yes
Battaglin	2005			Transformation products in streams	No	No
Bernal	2010			Liquid chromatography	No	No
Blair	2011			Exposure misclassification in AHS	No	No
Blakley	1997	immune function		Not relevant to carcinogenicity classification	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Bonini	2006			Oxidation of dye in antioxidant activity assay	No	No
Borggaard	2008			Fate of glyphosate in soil	No	No
Botero-Coy	2013a			Improvements in analytical assay	No	No
Botero-Coy	2013b			Liquid chromatography of glyphosate in rice, maize, soybeans	No	No
Brown	1990	carcinogenicity	Yes	No reference to glyphosate	No	No
Bruch	2013			Leaching assessment programme	No	No
Cantor	1992	carcinogenicity	Yes	No direct reference to glyphosate, reference to malathion	No	No
Carreon	2005	carcinogenicity	Yes	No direct reference to glyphosate	No	Yes
Cattaneo	2011	oxidative stress		Not a relevant human model—fish	No	No
Cavalcante	2008	genotoxicity		Not a relevant human model—fish	No	No
Cavas	2007	genotoxicity		Not a relevant human model—goldfish	No	No
CCM International	2011			Outlook for Chinese glyphosate industry	No	No
Centre de Toxicologie du Quebec	1988			Exposure of forestry workers	No	No
Chandra	1994			Spontaneous renal lesions in strains of mice	No	No
Chang	2011			Fate of glyphosate in the environment	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Chen	2012			DNA damage in cyanobacteria	No	No
Chen	2013			Residues on fruit and vegetables	No	No
Chen	2009			Glyphosate poisoning in Taiwan	No	No
Clair	2012	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Clements	1997	genotoxicity		Not a relevant human model—tadpoles	No	No
ColomboPage News Desk	2014			Media—Sri Lanka lifts ban on sale of glyphosate	No	No
Connors	2004	genotoxicity		Not a relevant human model—mussel	No	No
Costa	2008	oxidative stress		Not a relevant human model—tadpoles	No	No
Curwin	2005			Pesticide contamination inside farm and non-farm homes	No	No
Curwin	2007			Urinary pesticide conc.	No	No
de Castilhos	2013	genotoxicity		Not a relevant human model—fish	No	No
de Marco	1992			Soil breakdown of glyphosate	No	No
de Menezes	2011	oxidative stress		Not a relevant human model—fish	No	No
de Roos	2005a	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
de Roos	2005b	carcinogenicity	Yes	Response to criticism	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
de Souza	2013	genotoxicity		Not a relevant human model—fish, used roundup, concluded the results seen could have been due to excipients	No	No
Dill	2010			Glyphosate development, applications and properties	No	No
dos Santos	2014	genotoxicity		Not a relevant human model—clam, uses atrazine and glyphosate formulation	No	No
Duke	2009			Glyphosate resistant crops	No	No
EC	2002			EU report on glyphosate	No	No
EFSA	2008			Residues report	No	No
el-Gendy	1998	immune response		Not relevant to carcinogenicity classification, not a relevant human model—fish	No	No
EPA	1980a	teratology		Not relevant to carcinogenicity endpoint	No	No
EPA	1980b	teratology		Not relevant to carcinogenicity endpoint	No	No
EPA	1992			Glyphosate in drinking water	No	No
EPA	1997			Pesticides sales and usage	No	No
EPA	2015			Tox database	No	No
EPA	1991c			Peer review of glyphosate	No	No
EPA	1993a			Glyphosate RED	No	No
EPA	1993b			Glyphosate RED factsheet	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
EPA	2011			Pesticides sales and usage	No	No
Eustis	1994			Multiple-section histo sampling	No	No
FAO	2000			Review	No	No
Farm Chemicals International	2015			Crop protection database	No	No
Ferreira	2010	oxidative stress		Not a relevant human model—fish	No	No
Forgacs	2012			Model for evaluation of reproductive and developmental toxicants	No	No
Freedonia	2012			Industry forecast	No	No
Frescura	2013			Not a relevant human model—fish, glyphosate used as a positive control	No	No
Geret	2013	genotoxicity		Not a relevant human model—oyster	No	No
Gholami-Seyedkolaei	2013	genotoxicity		Not a relevant human model—fish	No	No
Glusczuk	2011	oxidative stress		Not a relevant human model—fish	No	No
Glyphosate Task Force	2014			Glyphosate use	No	No
Granby	2001			Development of a method to measure glyphosate in cereal	No	No
Guha	2013			Residential pesticide use	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Gui	2012			Neurotoxic effects, parkinsonism	No	No
Guilherme	2010	genotoxicity		Not a relevant human model—eel	No	No
Guilherme	2012a	oxidative stress		Not a relevant human model—fish	No	No
Guilherme	2012b	oxidative stress		Not a relevant human model—fish	No	No
Guilherme	2014a	oxidative stress		Not a relevant human model—fish	No	No
Guilherme	2014b	genotoxicity		Not a relevant human model—fish	No	No
Hardell	1999	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
Hardell	2002	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
HaYes	1991			Handbook of pesticide toxicology	No	No
Hidalgo	2004			Liquid chromatographic method in water	No	No
Hilton	2012			Global glyphosate market	No	No
Humphries	2005			Residues in atmosphere, soil and water	No	No
IARC	2006			Data for the monographs	No	No
IARC	2014			Key characteristics of carcinogens	No	No
IPCS	1994			Glyphosate environmental health criteria	No	No
IPCS	1996			Glyphosate data sheet	No	No
IPCS	2005			Glyphosate safety card	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Jacob	1988			Metabolism of glyphosate in pseudomonas	No	No
Jan	2009			Residues measured by spectrophotometric method	No	No
Jauhaianen	1991			Occupational exposure	No	No
Johnson	2005			Occupational exposure	No	No
Kalyanaraman	2012			Measuring reactive oxygen and nitrogen species method	No	No
Kavlock	2012			EPA toxcast program	No	No
Kojima	2004	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Kojima	2010	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Kolpin	2006			Glyphosate and AMPA in US streams	No	No
Kreutz	2011			Not a relevant human model—catfish	No	No
Kuang	2011			Analytical methods for determination of herbicides in food	No	No
Kumar	2014			Not relevant to carcinogenicity classification	No	No
Lavy	1992			Occupational exposure	No	No
Lee	2001			Methods of determination in water	No	No
Lopes	2014			Not relevant to carcinogenicity classification, not a relevant human model—fish	No	No
Lubick	2009			Environmental impact of the cocaine strategy	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Lushchak	2009	oxidative stress		Not a relevant human model—goldfish	No	No
Mahendrakar	2014			Effects and treatment of poisoning	No	No
Malatesta	2008	cytotoxicity		Uses round-up formulation	No	No
Mance	2012			Magazine article, not relevant to carcinogenicity classification	No	No
Mariager	2013			Acute effects, not relevant to carcinogenicity classification	No	No
Marques	2014	genotoxicity		Not a relevant human model—fish	No	No
Marques	2015	genotoxicity		Not a relevant human model—fish	No	No
Maza-Joya	2013	genotoxicity		Not a relevant human model—frogs	No	No
McDuffie	2001	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
McQueen	2012			Maternal and prenatal exposure in communities	No	No
Ministry of Chemicals & Fertilizers	2008			Industry performance report	No	No
MLHB	2013			Glyphosate in human urine samples	No	No
Modesto	2010a	oxidative stress		Not a relevant human model—fish	No	No
Modesto	2010b	oxidative stress		Not a relevant human model—fish	No	No
Mohamed	2011	immune response		Not a relevant human model—freshwater snail	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Moreno	2014	genotoxicity		Not a relevant human model—fish	No	No
Mortensen	2000			Effects and treatment of poisoning	No	No
Motojyuku	2008			Measurement of glyphosate in human serum by GC-MS	No	No
Muangphra	2014	genotoxicity		Not a relevant human model–earthworm	No	No
Nakashima	2002	immune response		Not relevant to carcinogenicity classification	No	No
NCBI	2015			Open chemistry database	No	No
Nedelkoska	2004			HPLC of glyphosate in water	No	No
Nordstrom	1998	carcinogenicity		Already reviewed by OCS	Yes	No
NPIC	2010			Fact sheet	No	No
Nwani	2013	oxidative stress		Not a relevant human model—fish	No	No
Omran	2013	endocrine disruption		Not relevant for carcinogenicity classification	No	No
Ortiz-Ordonez	2011			Not a relevant human model—fish	No	No
Paganelli	2010	teratology		Not a relevant human model—frogs	No	No
Park	2013			Effects and treatment of poisoning	No	No
Perry	2014			Reporting of exposures to pesticides in the UK	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Pesticides Residues Committee	2007			Pesticide monitoring report	No	No
Pesticides Residues Committee	2008			Pesticide monitoring report	No	No
Pesticides Residues Committee	2010			Pesticide monitoring report	No	No
Piola	2013	toxicity		Not a relevant human model—earthworm	No	No
Poletta	2009	genotoxicity		Not a relevant human model—caiman	No	No
Poletta	2011	genotoxicity		Not a relevant human model—caiman	No	No
Republica de El Salvador	2013			Notice on prohibited pesticides	No	No
Roberts	2010			Effects and treatment of poisoning	No	No
Rueppel	1977			Metabolism of glyphosate in soil and water	No	No
Rumack	2015			Effects and treatment of poisoning	No	No
Sanchis	2012			Glyphosate in groundwater	No	No
Siddiqui	2012	genotoxicity		Not a relevant human model—fenugreek	No	No
Simonsen	2008			Glyphosate and AMPA in soil	No	No
Sinhorin	2014	oxidative stress		Not a relevant human model—fish	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Slaninova	2009	oxidative stress		Not a relevant human model—fish	No	No
Sorensen	1999			Effects and treatment of poisoning	No	No
Sribanditmongkol	2012			Effects and treatment of poisoning	No	No
Stella	2004			Effects and treatment of poisoning	No	No
Szekacs	2012			Book about control of weeds	No	No
Temple	1992			Effects and treatment of poisoning	No	No
Thongprakaisang	2013	endocrine disruption		Not relevant for carcinogenicity classification	No	No
Tian	2012			Synthetic alternative to glyphosate	No	No
Tice	2013			Human hazard characterisation of chemicals	No	No
Tomlin	2000			Pesticide manual	No	No
Transparency Market Research	2014			Global glyphosate market	No	No
Truta	2011	genotoxicity		Not a relevant human model—barley	No	No
Tu	2001			Weed control handbook	No	No
Uren Webster	2014	reproductive/ developmental		Not a relevant human model—fish	No	No
Vasiluk	2005			Oral bioavailability of glyphosate in vitro	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Vera-Candioti	2013	genotoxicity		Not a relevant human model—fish	No	No
Walsh	2000	reproductive/ developmental		Not relevant to carcinogenicity classification	No	No
Wang	2012	genotoxicity		Not a relevant human model—cyanobacterium	No	No
Wester	1991			Not relevant to carcinogenicity classification, dermal absorption	No	No
Xie	2005	endocrine disruption		Not relevant to carcinogenicity classification, not a relevant human model—fish	No	No
Yadav	2013	genotoxicity		Not a relevant human model—tadpoles	No	No
Yin	2011			Glyphosate use review	No	No
Yoshioka	2011			Measurement of glyphosate by liquid chromatography	No	No
Zahm	1990	carcinogenicity	Yes	2,4-D study	No	No
Zhao	2013	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Zouaoui	2013			Effects and treatment of poisoning	No	No

ABBREVIATIONS

APVMA	Australian Pesticides and Veterinary Medicines Authority
AHS	Agricultural health survey
BfR	Federal Institute for Risk Assessment
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organisation
HSIS	Hazardous Substances Information System
IARC	International Agency for Research on Cancer
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
NTP	National Toxicological Program
OCS	Office of Chemical Safety
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

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IPCS 2009, *Environmental health criteria 240: Principles and methods for the risk assessment of chemicals in food*, International Programme on Chemical Safety, Geneva, Switzerland, available at http://www.who.int/ipcs/publications/ehc/methodology_alphabetical/en/.