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**Australian Pesticides and
Veterinary Medicines Authority**



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**Regulatory position:
consideration of the
evidence for a formal
reconsideration of
glyphosate**

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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 Codes.

A reconsideration may be initiated when new research or evidence raises concerns about the use or safety of a particular chemical, a product containing that chemical, or its label. The scope of each reconsideration can cover a range of areas including human health (toxicology, public health, occupational health and safety), the environment (environmental fate and ecotoxicology), residues and trade, chemistry, efficacy or target crop/animal safety. However, the scope of each reconsideration is determined on a case-by-case reflecting the specific issues raised by the new research or evidence.

The reconsideration process (illustrated in Figure 1) 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 target animals, humans or the environment) or efficacy of a registered chemical, the APVMA assesses the new information to determine whether a formal reconsideration of that chemical and/or products containing that chemical should be initiated.

In undertaking this process, the APVMA works in close cooperation with external experts including the Department of Health, Food Standards Australia New Zealand (FSANZ), the Department of the Environment and Energy and the state departments of agriculture, as well as other expert advisers as appropriate.

This document sets out the nomination assessment process for glyphosate that was initiated following the classification of glyphosate as 'probably carcinogenic to humans' by the International Agency for Research on Cancer (IARC) in March 2015.

This document and the technical reports relating to glyphosate are available from the APVMA website at www.apvma.gov.au. The technical reports are:

- Review of IARC Monograph 112 (Glyphosate): Tier 1
- Review of IARC Monograph 112 (Glyphosate): Tier 2.

1. Nomination	<p>Nomination. Any person or group (including the APVMA and its partner agencies) may nominate an active constituent, product or label for reconsideration. The APVMA assesses the supporting scientific information and determines whether a reconsideration is warranted. Not all nominations will proceed to a formal reconsideration—there are other regulatory pathways available that may more efficiently address concerns.</p> <p>The APVMA nominated glyphosate for reconsideration following the classification of glyphosate as ‘probably carcinogenic to humans’ by the International Agency for Research on Cancer in 2015.</p>	
2. Prioritisation	<p>Prioritisation. The APVMA (with input from its advisory agencies) determines the priority of the reconsideration.</p>	
3. Scoping and work plan	<p>Scope. A scope document is prepared that outlines the areas of concern to be reconsidered. From 1 July 2015 the APVMA is legislatively required to publish a work plan for all reconsiderations to provide predictability about the timeframe for the reconsideration.</p>	
4. Notice of reconsideration	<p>Notice of reconsideration. To begin the reconsideration, the APVMA gives each holder a written Notice of Reconsideration that invites the holder to make a written submission to the APVMA. The holder is legally obliged to submit any available data relevant to the scope of the reconsideration. The APVMA supplements the submitted data with data available in the public domain (eg peer-reviewed scientific journal articles or international assessment reports).</p>	
5. Assessment	<p>Toxicology assessment. The toxicology assessment characterises all of the adverse health effects that a compound may cause and establishes health-based guidance values (also known as public health standards) for exposure to the chemical. The toxicology assessment recommends first aid directions, poisons scheduling and any necessary warnings for product labels.</p>	<p>Environment risk assessment. Where indicated in the scope of the reconsideration, an environmental risk assessment is conducted. The environmental risk assessment may include an evaluation of environmental fate and ecotoxicology.</p>
	<p>Human exposure assessment. The Toxicology assessment findings are used in the Occupational Health and Safety (human exposure) assessment. This assessment recommends safety directions, re-entry periods and restraints for all the uses supported by the assessment.</p>	<p>Residues and dietary exposure risk assessment (includes trade). The available residues data are used in the residues and dietary exposure risk assessment. This assessment recommends withholding periods, MRLs and restraints for all use patterns supported by this assessment. It also considers the potential trade risks arising from all the supported uses of products.</p>
	<p>Efficacy: If included in the scope of the review efficacy assessments are conducted by the APVMA.</p>	

<p>6. Draft regulatory measure</p>	<p>Interim Regulatory Action. At any time during a reconsideration, the APVMA may take regulatory action to mitigate any risks identified in relation to the use of a chemical. The aim of any such action is to protect human health or the environment (or both) while a final decision is being reached through the reconsideration process.</p> <p>Proposed Regulatory Decision. The APVMA considers all the assessments and develops draft recommendations for the reconsideration which summarise the results of the assessment, identified risks, risk mitigation measures, proposed review findings and draft regulatory decisions. The PRD and the component assessment reports are released for public consultation.</p>
<p>7. Consultation</p>	<p>Consultation. Further data or information may be submitted to the APVMA from a range of stakeholders including holders, users of the chemicals, peak industry bodies, interest groups, non-government organisations, state and territory governments or the public.</p> <p>Usually a 3-month public consultation period is conducted following publication of the PRD. Any further data or information submitted during consultation will be taken into consideration before making the final regulatory decision.</p>
<p>8. Regulatory decision</p>	<p>Regulatory decision. After the public consultation period has closed, the APVMA assesses all the comments received and amends the assessment, review findings and the proposed regulatory measures as necessary. We then make the final regulatory decision.</p> <p>There are three possible regulatory outcomes from a reconsideration:</p> <ul style="list-style-type: none"> • affirm the approvals or registrations • vary the relevant particulars or conditions and affirm the approval or registration, or • suspend or cancel the approval or registration. <p>The APVMA will affirm the approval or registration only if satisfied that it meets all statutory safety, efficacy, trade and labelling criteria and also complies with all requirements in the regulations</p> <p>If the active constituent, product or label does not meet the criteria as described above, the APVMA will examine whether the relevant particulars or conditions of the approval or registration can be varied so that the criteria can be met. This may include varying the instructions for use on the label.</p> <p>If product registrations or label approvals are cancelled the APVMA will examine whether a phase out period for dealing with or using cancelled products or products bearing cancelled labels is appropriate. Additional instructions may be applied during phase out. If a phase out period is not appropriate then recall action may be required.</p>
<p>END OF RECONSIDERATION (regulatory decision)</p>	
<p>9. Implementation</p>	<p>Implementation. Once the decision is made to affirm, cancel or vary conditions of registrations or approvals the APVMA will send written Notices to the holders of registrations and approvals and publish Notices of affirmation, variation of conditions, and cancellation of actives, products or label approvals.</p> <p>These Notices will include brief statements of the reasons for the actions, relevant particulars for any affirmed approvals or registrations and any appropriate instructions of use or phase-out periods for cancellations. The APVMA will publish details of any applicable phase out periods if any approvals of actives, registration of products or label approvals are cancelled. The maximum legislated phase out period is 12-months.</p>

Figure 1: The chemical reconsideration process

SUBMISSIONS FROM THE PUBLIC ARE INVITED

This draft regulatory position report:

- outlines the APVMA chemical reconsideration process
- advises interested parties how to respond to the assessment
- summarises the nomination assessment methodology and outcomes
- outlines the proposed regulatory position to be taken in relation to the nomination for reconsideration of glyphosate and products containing glyphosate.

The APVMA invites persons and organisations to submit their comments and suggestions on this nomination assessment report directly to the APVMA. Comments on this report will be assessed by the APVMA before the report is finalised and the final regulatory position report is published.

Submissions can be sent to:

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Preparing your comments for submission

Please limit any comments you have to the scientific justification for the proposed regulatory position on glyphosate.

When making your comments:

- clearly identify the issue and clearly state your point of view
- give reasons for your comments, supporting them with relevant scientific information and indicating the source of the information you have used.

Please try to structure your comments in point form, referring each point to the relevant section in the regulatory position report. This will help the APVMA assemble and analyse all of the comments it receives.

When making a submission, please include:

- contact name

- company name or group name
- postal address
- email address (if available)
- the date you made the submission.

Finally, tell us whether the APVMA can quote your comments in part or full.

Please note that, subject to the *Freedom of Information Act 1982*, the *Privacy Act 1988* and the Agvet Code, all submissions received may be made publicly available. They may be listed or referred to in any papers or reports prepared on this subject matter.

The APVMA reserves the right to reveal the identity of a respondent unless a request for anonymity accompanies the submission. If no request for anonymity is made, the respondent will be taken to have consented to the disclosure of their identity for the purposes of Information Privacy Principle 11 of the *Privacy Act 1988*.

The contents of any submission will not be treated as confidential or confidential commercial information unless they are marked as such and the respondent has provided justification for the material to be classified as confidential or confidential commercial information in accordance with the *Freedom of Information Act 1982* or the Agvet Code, as the case may be.

THE CLOSING DATE FOR SUBMISSIONS IS FRIDAY 30 DECEMBER 2016.

EXECUTIVE SUMMARY

Introduction

Glyphosate is a broad-spectrum, non-selective, post-emergent, systemic herbicide that kills or suppresses all plant types (except those genetically modified to be resistant to glyphosate) and is commonly used to control annual and perennial broadleaf and grassy weeds in various agricultural and non-agricultural settings. Glyphosate acts by disrupting the shikimic acid pathway, which is unique to plants, to prevent protein biosynthesis and kill the plant.

The first product containing glyphosate was registered for use in Australia in the 1970s, under the trade name 'Roundup®'. Products containing glyphosate that are registered for use in Australia are formulated as solutions, granules, aerosols and gels and are generally applied using ground or aerial equipment.

Concerns have recently been raised about human exposure to glyphosate, following an assessment by the International Agency for Research on Cancer (IARC) that re-classified glyphosate as 'probably carcinogenic to humans'.

The APVMA chose to consider glyphosate for reconsideration following the publication of the IARC Monograph 112 in July 2015. Once a chemical has been nominated for reconsideration, the APVMA examines the new information to determine whether there are sufficient scientific grounds to warrant placing the chemical under formal reconsideration. This regulatory position report represents the outcome of that scientific nomination assessment process.

Evaluation methodology: a weight-of-evidence approach

The nomination assessment process involved a scientific weight-of-evidence evaluation of information in the IARC monograph, risk assessments undertaken independently by regulatory agencies in other countries and expert international bodies, in addition to Adverse Experience Reports (AERs) submitted to the APVMA. A weight-of-evidence assessment involves an examination of the quality, biological relevance and consistency of studies, assessment reports and scientific conclusions according to the scientific method.

The APVMA commissioned a review of the IARC monograph by the Office of Chemical Safety (OCS) within the Department of Health. This review was conducted in two phases: Tier 1 involved conducting a preliminary scoping review of the IARC monograph to ascertain the relevance of the carcinogenicity classification of glyphosate and any implications that this may have for glyphosate approvals and registrations in Australia; Tier 2 involved conducting a detailed assessment of those studies that were identified during the Tier 1 assessment as requiring further evaluation.

The APVMA also reviewed a number of very recent international assessments of glyphosate including those undertaken by the Joint Food and Agriculture Organisation of the United Nations/World Health Organisation (FAO/WHO) Meeting on Pesticide Residues, the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA), Health Canada and the New Zealand Environmental Protection Authority (NZ EPA).

Assessment of the IARC glyphosate monograph

The OCS undertook a screening level assessment of the IARC monograph (Tier 1) and identified 19 references relevant to the carcinogenicity classification of glyphosate requiring a more in-depth evaluation, with an additional 74 references requiring further review to determine their relevance—the APVMA utilised recent independent international assessments of these references. Following the assessment of the 19 studies relevant to the IARC carcinogenicity classification of glyphosate (Tier 2), the OCS concluded that there did not appear to be any new information to indicate that glyphosate poses a carcinogenic or genotoxic risk to humans.

Evaluation of international assessments of glyphosate

The JMPR, EFSA, ECHA and Health Canada assessments of glyphosate all evaluated the publicly available data that was considered in the IARC monograph, as well as other published and unpublished data not available to IARC. In addition, the NZ EPA assessed the publicly available data contained in the IARC monograph and assessments by JMPR and EFSA.

Carcinogenicity studies in laboratory animals: EFSA concluded that the weight-of-evidence is that there is no carcinogenic risk to humans related to the use of glyphosate. JMPR concluded that glyphosate is not carcinogenic in rats but was unable to exclude the possibility that glyphosate is carcinogenic in mice at very high doses. The assessment conducted by ECHA concluded that there was no evidence of carcinogenicity in mice or rats due to a lack of statistical significance in pair-wise comparisons, a lack of consistency across studies, that slightly increased tumour incidences were only evident at doses exceeding the maximum tolerated dose, the absence of early cellular changes or pre-neoplastic lesions and/or incidences that tumour incidences were in the range of normal biological variation. Health Canada concluded that there was no evidence that glyphosate was carcinogenic or genotoxic in rats but that there was some evidence for a marginal increase in the incidence of ovarian tumours in mice only at the highest tested dose—however, these results were considered to be of low concern for human health risk assessment. The assessment commissioned by the NZ EPA concluded that long-term carcinogenicity studies produced consistently negative results and that the IARC assessment attributed inappropriate weight to the studies included in its assessment, which did not demonstrate a dose-response relationship, reported only minor positive results at the maximum dose tested, did not consider relevant historical control data and excluded some studies that did not report positive associations between glyphosate exposure and carcinogenicity.

Genotoxicity studies: JMPR concluded that the overall weight-of-evidence is that glyphosate is unlikely to be genotoxic to humans at anticipated dietary exposures. EFSA, ECHA, Health Canada and the NZ EPA similarly concluded that the weight-of-evidence does not support the hypothesis that glyphosate is genotoxic. Again, these assessments concluded that the evidence presented by IARC as representative of strong evidence for genotoxicity and oxidative stress was primarily based on exposure scenarios not relevant to humans.

Epidemiological studies: ECHA concluded that the value of the human data for hazard classification purposes is questionable and limited because it is difficult to distinguish between the effects of the active constituent and co-formulants, as humans are never exposed to the active constituent alone, and humans are exposed to a many environmental chemicals, making it difficult to attribute health effects to one specific chemical. The JMPR, EFSA, ECHA and NZ EPA assessments concluded that while there was some evidence of a positive statistical association between glyphosate exposure and the risk of non-Hodgkin's lymphoma (NHL) in some retrospective

case-control studies, the one large, high-quality prospective cohort study found no statistical association at any exposure level. The EFSA assessment further noted that it was not possible to differentiate between the effects of glyphosate and the co-formulants in the epidemiological data available. The ECHA assessment describes a number of papers that did not identify a risk between glyphosate exposure and various specific cancer types, including NHL, lymphomas in general or multiple myeloma. The ECHA concluded that a comprehensive review of epidemiological studies assessing the possible association between glyphosate exposure and cancer found no consistent pattern of positive associations that would suggest a causal relationship between glyphosate exposure and the development of cancer in adults or children. The ECHA further concluded that, while epidemiological data is of limited value for detecting the carcinogenic potential of a pesticide, the data do not provide convincing evidence for an association between glyphosate exposure in humans and any cancer type. The Health Canada assessment concluded that the majority of epidemiological data considered by IARC lacked adequate characterisation of glyphosate exposure and that as a result these studies were of limited use for supplementing the hazard assessment of glyphosate.

Assessment of adverse experience reports (AER)

Between 1996 and 2013, a total of four AERs relating to human safety were submitted to the APVMA's Adverse Experience Reporting Program (AERP). All were classified as 'possible' or 'probable' by the APVMA. Of the four reports, one was of skin irritation while the remaining three were reports of eye irritation. The APVMA is confident that the current safety and use directions included on approved labels for products containing glyphosate are sufficient to mitigate these known adverse effects.

Proposed regulatory position

Based on this nomination assessment, the APVMA concludes that the scientific weight-of-evidence indicates that:

- exposure to glyphosate does not pose a carcinogenic or genotoxic risk to humans
- there is no scientific basis for revising the APVMA's satisfaction that glyphosate or products containing glyphosate:
 - would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
 - would not be likely to have an effect that is harmful to human beings
 - would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment
 - would be effective according to criteria determined by the APVMA by legislative instrument, and
 - would not unduly prejudice trade or commerce between Australia and places outside Australia.
- **there are no scientific grounds for placing glyphosate and products containing glyphosate under formal reconsideration**
- the APVMA will continue to maintain a close focus on any new assessment reports or studies that indicate that this position should be revised.

1 INTRODUCTION

Glyphosate [*N*-(phosphonomethyl)glycine] is an aminophosphonic analogue of glycine, which is a naturally occurring amino acid. Glyphosate is classified as an organophosphate as it contains carbon and phosphorous; however, it does not affect the nervous system the way other organophosphates do. Glyphosate is a broad-spectrum, non-selective, post-emergent, systemic herbicide that kills or suppresses all plant types, except those that have been genetically modified to be resistant to glyphosate, 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, therefore when applied post-emergence, glyphosate demonstrates no pre-emergence or residual activity.

The water solubility of technical-grade glyphosate acid can be increased by formulating it primarily as its isopropylamine salt, or less commonly as monoammonium, potassium, trimesium, monoethanolamine or dimethylammonium salts, or various combinations of those salts. Furthermore, commercial formulated products contain various non-ionic surfactants to facilitate uptake by plants. Some commercial formulations also contain other active constituents in an attempt to mitigate herbicide resistance.

Glyphosate is taken up by the leaves and other green parts of the plant and translocated to the entire plant systemically. As a result, glyphosate is capable of total destruction of the plant. Glyphosate binds to and blocks the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), thereby disrupting the shikimic acid pathway and preventing the plant from synthesising the essential aromatic amino acids required for protein biosynthesis (phenylalanine, tyrosine and tryptophan), killing the plant. As this pathway is unique to plants and therefore is not present in mammals, glyphosate demonstrates low vertebrate toxicity.

The first product containing glyphosate was registered for use in Australia in the 1970s, under the trade name 'Roundup'. Products containing glyphosate that are registered for use in Australia are formulated as solutions, granules, aerosols and gels (Table 1) and can be applied using ground or aerial equipment, as well as some specialised application methods (eg aerosol).

1.1 Current regulatory status of glyphosate in Australia

As of February 2016 there were 80 active constituent approvals for glyphosate and 471 registered products containing glyphosate. Of the 471 registered products, 130 are for home garden use and 370 are for commercial/agricultural use (Table 1). In these registered products, glyphosate is present at varying concentrations and is formulated in various salt forms, including ammonium, dimethylammonium, isopropylamine, mono-ammonium, monoethanolamine and potassium salts. Some registered products contain additional active constituents, including amitrole, ammonium thiocyanate, butafenacil, carfentrazone-ethyl, diflufenican, imazapyr and oxyfluorfen.

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, such as:

- croplands for the control of emerged weeds prior to crop and fallow establishment, minimum tillage farming, direct drilling into seedbed, for pre-harvest desiccation

- non-cultivated land (eg industrial, commercial, domestic and public service areas) and rights of way
- forests, orchards, vines and plantations
- home garden use on rockeries, garden beds, driveways, fence lines, firebreaks, around buildings and prior to planting new lawns and gardens
- aquatic areas (restricted to dry drains and channels, dry margins or dams, lakes and streams)
- aquatic weed control and control of weeds on margins of dams, lakes and streams or in channels, drains or irrigation (selected products only).

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.

Table 1: Formulation types for glyphosate products

Formulation type	Level of active constituent	Product type
Aqueous concentrate	3.6 g/L	Home garden
	7.2 g/L	Home garden
	60 g/L	Commercial
	100 g/L	Home garden
	150 g/L	Commercial
	300 g/L	Commercial
	360 g/L	Home garden and commercial
	450 g/L	Home garden and commercial
	470 g/L	Commercial
	480 g/L	Commercial
	490 g/L	Home garden and commercial
	500 g/L	Home garden and commercial
	510 g/L	Commercial
	540 g/L	Home garden and commercial
	Soluble concentrate	7.2 g/L
15.2 g/L		Home garden
143 g/L		Home garden
150 g/L		Commercial

Formulation type	Level of active constituent	Product type
	360 g/L	Home garden and commercial
	450 g/L	Commercial
	470 g/L	Commercial
	480 g/L	Commercial
	490 g/L	Home garden
	495 g/L	Commercial
	500 g/L	Commercial
	510 g/L	Commercial
	517 g/L	Commercial
	535 g/L	Commercial
	540 g/L	Home garden and commercial
	570 g/L	Commercial
	600 g/L	Commercial
Emulsifiable concentrate	360 g/L	Commercial
Suspension concentrate	225 g/L	Home garden and commercial
	360 g/L	Home garden and commercial
	450 g/L	Commercial
	510 g/L	Commercial
	600 g/L	Commercial
	700 g/L	Commercial
Water dispersible granule	680 g/kg	Home garden and commercial
	690 g/kg	Commercial
	700 g/kg	Commercial
	835 g/kg	Commercial
Water soluble granule	680 g/kg	Commercial
	700 g/kg	Commercial
	720 g/kg	Commercial

Formulation type	Level of active constituent	Product type
	800 g/kg	Commercial
	840 g/kg	Commercial
	900 g/kg	Commercial
	875 g/kg	Commercial
Aerosol	10 g/kg	Home garden
Liquid	7.2 g/L	Home garden
	360 g/L	Home garden and commercial
	450 g/L	Commercial
Liquid concentrate	570 g/L	Commercial
Emulsion, oil in water	4.8 g/L	Home garden
	25.6 g/L	Home garden
	432 g/L	Commercial
Gel	7.2 g/L	Home garden
	40 g/L	Home garden
Dry flowable	225 g/L	Home garden
Other liquids to be applied undiluted	7.2 g/L	Home garden
	7.4 g/L	Home garden
	16 g/L	Home garden

Previous reconsideration of glyphosate by the APVMA in 1996

A formal reconsideration of glyphosate was initiated following concern by the then Commonwealth Environment Protection Agency that certain surfactants in glyphosate formulations were acutely toxic to tadpoles at concentrations that are likely to occur in shallow water when products were used according to approved label instructions. Seventy five products were placed under review and all 27 holders were invited to provide information to the APVMA (then the National Registration Authority; NRA) relating to the review.

The scope of the review was limited to:

- reviewing application methods of glyphosate formulations adjacent to aquatic environments of all registered agricultural products

- a proposal to include a warning statement on all agricultural glyphosate product labels precluding use on or adjacent to waterways unless otherwise authorised
- a proposal to only allow use of glyphosate formulations in sensitive aquatic situations where it can be demonstrated that there is no significant risk to the aquatic environment.

The conclusions of the reconsideration were that the aquatic toxicity of registered glyphosate formulations was undesirably high and was mainly due to the surfactants in the formulations. Therefore, a number of conditions of registration were modified to describe more clearly the situations in which products registered for use in aquatic situations could be used to avoid the risk of significant aquatic contamination. Use of the formulated products was restricted to dry drains and channels and dry margins of dams, lakes and streams. Warning statements on labels were amended to minimise any possible aquatic contamination. Only formulations with an acceptable margin of aquatic safety would be registered for controlling weeds growing in or over water. Holders were provided 12 months (until 30 June 1997) to make the necessary changes to their products. No changes were made to products registered solely for home garden use, as the risk of significant aquatic contamination was considered very low. The [final reconsideration report](#) is available on the APVMA website.

Response to claims that glyphosate is responsible for causing birth defects

In June 2011, Earth Open Source (EOS) published a document titled 'Roundup and birth defects: is the public being kept in the dark?' In this document, EOS questioned the safety of glyphosate and products that contain it. The claims made by EOS were:

- exposure to concentrations of glyphosate lower than those commonly used in agriculture and the home garden have been linked to developmental malformations affecting the skull, face, brain and spinal cord in frog and chicken embryos
- a range of developmental malformations, as well as endocrine disruption and reproductive toxicity have been observed in humans and experimental animals following exposure to glyphosate
- a variety of *in vitro* test systems have demonstrated that glyphosate can induce damage to DNA and genetic material in laboratory animals and humans
- glyphosate exposure has been linked to cancer of the testis in rats, skin cancer in mice and blood system cancers in humans
- glyphosate exposure has been linked to neurotoxicity and the development of Parkinson's disease in humans.

The APVMA commissioned an expert review of that document, which was published in July 2013, to address the concerns raised in the EOS article. In doing so, the APVMA evaluated both the published studies cited in the EOS document and other more recent publications and archived toxicology studies of glyphosate, compared the EU reviews of glyphosate with reviews prepared by other regulators, assessed the scientific merit of the claims made by EOS and the research upon which those claims were based and considered whether there were implications for the registration of products containing glyphosate in Australia. **The full review of the EOS document can be found on the [APVMA archive website](#).**

A number of conclusions were made in the review of the EOS document. These included:

- The available data do not indicate that glyphosate products registered for use in Australia and used according to label instructions present any unacceptable risks to human health, the environment or trade.
- The weight- and strength-of-evidence demonstrate that glyphosate is not genotoxic, carcinogenic or neurotoxic.
- Developmental malformations caused by glyphosate in toad and chicken embryos are not predictive of a developmental hazard to humans because of the routes of administration used. Some studies have reported fetal skeletal abnormalities, toxicity to the male reproductive tract during puberty and interference with the maturation of the male reproductive organs during puberty; however, these studies were affected by flawed design, methodology and/or reporting and the claimed effects on puberty are inconsistent.
- Glyphosate is extremely unlikely to cause reproductive or developmental toxicity in humans under normal conditions of exposure.
- At present, there is no scientific justification for classifying glyphosate as an endocrine disrupter.
- Effects on hormonal regulation and cellular toxicity observed *in vitro* may have been confounded by surfactants present in formulated products.
- Most studies utilising formulated products containing glyphosate have not identified which chemical constituent was responsible for causing the reported effects, or characterised their mode of action.
- The toxicological studies cited by EOS do not demonstrate a need to revise the current Australian Acceptable Daily Intake (ADI) of 0.3 mg/kg bw/day for glyphosate.
- New information that emerges from the United States (US) and Canadian reviews of glyphosate will be considered by the APVMA.

The Poisons Standard (SUSMP)

The Poisons Standard, or the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) controls how medicines and poisons are made available to the public and classifies them into Schedules according to the level of regulatory control that is required in order to maintain public health and safety. Scheduling of medicines and poisons in Australia is a legislative requirement administered by the [Therapeutic Goods Administration](#) (TGA). However, the scheduling controls are implemented through State and Territory legislation, therefore the implementation of any restrictions imposed by the TGA may differ between States and Territories. Model provisions about packaging and labels, a list of products recommended to be exempt from the provisions and recommendations about other relevant controls are also included.

When making a scheduling decision, various criteria are considered, including toxicity, purpose of use, potential for abuse, safety in use and the need for the substance. Medicines and poisons are classified in one of ten Schedules. Agricultural, domestic and industrial poisons are generally listed in Schedules 5 (caution), 6 (poison) or 7 (dangerous poison), which represent increasingly stricter container and labelling requirements. Products for domestic use must not be listed in Schedule 7.

Glyphosate is classified as a Schedule 5 (caution) substance, which is defined as a substance with a 'low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with strong warnings and safety directions on the label'. To classify as a Schedule 5 poison, the substance must adhere to the following criteria:

- the substance is non-corrosive and has a low toxicity
 - acute oral toxicity (rat): 2000 mg/kg to 5000 mg/kg
 - acute dermal LD₅₀: > 2000 mg/kg
 - acute inhalation LC₅₀ (rat): > 3000 mg/m³ (4 hours)
- the substance has a low health hazard from repeated use and is unlikely to result in irreversible toxicity
 - no other significant toxicity (eg carcinogenicity, mutagenicity, etc)
- the substance is capable of causing only minor adverse effects to humans in normal use
 - specialised personal protective equipment should not be necessary for safe use
- the likelihood of injury during handling, storage and use can be mitigated through appropriate packaging and label warnings
- the substance has a low potential for causing harm
 - potential harm is reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

1.2 Health-based guidance values for glyphosate

Health-based guidance values are established by regulatory authorities (and international bodies such as the JMPR) for the purpose of determining whether human exposure (via the diet or occupationally) to a particular chemical is safe. Health-based guidance values provide quantitative information to risk managers to enable them to make informed, scientific decisions related to protecting human health.

Acceptable Daily Intake (ADI)

The ADI is the amount of a chemical that can be ingested daily over a lifetime without any appreciable risk to health. The ADI is based on the lowest NOAEL (No Observed Adverse Effect Level) for the most sensitive adverse effect relevant to humans.

The ADI for glyphosate in Australia is 0.3 mg/kg bw/day based on the No-Observed-Adverse-Effect Level (NOAEL) of 30 mg/kg bw/day (the highest tested dose) in a 3-generation reproduction dietary study in rats and using a 100-fold safety factor to account for extrapolation from animals to humans as well as variation in sensitivity within the human population.

Acute Reference Dose (ARfD)

The ARfD is an estimate of the amount of a substance in food and drinking water, expressed on a milligram per kilogram bodyweight basis, which can be ingested in a period of 24 hours or less without appreciable health risk to the consumer. In 1998, JMPR concluded that an ARfD must be determined for all pesticides, unless the toxicological profile indicated that the pesticide was unlikely to present an acute hazard. As the toxicology assessments of glyphosate indicate that there is no likelihood of glyphosate presenting an acute hazard to human health, an ARfD has not been established for glyphosate in Australia or overseas.

Maximum Residue Limits (MRL) and National Residue Survey (NRS)

The maximum amount of a chemical that is legally permitted in a food is known as the MRL. The MRL is based on good agricultural and chemical use practices to ensure that an agricultural or veterinary chemical has been used according to the directions on the approved label. The MRL is set well below the level that would result in the health-based guidance values being exceeded if the chemical is used according to the approved label instructions. Therefore, while exceedance of the MRL may indicate a misuse of the chemical, it does not normally indicate that there is a public health or safety concern. The APVMA sets MRLs for agricultural and veterinary chemicals in agricultural produce. The states and territories are responsible for enforcing MRLs.

The *Agricultural and Veterinary Chemicals Code Instrument No. 4 2012* ([MRL Standard](#)) lists MRLs for chemicals that may arise from the approved use of products containing that chemical, and outlines the definitions of those residues. The glyphosate residue definition is the sum of glyphosate, *N*-acetyl-glyphosate and aminomethylphosphonic acid (AMPA) metabolite, expressed as glyphosate.

As a part of the Department of Agriculture and Water Resources strategy to minimise chemical residues in agricultural product, the NRS facilitates testing of animal and plant products for pesticide and veterinary medicine residues, and environmental contaminants. In the 2013–14 NRS report, glyphosate residues greater than half of the MRL were not detected in any samples of barley, canola, chickpea, faba bean, field pea, lentil, lupin, maize, sorghum, triticale, wheat, wheat durum or macadamias. In 1/28 samples of oats, glyphosate residues above the MRL were detected (NRS 2014b), while in 1/37 almond samples, glyphosate residues lower than the MRL were detected (NRS 2014a). In the 2014–15 report (not yet published), glyphosate residues above the MRL were reported in 1/42 oat samples and residues below the MRL (above half of the MRL) were reported in 4/42 oat samples (NRS 2015). No residues greater than half of the MRL were detected in any samples of barley, chickpea, faba bean, canola, cowpea, field pea, lentil, maize, lupin, maize, mung bean, sorghum or wheat.

Australian Total Diet Study (ATDS)

The ATDS is coordinated by FSANZ to monitor Australia's food supply and ensure that food regulatory measures are protecting consumer health and safety. The ATDS assesses dietary exposure to pesticide residues, contaminants and other substances and is conducted approximately every two years.

The 23rd ATDS examined dietary exposure to 214 agricultural and veterinary chemicals, nine contaminants, 12 mycotoxins and 11 nutrients in 92 commonly consumed foods and beverages in 2008 (FSANZ 2011a). Glyphosate residues were detected in 2/12 samples of multigrain bread (mean concentration 0.016 mg/kg) (FSANZ 2011b). Based on these results, FSANZ estimated the mean consumer dietary exposure to glyphosate as 0.12, 0.81, 0.87, 0.97 and 1.4 µg/day in children aged 9 months, 2–5 years, 6–12 years and 13–16 years and adults aged 17 years and above, respectively (FSANZ 2011b). These estimated exposures are well below (214–25 000 times) the ADI of 0.3 mg/kg indicating that there are no safety concerns for Australian and New Zealand consumers.

Drinking water standards

The [Australian Drinking Water Guidelines](#) (the Guidelines) are a joint publication of the National Health and Medical Research Council (NHMRC) and the Agricultural and Resource Management Council of Australia and New Zealand. The Guidelines are not legally enforceable but provide a standard for water authorities and state health authorities to ensure the quality and safety of Australia's drinking water.

The health-related guideline value (expressed as mg/L) is the concentration or measure of a water quality characteristic that, based on present knowledge, does not result in any significant risk to the health of the consumer over a lifetime of consumption (NHMRC 2011). Health values are derived so as to limit intake from water alone to approximately 10% of the ADI, on the assumption that (based on current knowledge) there will be no significant risk to health for an adult having a daily water consumption of 2 litres over a lifetime. The current health-related guideline value for glyphosate in drinking water is 1 mg/L—excursions above this value would need to occur over a significant period of time to be of a health concern (NHMRC 2011). Glyphosate is generally not reported in the analysis of Australian waters and is unlikely to be found at levels that may cause health concerns.

1.3 Legislative basis for a reconsideration of glyphosate

The basis for a reconsideration of the registration and approvals for a chemical is whether the APVMA is satisfied that the safety, efficacy and trade criteria listed in sections 5A, 5B and 5C of the Agvet Code for continued registration and approval are being met. These requirements are that the use of the product, in accordance with instructions approved, or to be approved, by the APVMA for the product or contained in an established standard:

- would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
- would not be likely to have an effect that is harmful to human beings
- would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment
- would be effective according to criteria determined by the APVMA by legislative instrument, and
- would not unduly prejudice trade or commerce between Australia and places outside Australia.

The APVMA may also consider whether labels for containers for chemical products containing glyphosate meet the labelling criteria as defined in section 5D of the Agvet Code which requires that labels have adequate instructions relating to:

- the circumstances in which the product should be used
- how the product should be used
- the times when the product should be used
- the frequency of the use of the product
- the re-entry period after use of the product
- the withholding period after the use of the product
- disposal of the product and its container
- safe handling of the product and first aid in the event of an accident
- any matters prescribed by the regulations.

2 INTERNATIONAL REGULATORY STATUS

Glyphosate is approved for use throughout the world, including in Europe and the United Kingdom (UK), the US, Canada, Australia, New Zealand, China, Brazil etc.

2.1 United States

The United States Environmental Protection Agency (US EPA) registers pesticides under the Federal Insecticide, Fungicide and Rodenticide Act and periodically (at least every 15 years) re-evaluates pesticides to ensure that they continue to meet registration standards, noting that new scientific information may be generated that should be taken into consideration. The registration of glyphosate is currently being reviewed as a part of this process. The re-assessment began in 2009 and was originally scheduled for completion in 2015; however, finalisation of the assessment was delayed following the re-classification of glyphosate by IARC. The final report is currently expected to be completed and published in 2016. The US EPA utilises a risk assessment process for evaluating the potential for health and ecological effects of a pesticide. The human health risk assessment process utilises the National Research Council's process for human health risk assessments, which is the procedure outlined by the International Programme on Chemical Safety (IPCS) and adopted by JMPR, as described in Section 4.3. In addition, the US EPA has developed a framework to incorporate epidemiological information into its risk assessment, which is based on peer-reviewed, robust principles and tools. The framework methodology was reviewed in 2010 by the Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel. Chemicals are assessed for carcinogenicity using the US EPA's [Guidelines for Carcinogen Risk Assessment](#) (2005).

In February 2016, the US Food and Drug Administration (US FDA) announced that they would begin testing for residues of glyphosate on various foods, including soybeans, corn, milk and eggs. Concurrently, the US Fish and Wildlife Service announced that they would commence an analysis in conjunction with the US EPA of the impacts of four commonly used pesticides (including glyphosate) on 1500 endangered species, which is due for completion by December 2022.

Glyphosate-based formulations are currently registered in the US to control weeds in various fruit, vegetable and other food crops, glyphosate-resistant transgenic crops, ornamental plantings, lawns and turf, greenhouses, aquatic areas, forest plantings and roadside rights of way. Products registered in the US that contain glyphosate are formulated as liquids, solids and ready-to-use formulations, and can be applied using ground and aerial equipment as well as small hand-held sprayers.

2.2 Canada

The registration of pesticides in Canada is regulated by Health Canada's Pest Management Regulatory Agency (PMRA). In 2010 Health Canada's PMRA commenced a re-evaluation of glyphosate in collaboration with the US EPA's re-evaluation of glyphosate. In April 2015, the PMRA published its Proposed Re-evaluation Decision (PRVD2015-01) for glyphosate. In that document, the PMRA proposed continued registration of products containing glyphosate for sale and use in Canada. However, as a condition of the proposed continued registration, new risk reduction measures were proposed for end-use products, aimed at protecting both human health and the environment (Table 2).

Table 2: New measures to minimise risk of glyphosate exposure proposed by Health Canada's Pest Management Regulatory Agency

Human health	Environment
A restricted-entry interval of 12 hours for agricultural uses to protect workers	Environmental hazard statements to inform users of toxicity to non-target species
Apply only when potential for drift to areas of human habitation or activity (eg houses, cottages, schools and recreational areas) is minimal, to protect bystanders	Spray buffer zones to protect non-target terrestrial and aquatic habitats
	Precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecast are proposed to reduce potential for runoff to adjacent aquatic habitats
	A vegetative strip between treatment area and edge of a water body to reduce runoff to aquatic areas

Following the publication of the proposed re-evaluation decision, the PMRA accepted written comments on the report for 60 days from the date of publication. The PMRA will consider all submissions prior to making a final, scientific decision on the registration of glyphosate in Canada.

2.3 Europe and the United Kingdom

All active constituents used in pesticide products in the EU are subject to approval by the European Commission (EC). However, individual Member States are responsible for authorising the final formulated pesticide products containing those active constituents in its territory. Therefore, whilst a chemical may be registered for use in the EU, Member States have the power to restrict use of that product in its territory. The EC approval is limited to a maximum of ten years—therefore, if manufacturers wish to continue using that active constituent in pesticide products, they must apply for renewed approval prior to the end of these ten years. The EC appoints a member state to act as the Rapporteur Member State (RMS) to conduct the assessment of a chemical.

The European Food Safety Authority (EFSA) is an agency that is funded by the EU but operates independently of the European legislation and member states. Legally established in 2002 by the EU, EFSA provides scientific advice and communication on risks associated with the food chain in Europe and is responsible for risk assessment of available science, but is not involved in legislative risk management or policy determination. Instead, the risk assessment conducted by EFSA is used to inform European policy and legislation by the EU risk managers, including the EC and the European Parliament (EP).

Glyphosate is registered for use throughout Europe and the UK and in August 2014 was subjected to a re-assessment by the RMS, Germany, as mandated by the EC and coordinated by EFSA. The Federal Republic of Germany was appointed as the RMS to conduct the assessment. The Federal Office of Consumer Protection and Food Safety was appointed by the German government as the lead authority for drafting the Renewal Assessment Rapport (RAR). The Federal Institute for Risk Assessment (BfR) was subsequently commissioned to assess the potential health risks of glyphosate. Once completed, the draft report was presented to EFSA and a consultation

period commenced. All comments and additional data resulting from the consultation period was incorporated into the draft, which was then submitted to EFSA in December 2014.

In February 2015, the BfR prepared a revised health risk assessment report on glyphosate, which was subsequently revised in April 2015 to include additional evaluation tables and clarify some factual information following consultation with EFSA. The assessment by EFSA was published in November 2015. The report concluded that glyphosate was 'unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential' (EFSA 2015).

In April 2015, the EC provided EFSA with a second mandate, to consider the findings of the IARC regarding the potential carcinogenicity of glyphosate or products containing glyphosate in the original assessment. In July 2015, the German government and EFSA commissioned BfR to review the IARC monograph on the re-classification of glyphosate. The review was completed in August 2015 as an addendum to the original RAR and was peer reviewed by EFSA. A detailed discussion of the BfR's review of the IARC monograph is provided below in Section 4.4).

Briefly, the BfR agreed with IARC's conclusion that there is 'limited evidence in humans for the carcinogenicity of glyphosate' but noted that no consistent positive association between glyphosate exposure and the development of cancer was demonstrated, and the most powerful study reported no effect. The BfR disagreed with IARC's conclusion that there is 'sufficient evidence in animals for the carcinogenicity of glyphosate', concluding that the weight-of-evidence suggests that there is no carcinogenic risk related to the use of glyphosate and that no hazard classification for carcinogenicity is warranted according to the Classification, Labelling and Packaging of Substances and Mixtures (CLP criteria) (Germany 2015). The BfR also disagreed with IARC's conclusion that there 'is mechanistic evidence for genotoxicity, oxidative stress, inflammation, immunosuppression, receptor-mediated effects, and cell proliferation or death of glyphosate' and concluded that the mechanistic and other studies do not provide evidence for a carcinogenic mechanism. The BfR concluded that the weight-of-evidence suggests that neither glyphosate nor AMPA (a metabolite of glyphosate) induce mutations *in vivo* and that no hazard classification for mutagenicity was warranted according to CLP criteria (Germany 2015).

The initial registration of glyphosate was scheduled to expire on 31 December 2015 (EC 2015). Following an expert meeting of EFSA, the EU member states, WHO, IARC and the US EPA, and in consideration of the revised RAR and addendum, EFSA completed its report for the assessment of glyphosate for the purpose of renewed approval and recommended that a renewal of the registration of glyphosate be granted. The EFSA RAR and addendum were subject to a thorough peer review by the competent authorities of the EU Member States and to accommodate that peer review process, the registration of glyphosate was provisionally extended until 30 June 2016. All but one of the Member States experts agreed that glyphosate is unlikely to be genotoxic or pose a carcinogenic risk to humans. The EC postponed a vote by EU member states to renew approval of glyphosate, which was originally scheduled for the meeting on 7 and 8 March 2016 of the EU Standing Committee on Plants, Animals, Food and Feed (hereafter referred to as the Standing Committee) until after the European Parliament vote in April 2016.

In March 2016, the EU Environment Committee Members of the European Parliament (MEPs) voted in favour of a resolution for the EC to abandon its proposal to renew approval of glyphosate in the EU for a further 15 years with no restrictions. The Environment MEPs instead requested that the EC conduct an independent review and disclose all of the scientific evidence used by EFSA in its assessment of glyphosate. They added that the EU Food and Veterinary Office should also be mandated to test and monitor glyphosate residues in food and drink.

The resolution was put to a vote at the plenary session of the EP scheduled for 11–14 April in Strasbourg, which again resulted in a postponement of the vote to re-register glyphosate, as a qualified majority consensus could not be reached. The Standing Committee again met on 18–19 May 2016 to discuss a 10 year re-registration for glyphosate in the EU. Again, the vote was postponed because a qualified majority was not reached. On 2 June 2016, the EC announced a proposal for the Standing Committee to meet on 6 June 2016 to consider a 2-year extension to the current registration of glyphosate so that the ECHA could complete an assessment of the carcinogenicity and potential for endocrine disruption of glyphosate. The EC also proposed banning polyethoxylated tallow amines (POEA; in glyphosate-based formulations only), minimising the use of glyphosate in public parks, playgrounds and gardens, and minimising pre-harvest use of glyphosate. In order for the proposal to pass, 55% of Member States (representing 65% of the EU's population) would be required to vote in favour. Of the 28 Member States, 20 voted in favour of the proposal, 7 abstained (did not vote for or against) and 1 (Malta) voted against the proposal. As a result of the relatively large populations of some of the countries that abstained from voting, the favourable votes accounted for only 52.91% of the EU's population and the proposal did not pass.

On 24 June 2016, the EC convened an Appeals Committee to consider the re-approval of glyphosate for 18 months to allow the ECHA to gather additional data and undertake a comprehensive analysis of the health risks association with its use. Again, a qualified majority position was not reached, with 19 countries in favour of the extended approval, two against (France and Malta) and seven abstaining, representing 51.49% of the EU's population in favour of the extension.

When a qualified majority is not obtained, the EC may bring forward its own decision to authorise the re-approval of a chemical. On 29 June 2016, the EC extended the approval of glyphosate in the EU to allow the ECHA to complete its assessment of glyphosate. This approval will expire either 6 months following the date of receipt of the ECHA report or 31 December 2017, whichever occurs first (EC 2016). On 11 July 2016, Member State experts voted as a qualified majority in favour of two recommendations proposed by the EC as conditions to the registration extension, at a meeting of the Standing Committee in Plants, Animals, Food and Feed. These restrictions included:

- an EU-wide ban on POEAs contained in some glyphosate-based formulations
- restricted use of glyphosate-based formulations in public parks, playgrounds and home gardens and for pre-harvest application.

In July 2016, the pesticide regulator in Malta (the Malta Competition and Consumer Affairs Authority) began implementing a policy decision by the Environment Ministry to withdraw authorisation for all glyphosate and glyphosate-based formulations.

Glyphosate is currently authorised throughout the EU and UK, predominantly for uses in agriculture (cereals, vineyards, olives, citrus, nuts etc), but also to manage weed growth on non-cultivated areas (eg railway tracks, verges), public amenities, forestry and aquatic environments, and in home gardens. Glyphosate is authorised for weed control use after harvest or sowing, before a new crop is planted. Glyphosate is also authorised for pre-harvest weed control use and desiccation (to promote the maturation of crops) in crops such as oilseed rape and cereals. It is not currently clear which uses will be affected as a result of the recently announced use restrictions described above.

2.4 New Zealand

In New Zealand, the registration of herbicides is the responsibility of the Environmental Protection Authority and the Ministry for Primary Industries. Glyphosate is listed on the Chief Executive Initiated Reassessment (CEIR) Programme and as such is being actively monitored by the Environmental Protection Authority.

Glyphosate has been registered in New Zealand since 1976 and is used in various settings, including orchards, vineyards, pastures, vegetable patches, along roadways and in parks, sporting fields and home gardens.

3 EVALUATION METHODOLOGY: THE WEIGHT OF SCIENTIFIC EVIDENCE

Consistent with the scientific method, a weight-of-evidence approach should be used to determine whether a chemical is carcinogenic. To conduct an initial quality assessment of each individual study, the study design should be assessed, taking into account OECD (Organisation for Economic Co-operation and Development) or national test guidelines where appropriate. In a weight-of-evidence assessment, any observation should be reproducible: the strength of any finding will be increased if it can be replicated under the same conditions in more than one laboratory. Plausible patterns in the hierarchy of the results will also strengthen the finding—ie where a finding *in vitro* is reproduced *in vivo*.

In toxicological science, there are a number of criteria that are used to determine whether an effect, such as cancer, is treatment-related and adverse:

- *Dose-response relationship*—the number of animals or subjects showing the effect and/or the severity of the effect should increase with dose. There should be a progression to a more severe state of toxicity as the dose and duration of dosing increases.
- *Consistency of the effect*— the effect should be observed consistently across studies of similar exposure duration and sexes (in unusual cases an effect may be sex-specific). Additionally, an effect should be corroborated by related toxicological endpoints – for example, increases in malignant neoplasms should be preceded by cellular changes that should be observed at lower doses or following shorter exposure durations.
- *Statistical significance*—differences between treated groups and the concurrent control group should be statistically significant. However, statistical significance on its own does not imply biological significance and the absence of statistical significance also does not necessarily mean the absence of an effect (for example a rare type of tumour may be highly biologically relevant).
- *Biological plausibility*—an observed effect needs to be mechanistically plausible based on the characteristics of the chemical and principles of biology/physiology.
- *Natural variation and incidental findings*—the normal range of natural variation of a parameter in the test species needs to be understood through the use of age- and sex-matched historical control data. All laboratory animal strains used in rodent bioassays have a background incidence of age- and sex-related neoplasms at different tissue sites. It is critical that this normal range of biological variation is documented and understood.

When assessing toxicological data associated with chemical residues in food, the APVMA has regard to the principles and methods outlined by the IPCS, described below in Section 4.3 (IPCS 2009) including guidance on the interpretation of toxicological data by JMPR¹ and OECD². For the evaluation of carcinogenicity via dietary or other exposure routes, the IPCS has published a mode-of-action (MOA) framework for chemical carcinogenesis (Meek et al 2013). In this framework, treatment-related cancer must first be demonstrated in laboratory animals

¹ http://www.who.int/foodsafety/publications/jmpr_guidance_document_1.pdf?ua=1

² <http://www.oecd-ilibrary.org/docserver/download/9750321e.pdf?expires=1472172141&id=id&accname=quest&checksum=28F68D5204F38A1B96055A611D12C4DF>

before proceeding to examine genotoxicity data, human epidemiological and mechanistic data in order to determine the mechanism for how cancer arises and the human relevance of adverse effects observed in laboratory animals.

The APVMA considered aspects of study design and reporting that may either increase or decrease confidence in the data. The presence of a dose-response relationship, consistency and reproducibility were considered to increase confidence in the data, while any unexplained inconsistencies and significant deviations from international test guidelines were considered to reduce confidence in the data. Therefore, those studies that demonstrated a dose-response relationship, adhered to international test guidelines (where appropriate) and were consistent and reproducible within and/or between laboratories were given more weight in the assessment.

For epidemiological data, the APVMA considered prospective cohort studies to be more powerful than retrospective case-control studies, which are more prone to recall bias and confounding by exposure to other chemicals and environmental situations. It is well known that study participants' memory may not be reliable: participants are often asked to provide information about use patterns that occurred many years previously, participants may be providing information relating to a family members' usage (not their own) and it is possible that a participant with cancer may have spent more time thinking about possible causes and exposure scenarios than participants without cancer. It is also very difficult to separate usage of one pesticide from another: those who routinely use glyphosate-based formulations are likely to have been using many other types of agricultural and/or industrial chemicals, or be exposed to other occupational scenarios that may confound the data.

3.1 Use of international test guidelines

All scientific studies considered by the APVMA are assessed on their scientific merits. However, studies that have been conducted according to principles of Good Laboratory Practice (GLP) and comply with international test guidelines are preferred because of the assurance of their scientific quality.

To ensure the scientific quality of studies submitted for regulatory purposes and to enable comparison of studies utilising the same methodology in different laboratories, a number of internationally accepted test guidelines have been developed for various toxicological studies. The testing guidelines produced by the OECD are commonly used throughout the world and provide quality standards for different types of studies. Guidance is provided regarding test species and strain, the number of animals to be used, choice of chemical doses and duration of exposure, as well as parameters to be measured, observed and reported. By comparing studies that were conducted using equivalent test guidelines, regulators can identify potential human health hazards and set appropriate endpoints for risk assessment and management.

When assessing toxicology studies, consistency with international test guidelines is not the only measure of scientific quality. For some types of studies, guidelines have not yet been developed while for studies that were never intended for regulatory or risk assessment purposes (eg most studies published in scientific journals) some criteria may rarely be met. However, depending on how the study design, interpretation or reporting differs from the guidelines, the discrepancies may not affect the validity of the results. Specifically, data for individual animals is rarely reported in scientific publications; instead the data is presented as group means along with a measure for variance between control and treatment groups. This omission would not be considered a serious flaw and invalidate the study results. However, other elements of the testing guidelines may be considered more critical and omission may invalidate the study findings. For example, failure to independently code slides (or failure to report independent coding) used to visually score assay results would be considered as a potentially critical flaw, as it

would not be clear that the scoring was performed by an independent observer who was not aware of the treatment or control group being scored. In other cases, test guidelines may stipulate a maximum dose that is associated with minimal toxicity, for determining a specific carcinogenic or genotoxic end-point. In some experimental studies, that maximum dose may be exceeded up to ten-fold. In the absence of appropriate cytotoxicity tests, it may not be possible to determine whether any positive effects are indeed indicative of genotoxicity.

3.2 Statistical significance and biological or toxicological relevance

Statistical analysis is a useful tool for detecting differences between groups exposed to a test compound or not. Biologically this difference may be real or a chance or incidental finding. That is why a statistically significant result on its own without an evaluation of its biological and ultimately toxicological relevance provides only limited insight into the possible effects of a chemical. As described above, there are a range of other criteria that must be met in order to conclude that an effect is truly treatment-related and adverse.

Epidemiological data is often presented using an Odds Ratio (OR) with an associated confidence interval (CI; usually 95%). An OR is a relative measure of effect and is used in this context to compare the incidence of cancer (or some other health outcome) in individuals exposed to glyphosate with those who have not been exposed. If the OR is 1, the statistical analysis implies that there is no difference between the incidences of cancer in either group. The CI is used to determine the level of uncertainty around the OR, because the sample population used in the study is only a representative group of the overall population. The statistical test infers that the true population effect lies between the upper and lower CI. Therefore, a very narrow CI infers that the true effect is very close to the estimated OR, while a wide CI infers that the OR is less reliable. In addition, if the CI crosses 1 (eg 0.5–1.5), the statistical test is inferring that there is no difference between the two groups, in terms of cancer incidence. Therefore, the APVMA considered studies reporting positive associations between glyphosate exposure and cancer incidence that presented an OR greater than 1 and a narrow CI range that did not cross 1 to be more powerful than studies that had a wide CI range that crossed 1.

3.3 Historical control data and spontaneous tumour incidence

Consideration of historical control data is an important aspect of interpreting toxicology studies. Historical control data is a compilation of the findings from strain-, age- and sex-matched control animals from all the studies undertaken by the performing laboratory and provides an indication of the background frequency of tumours that occur in that species/strain of animals by chance. A statistically significant increase in tumour frequency may be observed in treated animals when a lower than normal tumour frequency is observed in control animals in that study. Conversely, a non-significant result may be observed when a higher than normal tumour frequency is observed in the control group. Therefore, historical control data is used to determine whether an increase in tumours is within the realms of normal biological variation or is in fact truly treatment related. For some common tumours (eg liver, pituitary or adrenal), the historical control ranges are so wide that the incidences of tumours in both the concurrent control and treated groups often fit within their bounds. In these cases, the mean value or distribution of historical control data may be more useful than the range only.

3.4 Test species and route of administration

Data obtained from humans is preferable to data obtained from experimental animals because it increases the certainty that an observed effect is relevant to humans. Volunteer studies and human clinical trials provide accurate exposure metrics that can be directly linked with adverse outcomes. However, the extent of exposure can be difficult to determine in human observational studies (such as epidemiological studies), because subjects are often expected to rely on memory recall to provide exposure details and subjects are frequently exposed to more than one chemical. When evaluating studies conducted using animal models, those that use mammals are considered more relevant to human outcomes than non-mammalian species or *in vitro* cell culture studies.

When evaluating the toxicological effects of pesticides, such as glyphosate, studies in which the chemical was administered via the oral (gavage, diet, drinking water), dermal or inhalational routes are highly relevant because these are the only possible routes of exposure for humans. Subcutaneous (skin injection), intravenous (vein injection) and intraperitoneal (stomach cavity injection) administration are generally not directly relevant for chemical risk assessment purposes because humans would not be exposed via these routes. In addition, these routes of exposure bypass normal metabolic processes.

4 SUMMARY OF ASSESSMENTS AND CONCLUSIONS

4.1 The IARC glyphosate monograph

The IARC is a specialist cancer agency of the WHO and, as such, follows the general governing rules of the United Nations. However, IARC has its own Governing Council and Scientific Council. Currently, 25 countries are IARC members, including Australia.

The IARC assessment process

The IARC appoints a Working Group to evaluate carcinogenic risks to humans, which is guided by the [Preamble](#) (IARC 2006). The Preamble is a statement of scientific principles; however, the procedures that each Working Group use to implement those scientific principles are not specified and are the prerogative of each individual Working Group. The Monographs produced by the Working Groups assess the strength of available evidence that an agent could alter the age-specific incidence of cancer in humans. Working Group members have usually published significant research related to the carcinogenicity of the agents being reviewed.

The IARC Monographs evaluate cancer hazards and the Preamble emphasises the distinction between a hazard and a risk. A cancer hazard is defined in the Preamble as ‘an agent that is capable of causing cancer under some circumstances’ while a cancer risk is defined as ‘an estimate of the carcinogenic effects expected from exposure to a cancer hazard’. The Preamble cautions that the Monographs identify cancer hazards even when the risks are very low at current exposure levels (IARC 2006).

The IARC assessments also utilise a ‘strength-of-evidence’ approach, rather than the ‘weight-of-evidence approach’ more common in regulatory assessments. The weight-of-evidence approach assesses the predictive validity of a hypothesis, while the strength-of-evidence determines its level of extremeness (Simon 2014). Predictive validity is dependent on factors such as study design, sample size, background rates etc. A strength-of-evidence assessment may be based on a single study where the effect was easily noticeable or was apparent in a large population, even though the predictive value of the study was weak.

The IARC Preamble states that while the Monographs are used by regulatory authorities worldwide to make risk assessments and formulate regulatory decisions, they represent only one part of the body of information that informs regulatory decisions (IARC 2006). The Preamble acknowledges that public health options vary according to circumstance and geographical location and relate to a multitude of factors. As a result, the IARC does not regard regulation or legislation while developing Monographs, as it acknowledges that this is the responsibility of individual governments or other international organisations.

When assessing an agent for a Monograph, the Working Group reviews epidemiological studies, cancer bioassays in experimental animals, as well as exposure, mechanistic and other relevant data. In each case, the Working Group only considers data that has been determined by them to be relevant to the evaluation. Only reports that have been published or accepted for publication in the openly available scientific literature and data from government agency reports that are publicly available are reviewed (IARC 2006). Unlike regulatory authorities, IARC does not consider the often large number of unpublished studies submitted for regulatory assessment.

The outcome of the Working Group's assessment is a categorisation of an agent that reflects the strength-of-evidence from studies in humans and experimental animals and other relevant data. The classifications used by IARC and the circumstances that may lead to an agent being assigned to each group are listed below (IARC 2006):

- Group 1 – the agent is carcinogenic to humans
 - there is sufficient evidence of carcinogenicity in humans
 - evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence that the agent acts through a relevant mechanism of carcinogenicity in humans (exceptional circumstances)
- Group 2A – the agent is probably carcinogenic to humans
 - limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals
 - inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that carcinogenesis is mediated by a mechanism that also operates in humans
 - limited evidence of carcinogenicity in humans but the agent clearly belongs to a class of agents for which one or more members have been classified in Group 1 or Group 2A (exceptional circumstances)
- Group 2B – the agent is possibly carcinogenic to humans
 - limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals
 - inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals
 - inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals, as well as supporting evidence from mechanistic and other relevant data
 - strong evidence from mechanistic and other relevant data.
- Group 3 – the agent is not classifiable as to its carcinogenicity to humans
 - inadequate evidence of carcinogenicity in humans and inadequate or limited evidence of carcinogenicity in experimental animals
 - inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans (exceptional circumstances)
 - agents that do not fall into any other group.
- Group 4 – the agent is probably not carcinogenic to humans
 - evidence suggesting lack of carcinogenicity in humans and experimental animals
 - inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data.

Assessment of glyphosate by IARC

In March 2015, IARC evaluated the potential carcinogenicity of five organophosphate pesticides and classified glyphosate (as well as malathion and diazinon) as 'probably carcinogenic to humans', Group 2A. The complete monograph was published in July 2015. Note that where the Working Group cited an unpublished study, it relied on the published summary report as the complete, original study report was not available.

The Working Group concluded that there was 'limited evidence of carcinogenicity' in humans, with a positive association observed between exposure to glyphosate and NHL (IARC 2015). The IARC preamble explains that 'limited evidence of carcinogenicity' in humans is concluded when the Working Group has determined that a credible causal link between the agent and cancer may have been identified 'but chance, bias or confounding could not be ruled out with reasonable confidence' (IARC 2006). The Working Group also concluded that there was 'sufficient evidence of carcinogenicity' in experimental animals (IARC 2015). The IARC Preamble describes that sufficient evidence of carcinogenicity is concluded when a causal relationship between the agent and an increased incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms has been established in either two or more species of animals, or two or more independent studies in one species. Sufficient evidence is also considered to be established when an increased incidence of tumours is observed in both sexes of a single species in a well conducted study (preferably conducted according to GLP). Alternatively, sufficient evidence of carcinogenicity may be considered established in a single study in one species and sex when malignant tumours occur to an 'unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites' (IARC 2006).

The studies relied on by the Working Group for human carcinogenicity comprised reports of the Agricultural Health Study (AHS) and various case-control studies conducted in the US, Canada and Sweden. The Working Group concluded that these studies presented increased risks for the development of NHL associated with exposure to glyphosate (IARC 2015).

The AHS was a prospective cohort study of 54 315 licensed pesticide applicators from Iowa and North Carolina, which has produced data relating to the use of pesticides, such as glyphosate on the risk of cancer at various sites. Overall, the study concluded that exposure to glyphosate was not associated with all cancers combined (RR 1.0; 95% CI 0.90–1.2) or any cancer at a specific anatomical site (De Roos et al. 2005).

A study conducted in Canada reported an increased risk of NHL following more than 2 days per year of exposure to glyphosate in 51 exposed cases (OR 1.20; 95% CI 0.83–1.74 when adjusted for age, province and medical variables) (McDuffie et al. 2001); however, no adjustment for other pesticides was performed and the OR spans 1 (indicating that there was no difference between the incidence of cancer in either group). A study conducted in the US (De Roos et al. 2003) and two studies conducted in Sweden (Hardell & Eriksson 1999; Eriksson et al. 2008) reported an increased risk of NHL following glyphosate exposure, which persisted following adjustment for other pesticides. However, the results of Hardell & Eriksson (1999) should be treated with caution, as only 4 glyphosate-exposed cases and 3 controls were included and while an increased OR was reported (2.3), the 95% CI was wide (0.40–13.0), indicating poor precision and spans 1, indicating that there was no difference between the incidence of cancer in either group. Hardell et al. (2002) analysed pooled data that included the data presented in Hardell & Eriksson (1999)—a non-statistically significant elevated risk for NHL following glyphosate exposure with poor precision and an OR that spans 1 was identified (OR 1.86; 95% CI 0.55–6.20). In 29 exposed cases and 18 controls, Eriksson et al. (2008) reported an increased risk for NHL following more than 10 days/year exposure to glyphosate (OR 2.36; 95% CI 1.16–4.40) following adjustment for exposure to other pesticides. After pooling

data from three case-control studies of NHL conducted in the Midwest US in the 1980s, De Roos et al. (2003) reported an increased incidence of NHL following exposure to a number of individual pesticides, including glyphosate (OR 2.1; 95% CI, 1.1–4.0), based on 36 cases. However, while an increased risk was still identified following adjustment for exposure to other pesticides (OR 1.6, 95% CI 0.90–2.8), it was no longer significant. A case-control study also conducted among males in the Midwest US reported an increased risk of developing NHL for men who had ever farmed (OR 1.2; 95% CI, 1.0–1.5) and men who had ever handled glyphosate (OR 1.1; 95% CI, 0.7–1.9); however, no adjustment was made for other pesticides (Cantor et al. 1992). No association between glyphosate exposure and development of NHL was calculated in a hospital-based case-control study conducted in France (OR 1.0; 95% CI 0.5–2.2) (Orsi et al. 2009); however, only 12 exposed cases were assessed. One study conducted in Europe reported an elevated risk for B-cell lymphoma following glyphosate exposure (OR 3.1; 95% CI 0.6–17.1), but again, this study was based on few exposed cases (n=4) and controls (n=2), with a very wide CI (poor precision) that spans 1 and the authors of the paper concluded that no increased risk of either lymphoma overall, or B cell lymphoma was associated with glyphosate exposure (Cocco et al. 2013).

The Working Group also relied on three studies that reported an increased risk of multiple myeloma (a subtype of NHL) following more than 2 days glyphosate exposure per year (Brown et al. 1993; Orsi et al. 2009; Kachuri et al. 2013). However, none of these studies adjusted for the effect of other pesticides and in all three studies, the results were not statistically significant. Therefore, the variation observed in the results could be attributable to normal biological variation and not exposure to glyphosate or other pesticides. A report of data obtained by the AHS found no association between glyphosate exposure and NHL (OR 1.1; 95% CI 0.5–2.4; n=54 315) but saw an increased risk of multiple myeloma when the data were adjusted for multiple confounders, such as demographic and lifestyle factors, as well as other pesticides (OR 2.6; 95% CI 0.7–9.4; n=40 716) (De Roos et al. 2005). However, the number of myeloma cases included in the study was small (32 cases out of 2088 total cancer cases) and the wide CI spanning 1 indicates poor precision and a lack of difference between groups. Re-analysis of the data determined that the increased risk of multiple myeloma (OR 1.24; 95% CI 0.52–2.94) was only present in the subset of subjects for which there was no missing data (22 cases); however, again, the CI spans 1 (Sorahan 2015). This re-analysis of the data concluded that the observed increased risk of developing multiple myeloma following glyphosate exposure resulted from the use of an unrepresentative restricted dataset and that analysis of the full dataset provided no convincing evidence that glyphosate exposure is linked with the development of multiple myeloma (Sorahan 2015).

The studies relied on by the Working Group for animal carcinogenicity comprised two dietary studies in male and female mice, five dietary studies in male and female rats, as well as one drinking-water study of a glyphosate-based formulation in male and female rats.

In mice, one dietary study reported in summary form by the US EPA calculated a positive trend in the incidence of renal tubule carcinoma and renal tubule adenoma/carcinoma combined in male, but not female mice (IARC 2015). A second dietary study reported by the JMPR (2006) in mice observed a significant positive trend in the incidence of haemangiosarcoma incidence in male, but not female mice (IARC 2015). However, haemangiosarcomas were only observed at the highest dose tested in male mice (4/50; 8%). In females, haemangiosarcomas were reported at the lowest (2/50, 4%) and highest (1/50, 2%) doses tested.

Three dietary studies in rats evaluated by the JMPR found no significant increase in tumour incidence in any tissue (JMPR 2006). Of the remaining two studies (evaluated by the US EPA), one reported an increase in the incidence of pancreatic cell adenoma in male rats only; however, no statistically significant dose-response was evident and there was no progression to carcinomas (IARC 2015). In the final study, a significant increase in the incidence of

pancreatic islet cell adenoma and hepatocellular adenoma in males and thyroid C-cell adenoma in females was reported. However, again, there was no statistically significant dose-related trend in the incidence of pancreatic islet cell adenomas and no progression to carcinoma for any tumour type (IARC 2015). No significant increase in tumour incidence was observed following administration of a glyphosate formulation (13.85% solution, purity of glyphosate not reported) to rats in drinking water.

The Working Group concluded that there was strong evidence that glyphosate and glyphosate-based formulations are genotoxic and, along with the main metabolite, AMPA can act to induce oxidative stress. Two studies investigated genotoxicity following exposure of community residents to glyphosate-based formulations, reporting chromosomal damage (micronucleus formation) in blood (Paz-y-Miño et al. 2007) and significant increases in DNA damage (DNA strand breaks) (Bolognesi et al. 2009) four or two months following spraying, respectively. Other studies assessing the effects of either glyphosate or glyphosate-based formulations in human cells *in vitro* produced varied results (IARC 2015). The majority of the studies relied on by the Working Group that assessed genotoxicity in human cells *in vitro* reported DNA damage (DNA strand breaks), which can also be indicative of cytotoxicity and not just genotoxicity. Two studies were relied on by IARC as evidence of chromosomal damage in human lymphocytes *in vitro*. Both studies reported that glyphosate did not produce chromosomal damage without metabolic activation (Manas et al. 2009; Mladinic et al. 2009b). One study reported micronucleus formation following metabolic activation at the highest concentration tested only, but no concentration-related increase in micronucleus formation was evident (Mladinic et al. 2009b). Similarly, experiments utilising glyphosate or glyphosate-based formulations conducted in animals, both *in vivo* and *in vitro* produced varied results (IARC 2015). As for mammalian cells *in vitro*, many of the non-human mammalian genotoxicity studies utilised a DNA damage endpoint, which may be associated with cytotoxicity, rather than genotoxicity. One study assessing mutations in mouse uterine cells reported negative results. Four of the nine studies that assessed chromosomal damage (micronucleus formation) in mouse bone marrow cells produced negative results. Of the remaining five studies that reported positive results, three tested a single dose only, one reported a positive effect at the highest dose tested only and one reported a positive effect at the lowest dose tested only (IARC 2015). No chromosomal aberrations were reported following exposure to glyphosate (single ip dose) (Li & Long 1988) or a single oral dose of a glyphosate-based formulation in mouse bone marrow cells (Dimitrov et al. 2006); however, a single ip dose of a glyphosate-based formulation increased chromosomal aberration in a dose- and time-dependent manner (Prasad et al. 2009).

The Working Group concluded that there was weak evidence that glyphosate may affect the immune system and that glyphosate or glyphosate-based formulations induce receptor-mediated effects, such as aromatase activity. The Working Group also concluded that glyphosate-based formulations may affect cell proliferation or death, the latter via apoptosis; however, glyphosate alone either had no effect or had a weaker effect than the formulated products (JMPR 2006; IARC 2015).

4.2 Assessment of the IARC Monograph

The assessment of the IARC Monograph was undertaken by the Department of Health (OCS). The APVMA requested that OCS conduct a preliminary scoping review of the IARC Monograph to ascertain the relevance of the carcinogenicity classification of glyphosate and any implications that this may have to the registration of glyphosate and glyphosate-based formulations in Australia. In particular, the APVMA requested that OCS identify any relevant data not previously evaluated by Australia. This constituted Tier 1 of the OCS assessment (Supporting document 1).

Tier 2 of the OCS scoping assessment involved a detailed review of any studies that had been reviewed by IARC as part of its assessment of glyphosate and were identified by OCS as requiring further review during the Tier 1 assessment (Supporting document 2).

Previous OCS epidemiological review in 2005

An association between reported glyphosate use and an increased risk of NHL was reviewed by the OCS in 2005 (unpublished). Therefore, the OCS did not assess the epidemiological studies described in the IARC monograph published prior to 2005 and recommended that the APVMA rely on international assessments for any additional epidemiological information relating to glyphosate exposure. The OCS' unpublished 2005 assessment of epidemiological information relating to glyphosate exposure is summarised below.

The first report of an association of glyphosate exposure with NHL was from a case-control study conducted in Sweden; however, this estimate was based on only four exposed cases and three controls (Hardell & Eriksson 1999). A pooled analysis of this initial study with a study of hairy cell leukaemia (a rare subtype of NHL) suggested a relationship between glyphosate exposure and an increased risk of the disease (unadjusted analysis with an OR of 3 and 95% CI 1.1–8.5) (Hardell et al. 2002). A more extensive study across a large region of Canada found an increased risk of NHL associated with glyphosate use of 2 days or more per year, based on 23 exposed cases and 31 controls (OR = 2.1; 95% CI 1.2–3.7) (McDuffie et al. 2001). In a pooled analysis of case-control studies conducted in the US, De Roos et al. (2003) reported an association between glyphosate exposure and increased NHL risk in men after adjustment for other commonly used pesticides, based on 36 exposed cases and 61 controls (OR = 2.1; 95% CI 1.2–4.0).

By contrast, in another cohort study, De Roos et al. (2005) reported that glyphosate exposure was not associated with increased NHL risk in men after adjustment for other commonly used pesticides, based on 92 exposed cases. One plausible explanation for this conflicting result is that all previous studies had a lower number of exposed cases and were retrospective in design, and thereby susceptible to recall bias of exposure reporting. As information on exposures is obtained by questionnaires and interview of farmers or their next-of-kin, often years after the event, the quality of data on pesticide use obtained by recall is questionable (Blair et al. 2002). Indeed, recall bias is particularly problematic for widely used products such as Roundup and the potential for recall bias and for misclassification of pesticides were acknowledged as one of the limitations in all such studies. On the other hand, the study by De Roos et al. (2005) reported a higher number of exposed cases and was prospective in design, which should have largely eliminated the possibility of recall bias. On this basis and also based on the toxicity profile of glyphosate derived from animal studies, it is unlikely that exposure to this chemical is associated with an increased risk of NHL.

This is further supported by a recent epidemiological report showing that NHL incidence decreased between 1991–2000 in Sweden, Finland, Denmark and the US (Hardell & Eriksson 2003), a period in which glyphosate use increased very significantly. It is of interest to note that decreased NHL incidence during this period in Sweden also coincides with a decline in the prevalence of human immunodeficiency virus (HIV), which has been shown to be a risk factor for NHL (Pluda et al. 1993).

Tier 1 assessment of the IARC glyphosate monograph

Tier 1 assessment outcomes

REFERENCE LIST AND KEY STUDY REVIEW

The OCS examined the reference list from the IARC Monograph 112, which included 264 published papers. Publicly available papers were sourced and designated as either:

- relevant for the carcinogenicity classification for humans and requiring further analysis (Tier 2, Part 1)
 - studies previously reviewed by the EU or
 - 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 relevant test animal models or cell lines, eg mouse, rat, human lymphocytes
- relevance for the carcinogenicity classification for humans unclear and to be determined internationally (the APVMA will rely on international assessment of these studies)
 - studies previously reviewed by the EU or
 - 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 constituents used
 - Studies that do not fit the criteria for the other designations
- not relevant to the classification and excluded
 - 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
 - determination of glyphosate in air, soil, water or in vivo
 - market/industry summary publications
 - case studies regarding glyphosate poisoning
 - occupational exposure or biomonitoring studies.

Following analysis of the study abstracts, 174 references were excluded from requiring further review. The majority of these papers were excluded because the study utilised non-conventional species or methodology for evaluating human toxicity (eg fish). A total of 19 references were considered relevant to the carcinogenicity classification of glyphosate, requiring further in-depth revision. Of these 19 studies, 9 had been previously reviewed by the EU in

2013 and 10 had not previously been reviewed by either the OCS or the EU. The remaining 71 references were considered to require further review to determine their relevance to the carcinogenicity classification. Of these 71 references, 19 had been previously reviewed by the EU in 2013, five were referenced as US EPA papers (not referenced by the EU) and 47 had not been previously reviewed by either the OCS or EU. These studies will be assessed in detail by the JMPR in 2016.

RECOMMENDATIONS

Based on the Tier 1 assessment, the OCS recommended an evaluation of the studies listed in Table 4 (Appendix A) and an evaluation of the EU position for the key studies listed in Table 5 (Appendix B). This review constituted Tier 2 of the OCS scoping assessment of glyphosate. The studies referenced in the IARC Monograph that were not recommended for evaluation by the OCS are listed in Appendix C (Table 6).

The OCS noted that parallel reviews of the IARC Monograph were being planned or were in progress by independent expert international bodies (eg JMPR). Therefore, the OCS recommended that rather than undertaking a full review in isolation, the APVMA make use of this international assessment. This approach is consistent with the APVMA's policy on the use of [international assessments](#).

Tier 2 assessment of the IARC glyphosate monograph

The Tier 2 assessment involved:

- Evaluation of 19 studies relevant to the carcinogenicity classification of glyphosate (Table 4, Appendix A). Of these, 16 were either considered or critically appraised by EFSA (2015).
 - 12 genotoxicity studies
 - 5 oxidative stress studies
 - 1 epidemiology study
 - 1 classification review report.

The Tier 2 assessment did not include a detailed review of the epidemiological studies or studies that evaluated the possible carcinogenicity of glyphosate-based formulations, as a number of international reviews of the IARC Monograph will be undertaken concurrently with the OCS assessment. A total of 47 studies that were not reviewed by the EU Renewal Assessment Report (RAR) and 19 studies that were reviewed by the EU RAR (Table 5, Appendix B) were not reviewed by the OCS in the Tier 2 assessment of glyphosate because their relevance to the carcinogenicity classification for humans was unclear. The APVMA will rely on international assessments of these studies.

Animal carcinogenicity studies

The OCS evaluated one published study that reviewed animal carcinogenicity studies to support regulatory requirements (Greim et al. 2015). The review paper included nine rat and five mouse studies in a weight-of-evidence assessment of the carcinogenicity of glyphosate that included a review of absorption, distribution, metabolism and excretion (ADME), acute toxicity, genotoxicity, epidemiology and animal chronic toxicity studies.

The authors refer to an article that qualitatively analysed the outcomes from seven cohort studies and 14 case-control studies that examined an association between glyphosate and cancers. No consistent pattern of positive statistical associations between total cancer or site-specific cancer in adults or children exposed to glyphosate was evident (Mink et al. 2012). All studies cited by Mink et al. (2012) were referenced in the IARC Monograph and five (Nordstrom et al. 1998; Hardell & Eriksson 1999; McDuffie et al. 2001; Hardell et al. 2002; De Roos et al. 2005) were included in a previous assessment of glyphosate by the OCS in 2005, which concluded that glyphosate is not mutagenic or carcinogenic and it is unlikely that exposure to glyphosate is associated with an increased risk of NHL. Of the remaining studies cited by Mink et al. (2012), four (Brown et al. 1990; Cantor et al. 1992; Carreon et al. 2005; Andreotti et al. 2009) were considered during the Tier 1 assessment as not appropriate for review because glyphosate was not referred to in the abstract and the remaining 12 were identified as requiring additional assessment in order to determine their relevance to the assessment. Therefore, a detailed appraisal of this paper was not conducted by the OCS as a part of the Tier 2 assessment.

Several one year toxicity studies in animals were reviewed by Greim et al. (2015) but not discussed in detail, as they were not designed to detect neoplasms. However, studies conducted in both rats and dogs indicated low toxicity of glyphosate following repeated daily exposure.

Greim et al. (2015) evaluated five chronic toxicity/carcinogenicity studies (conducted over a minimum duration of 18 months) in mice, four of which were considered reliable and were performed according to GLP following OECD testing guidelines (OECD TGs). In four of those studies, spontaneous tumours were observed at all doses. As no dose-response was observed, these were not considered to be treatment-related. One study observed evidence for an increase in the incidence of malignant melanomas at the highest dose tested; however, this tumour is known to be a common spontaneous tumour in the strain of mouse tested. Another study reported increased incidence of bronchio-aveolar adenocarcinoma and malignant lymphoma at the highest dose tested only; however, these were only observed in males and are known to be a common age-related neoplasm in the strain of mouse tested.

Greim et al. (2015) evaluated nine chronic toxicity/carcinogenicity (24 to 29 months) studies in rats submitted by industry, seven of which were conducted according to principles of GLP. Of the two non-GLP studies, one was conducted prior to the introduction of GLP. Some of the studies reported spontaneous and/or age-related neoplasms that did not exhibit a dose-response relationship and were therefore not considered treatment-related. In some cases, the tumours observed were known to be common age-related tumours in the particular strain of rat used. In addition, some studies reported the development of benign tumours that did not exhibit a dose-response relationship and did not progress to malignant neoplasms. Other studies reported no increase in tumour incidence following glyphosate exposure.

Greim et al. (2015) combined the results from the animal studies with results from human carcinogenicity epidemiology conclusions reported by Mink et al. (2012)³ and concluded that glyphosate is not carcinogenic. They noted that while some studies reported an increase in a specific neoplasm at high dose, the pooled data did not identify any consistent pattern of neoplasm development or dose-response relationship. Therefore, the authors

³ Mink et al (2012) concluded that there was no consistent evidence of an association between exposure to glyphosate and cancer in humans.

concluded that the observed effects were not consistent or reproducible and were not treatment related. The OCS agreed with the conclusion that the evidence indicates that glyphosate is not carcinogenic in animals.

Genotoxicity

The OCS appraised 11 studies and one review paper that assessed the genotoxicity of glyphosate.

DNA DAMAGE

Of these studies, six assessed genotoxicity via the comet assay (or single cell gel electrophoresis; SCGE) *in vitro*, using lymphocytes (Mladinic et al. 2009a; Mladinic et al. 2009b; Alvarez-Moya et al. 2014), HepG2 cells (liver carcinoma cells) (Gasnier et al. 2009), Hep-2 cells (epithelial carcinoma cells derived from a cervical cancer) (Manas et al. 2009), GM38 cells (diploid fibroblast cells) or HT1080 cells (fibrocarcinoma cells) (Monroy et al. 2005). All of these studies were considered by the EFSA RAR (2015). As previously described, DNA damage observed using sister chromatid exchange (SCE) or the comet assay is regarded as an indirect measure of genotoxicity and positive results using these endpoints may reflect induction of cytotoxicity, rather than genotoxicity, as DNA damage does not directly measure heritable events or effects that are closely associated with heritable events (Kier & Kirkland 2013).

The OECD TG 489 (2014) for comet assays specifies that exposure to the test substance should occur *in vivo* and cells subsequently isolated and analysed. In contrast, the study by Alvarez-Moya et al. (2014) exposed isolated human peripheral blood lymphocytes directly *in vitro* to the test substance. Therefore, it is difficult to compare these results with other studies as the exposed cells are likely to be more sensitive to direct exposure. Given this and other limitations in study design and reporting (including a lack of data relating to cytotoxicity), the OCS concluded that the genotoxic effects of glyphosate could not be determined from this study and that it was not reliable for regulatory purposes. Mladinic et al. (2009a) concluded that glyphosate technical is not genotoxic and does not cause oxidative stress at levels relevant to human exposure, and recommended further research utilising a larger sample population. The EFSA RAR (2015) noted that, while the study was a non-GLP, non-guideline study, it met broad scientific principles to determine genotoxicity; however, the positive results obtained at the highest dose tested may reflect cytotoxicity, rather than a true chromosome effect that would indicate genotoxicity. The OCS agreed with the assessment and concluded that the study demonstrated that glyphosate is not genotoxic and does not cause oxidative stress at concentrations relevant to human exposure, but that the results are only reliable as supporting evidence for regulatory purposes. In another study, the same research group concluded that glyphosate technical did not damage DNA at levels of expected human exposure (Mladinic et al. 2009b). However, the EFSA RAR noted a number of critical deficiencies in the study design and reporting (eg the study was not conducted according to GLP or international guidelines, and the proposed mechanism of genotoxicity is not relevant to human exposure levels). The OCS agreed with the conclusion of EFSA that the study is not suitable for regulatory (ie risk assessment) purposes.

Manas et al. (2009) concluded that glyphosate technical was genotoxic (as evidenced by DNA damage) in human Hep-2 cells between 3.00 and 7.50 mM (higher concentrations were cytotoxic) and Gasnier et al. (2009) concluded that exposure to a glyphosate-based formulation was genotoxic to human liver carcinoma (HepG2) cells. However, the study design and level of reporting detail of both studies was criticised by both EFSA and the OCS for a number of reasons. The positive results obtained by Gasnier et al. (2009) were observed only at exceedingly high concentrations that were above the limit dose limit, the potential for cytotoxicity due to membrane damage from surfactants is well known and was not controlled for, the results cannot be fully attributed to glyphosate technical

but may be related to the surfactants, no statistical analysis was performed, variation within the datasets were not reported (despite each experiment being conducted in triplicate) and there was an inadequate level of data reporting. Therefore, both EFSA and the OCS concluded that neither of the studies were suitable for regulatory purposes.

Monroy et al. (2005) reported a concentration-related increase in DNA migration in both normal human GM38 cells and human fibrosarcoma (HT1080) cells, which were statistically significant between 4 and 6.5 mM glyphosate and 4.75 and 6.5 mM glyphosate, respectively. At the highest dose (6.5 mM), DNA damage was approximately 5% and 30% for GM38 and HT1080 cells, respectively. Therefore, the authors concluded that glyphosate induces single-strand DNA breaks in mammalian cells. However, the EFSA RAR and OCS both identified a number of deficiencies in study design and reporting. The EFSA RAR (2015) suggested that the positive results seen may be secondary to cytotoxicity and the concentrations used may be at the threshold for cytotoxicity. When the cytotoxicity and genotoxicity results are combined, significant cytotoxicity (as defined by the authors as < 80% cell viability) was evident at 4.75 mM in HT1080 cells, at which genotoxicity results should therefore no longer be considered reliable. No negative control DNA migration results were reported for the HT1080 cells.

At concentrations at and below 5.5 mM, there was no significant change in the length of migration. The percentage of DNA that was not damaged remained higher than the 'DNA damage' scores combined until 5.5 mM.

In combination, these results suggest a lack of genotoxic potential at non-cytotoxic concentrations (4.75 mM).

For the GM38 cells, 80% of cells were viable at the highest concentration (6.5 mM) tested. Therefore, the data that reported significant DNA migration for the GM38 cells appear reliable. The DNA migration data support the DNA morphology data, with the percentage of cells with no DNA damage only remaining higher than the DNA damage combined up to 4 mM. Therefore, the OCS concluded that the results for HT1080 cells were not reliable for regulatory purposes and that the results for GM38 cells are reliable as supporting evidence only, due to a number of study design and reporting limitations.

One study utilised the SCE assay to assess genotoxicity in human lymphocytes, which was also considered by EFSA. Bolognesi et al. (1997) reported both glyphosate technical (purity not specified) and a glyphosate-based formulation induced a concentration-related increase in SCEs from 1 to 6 mg/mL and 0.1 to 0.33 mg/mL, respectively, and that a larger effect occurred with the formulated product than glyphosate technical. However, the EFSA and OCS identified a number of critical deficiencies in study design and reporting, including deviations from OECD guidelines: the experiment was conducted only in the absence of an exogenous source of metabolic activation; positive controls were not included and therefore the validity of the test system was not confirmed; only pooled data were provided (precluding assessment of the influence of inter-individual variation) and only two subjects were included, which does not allow a meaningful statistical analysis). Therefore, both EFSA and OCS concluded that the study was not reliable for regulatory purposes.

Bolognesi et al. (1997) investigated the potential for glyphosate (300 mg/kg) or Roundup® (900 mg/kg) to induce single-strand DNA breaks following ip administration, using the alkaline elution assay. EFSA concluded that the positive results of this assay may be secondary to cytotoxicity, as the doses of glyphosate were close to or in excess of the ip LD50 of glyphosate in mice. The OCS agreed with this assessment and concluded that the results of the alkaline elution assay are not reliable for regulatory purposes.

GENE MUTATION AND CHROMOSOMAL DAMAGE

Chromosomal effects, such as induction of chromosomal aberrations or micronuclei in cultured mammalian cells are considered direct measures of genotoxicity. Five studies assessed genotoxicity of glyphosate using the *in vivo*

micronucleus assay in various strains of mice, while one utilised the *in vitro* micronucleus assay in human lymphocytes. Significantly increased micronuclei, nuclear buds and nucleoplasmic bridges were reported following glyphosate treatment in the presence of metabolic activation at the highest concentration tested (580 µg/mL glyphosate) in human lymphocytes, but not at concentrations likely to be encountered by humans (Mladinic et al. 2009b). However, both the OCS and EFSA concluded that this study was not suitable for regulatory purposes: positive and negative control results were virtually indistinguishable, negative control data were not reported and despite the authors' claims that the concentrations of glyphosate tested correspond to acceptable safety levels based on evaluated *in vitro* endpoints, these findings need to be validated *in vivo*.

Four of the five reported *in vivo* micronucleus assays (Rank et al. 1993; Bolognesi et al. 1997; Manas et al. 2009; Prasad et al. 2009) utilised the ip administration route, which is not considered relevant for human exposure. Only one *in vivo* study (Chan & Mahler 1992) utilised a more appropriate dietary exposure model. A small but significant increase in micronucleus frequency was observed in male CD-1 mice, following ip exposure (two injections at a 24 hourly interval) to either 300 mg/kg glyphosate technical or 450 mg/kg Roundup® (equivalent of approximately 135 mg/kg glyphosate) (Bolognesi et al. 1997). However, positive controls were not used to validate the assay and the assay was not conducted according to international test guidelines, which specify that a minimum of three doses of the test substance be assessed in order to determine whether a dose-response relationship exists. In Balb-C mice, a significant increase in micronucleated erythrocytes was observed at high concentrations of glyphosate only (400 mg/kg) (Manas et al. 2009); however, this study was criticised by both EFSA and the OCS for major deviations from international test guidelines. In particular, erythrocytes (instead of immature, polychromatic erythrocytes) were scored for micronuclei and it did not appear that scoring was blinded. In Swiss albino mice, it was reported that glyphosate induced a significant dose- and time-dependent increase in bone marrow micronucleated polychromatic erythrocytes (Prasad et al. 2009). Again, this study was criticised by both EFSA and the OCS as the use of dimethyl sulphoxide (DMSO) as a solvent is highly unusual (glyphosate is soluble in water) and ip administration of DMSO has been shown to enhance the toxicity of glyphosate-based formulations. In contrast, no increase in micronucleus frequency was observed following dietary exposure in B6C3F1 mice (Chan & Mahler 1992) or ip exposure in NMRI-Bom mice (Rank et al. 1993). Positive control animals were treated for only 4 weeks (compared with 13 weeks for treated animals) in the dietary exposure study (Chan & Mahler 1992); therefore, the OCS concluded that the results were reliable only as supportive data for regulatory purposes. The other studies were not considered reliable for regulatory purposes, due to the limitations described above.

By applying centromere probes, Mladinic et al. (2009a) analysed micronuclei and nuclear instability in human lymphocytes exposed to glyphosate, with and without metabolic activation. The authors reported a significant increase in the proportion of micronuclei that contained centromeres only at the highest concentration of glyphosate tested (580 µg/mL) with metabolic activation, which the authors suggested could indicate aneugenic activity that is exhibited only above a threshold concentration. The number of early apoptotic and necrotic cells were significantly increased at 580 µg/mL, with and without metabolic activation. The authors concluded that glyphosate technical is not genotoxic at concentrations relevant to human exposure. The OCS agreed with the authors' conclusion and with EFSA's conclusion that the results are reliable as supporting evidence for regulatory purposes. Furthermore, the OCS agrees with EFSA that the positive results obtained at the highest dose tested indicated a possible threshold aneugenic effect associated with cytotoxicity, rather than a DNA-reactive clastogenic effect.

Three studies assessed genotoxicity using chromosome aberration studies in bone marrow cells obtained from Swiss albino mice (Prasad et al. 2009), SD mice (Li & Long 1988) and human lymphocytes (Manas et al. 2009).

The authors reported that glyphosate induced a significant dose- and time-dependent increase in aberrant cells compared with untreated cells in Swiss albino mouse bone marrow cells (Prasad et al. 2009), but not SD mice (Li & Long 1988) or human lymphocytes even at very high concentrations (up to 6 mM glyphosate) (Manas et al. 2009). However, as described above, the study by Prasad et al. (2009) was not considered suitable for regulatory purposes, as DMSO was used as the solvent (instead of water) and the glyphosate/DMSO solution was administered via ip injection. Li & Long (1988) deviated from international guidelines by testing only one concentration of glyphosate, examining only 50 cells per animal for aberrations and by administering glyphosate by ip injection. Manas et al. (2009) deviated from international guidelines by scoring 100 cells per treatment (instead of 200 cells), not reporting replicate data and not concurrently assessing cytotoxicity.

In addition to the chromosome aberration assay, Li & Long (1988) utilised a variety of other methods to assess genotoxicity, including prokaryotic genotoxicity tests (*Salmonella*/histidine plate incorporation reversion assay, *E. coli* WP2 reverse mutation assay, *B. subtilis* Rec-assay) and *in vitro* mammalian genotoxicity tests (Chinese hamster ovary hypoxanthine-guanine phosphoribosyl transferase or CHO-HGPRT gene mutation assay, unscheduled DNA synthesis). No positive responses were reported in any of the tests performed and the authors concluded that glyphosate is not genotoxic. Despite some deviations from international guidelines (only one positive control used and duplicate (rather than triplicate) plating was used in the *Salmonella*/histidine reversion assay and *E. coli* WP2 reverse mutation assay), the OCS and EFSA both concluded that the negative genotoxicity results of Li & Long (1988) were acceptable for regulatory purposes. Rank et al. (1993) also utilised the *Salmonella* plate incorporation reversion assay to assess genotoxicity; however, only Roundup® was tested and only two of the five recommended bacterial strains were used. The authors reported a weak mutagenic effect at 360 µg/plate in one strain (TA98) without metabolic activation and at 720 µg/plate in another strain (TA100) with metabolic activation. However, EFSA concluded that a reliable assessment was not possible due to marked cytotoxicity at and above 360 µg/plate and the lack of a concentration-response relationship. The OCS agreed with EFSA's assessment and concluded that the results were not reliable for regulatory purposes.

Overall, the OCS concluded that the weight-of-evidence indicates that glyphosate is not genotoxic in mammals at concentrations relevant to human exposure.

Oxidative stress

Overall, seven studies assessed the potential for glyphosate to induce oxidative stress. Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and their elimination. ROS are important for cell signalling and cycling and are normally physiologically-controlled to prevent cell damage.

Three studies assessed ROS production in response to *in vitro* treatment of human HepG2 cells with glyphosate (Chaufan et al. 2014), keratinocytes (HaCaT) (Elie-Caille et al. 2010) and erythrocytes (Kwiatkowska et al. 2014). In human HepG2 cells, a significant increase in ROS formation was observed in cells treated with a glyphosate-based formulation (140% of control), but not glyphosate technical or the glyphosate metabolite, AMPA (Chaufan et al. 2014). However, the OCS concluded that this study was of limited regulatory value, as: the product assessed is not registered for use in Australia; the concentration of glyphosate in the formulated product was unclear and cytotoxicity was higher than that observed for glyphosate technical. In addition, the LC₅₀ for the formulation was used in the experiments on ROS formation, while the LC₂₀ was used for the other treatments. In human keratinocytes, hydrogen peroxide (H₂O₂) was increased in cells treated with 50 mM glyphosate for 30 minutes (Elie-Caille et al. 2010). The concentrations of glyphosate used in this study were very high (between 10 and 70 mM). As the experiments were performed at the IC₅₀, cell responses due to osmotic stress rather than

glyphosate toxicity cannot be excluded. Furthermore, the EFSA RAR noted that the conclusion that treatment with glyphosate (50 mM) for 30 minutes resulted in overproduction of H₂O₂ was based on a qualitatively thicker and more intense fluorescent area in the cell cytosol, but no quantitative measurement was obtained. The OCS added that light microscopy images of the cells were not included. In human erythrocytes, significantly increased ROS production was observed following exposure to glyphosate, its metabolites and impurities at concentrations up to 5 mM (Kwiatkowska et al. 2014). However, the results were provided graphically without actual data, hence it is not possible to independently evaluate these results. Furthermore, no positive controls were tested, therefore the validity of the assays cannot be ascertained.

Chaufan et al. (2014) also investigated the enzymatic (catalase, CAT; glutathione-S-transferase, GST; superoxide dismutase, SOD) and non-enzymatic antioxidant activity (glutathione equivalents, GSH) in human HepG2 cells *in vitro* following exposure to either glyphosate, AMPA or a glyphosate-based formulation. Exposure to glyphosate did not increase the activity of any of the antioxidants evaluated. Exposure to a glyphosate-based formulation caused a significant increase in SOD and GSH activity, while exposure to AMPA also caused a significant increase in GSH. Tyrosine kinases are also important mediators of the cell signalling processes that are involved in various process such as cell proliferation and apoptosis, and have also been implicated in the development of cancer (Paul & Mukhopadhyay 2004). Chaufan et al. (2014) reported that exposure to the glyphosate-based formulation, but not glyphosate or AMPA increased tyrosine nitration compared with controls.

Overall, the OCS concluded that there was limited evidence for an increase in ROS production following exposure to glyphosate, its metabolites or impurities, or a glyphosate-based formulation in *in vitro* cell culture studies using high concentrations of the test substances; however, the weight-of-evidence indicates that exposure to glyphosate at concentrations relevant to human exposure is unlikely to result in increased ROS production in humans.

Caspases participate in the programmed cell death pathway. Some apoptotic cells display caspase 3/7 activity, in contrast to necrotic cells. Two studies investigated caspase activity *in vivo* in male Wistar rats, following ip administration of glyphosate (alone or in combination with other pesticides) (Astiz et al. 2009) and *in vitro* in human HepG2 cells (Chaufan et al. 2014). In rats, ip administration of glyphosate alone did not induce caspase 3 activity in liver or brain (Astiz et al. 2009). However, the sample size was small (n=4), the study was only conducted in males and the administration route (ip injection) is not directly relevant to human exposure scenarios. In human HepG2 cells, caspase 3/7 activity was indirectly measured in cell lysates. Caspase 3/7 activity was significantly increased by a glyphosate-based formulation, but not glyphosate technical. The OCS concluded that oxidative stress and apoptosis may be plausible mechanisms of action for the *in vitro* cytotoxicity of the glyphosate-based formulation; however, the concentrations of treatments were not specified, limiting the value of the study. Furthermore, the product assessed by Chaufan et al. (2014) is not registered for use in Australia, the concentration of glyphosate in the formulated product was unclear and the concentrations of treatments were not specified.

Calpains have also been implicated in apoptosis. In addition to investigating caspase activity, Astiz et al. (2009) also investigated calpain activity *in vivo* in male Wistar rats following exposure to glyphosate alone and in combination with dimethoate and/or zineb. In the liver, milli-calpain activity was not affected by glyphosate alone. In the brain, milli-calpain activity was significantly reduced in both the substantia nigra and cerebral cortex by glyphosate alone. The authors reported that similar data were obtained for μ -calpain activity, but the data were not presented in the publication. While the results presented by Astiz et al. (2009) were considered by IARC to be supportive of an oxidative stress mechanism of action for carcinogenicity by glyphosate, EFSA and the OCS both concluded that the results reported in brain tissue were not biologically plausible for humans, due to the

blood-brain barrier and rapid elimination of glyphosate via urine. Therefore, the OCS concluded that there was no reliable evidence that glyphosate exposure would be likely to increase caspase or calpain activity in humans following exposure via relevant administration routes.

Bolognesi et al. (1997) investigated oxidative stress in Swiss CD-1 male mice (n=3 per dose) following administration of either 300 mg/kg glyphosate technical or 900 mg/kg of Roundup® (~270 mg/kg glyphosate) via ip injection. Glyphosate technical increased 8-OhdG (8-hydroxy-2'-deoxyguanosine)—a marker of oxidative stress—in the liver 24 hours post-treatment, but did not stimulate a response in the kidney. In contrast, Roundup® increased 8-OhdG in the kidney at 8 and 24 hours post treatment, but did not induce a response in the liver. However, as no positive controls were used the validity of the assay cannot be confirmed.

Oxidative potential and impact on DNA was measured in human lymphocytes using Ferric-inducing ability of plasma (FRAP), thiobarbituric acid reactive substances (TBARS) and the human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) modified comet assay (Mladinic et al. 2009a). The authors reported significantly increased oxidative activity (increased frequency of micronuclei, nuclear buds, nucleoplasmic bridges, total antioxidant capacity (FRAP) and lipid peroxidation (TBARS)) at 580 µg/mL glyphosate. These effects were generally greater in the presence of an exogenous source of metabolic activation. However, no clear concentration-dependent effect was observed for any parameter. The number of early apoptotic and necrotic cells were significantly increased at 580 µg/mL, with and without metabolic activation. The authors concluded that glyphosate does not cause oxidative stress at concentrations relevant to human exposure. The OCS agreed with the conclusion by EFSA that as the study was not conducted according to international guidelines, it can only be used as supporting evidence for regulatory purposes and agrees with the authors' conclusions that the lack of a clear dose-response relationship coupled with positive effects only being apparent at the highest concentration of glyphosate tested indicate that glyphosate is not likely to cause oxidative stress at levels relevant to human exposure.

Three studies assessed various aspects of cell morphology and structural integrity *in vitro* in various human cell lines: HepG2 cells (Chaufan et al. 2014), keratinocyte HaCaT cells (Elie-Caille et al. 2010) and erythrocytes (Kwiatkowska et al. 2014). Human HepG2 cells treated with a glyphosate-based formulation exhibited a higher percentage of condensed and fragmented nuclei (23.5%) indicative of apoptotic cell death compared with negative controls, but positive control data was not provided (Chaufan et al. 2014). Although the OCS concluded that the glyphosate-based formulation was likely to be a stimulator of apoptosis, based on the changes in nuclear morphology and increased caspase 3/7 activity *in vitro*, they also concluded that this study was considered to be of limited regulatory value, for the reasons stated above. In human keratinocytes, exposure to glyphosate resulted in shrunken, elongated cells with significantly affected cell adhesion potential, indicative of apoptosis (Elie-Caille et al. 2010). However, the authors cautioned that the cell line used (HaCaT) exhibits possible distinct functional deficiencies compared with normal human keratinocytes and the results cannot be directly extrapolated to *in vivo* keratinocyte behaviour. Furthermore, a two-fold reduction in cell numbers was also observed. The OCS concluded that it was not possible, based on the information provided in the paper, to determine whether glyphosate induced structural cellular changes or whether sub-confluent cells may inherently develop abnormal morphology due to the reduction in cell numbers. In human erythrocytes, glyphosate exposure did not induce morphological changes (Kwiatkowska et al. 2014). In addition, Astiz et al. (2009) investigated the integrity of the inner and outer mitochondrial membranes and peroxidation of mitochondrial membrane lipids *in vivo* in male Wistar rats, again in both liver and brain cells. As the OCS concluded that the results in brain tissue were not biologically plausible in humans, only the results obtained from liver tissue are considered here. Glyphosate alone did not significantly reduce either inner or outer mitochondrial membrane potential and did not affect mitochondrial cardiolipin content in liver (Astiz et al. 2009). Nevertheless, the OCS and EFSA concluded that the study by Astiz et al. (2009) was

not reliable for regulatory purposes. Although the OCS concluded that there was limited evidence that a glyphosate-based formulation may be capable of stimulating apoptosis, there was not sufficient reliable information indicating that glyphosate is involved in apoptosis in humans, at realistic exposure concentrations and administration routes.

Overall, the OCS concluded that no definitive conclusions could be drawn on the ability of glyphosate products and their associated impurities to induce oxidative stress, as there is limited reliable information available regarding the involvement of an oxidative stress mechanism for inducing cytotoxicity.

4.3 Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

The JMPR is an expert scientific body that was established in 1963 and meets annually to scientifically evaluate pesticide residues in food. The JMPR provides expert scientific advice to the Codex Alimentarius Commission and its specialist committee on pesticide residues, the Codex Committee on Pesticide Residues. The Codex Alimentarius develops international food standards and guidelines, with the aim of protecting consumer health, ensuring fair trade practices and promoting coordination of all food standards work undertaken by government and non-government organisations.

There are two expert panels that meet in parallel (hence the term 'Joint Meeting'), the Toxicology Panel (the WHO's Core Assessment Group on pesticides), and the Residues Panel (Organised by the Food and Agricultural Organisation of the United Nations). The Toxicology Panel of the JMPR is responsible for evaluating the adverse effects of pesticides on human health (including carcinogenicity) and establishing health-based guidance values which in turn are important for establishing MRLs used in international trade. The Residues Panel are responsible for evaluating the dietary risks from residues present on food commodities and for setting MRLs. The JMPR is also at the forefront of developing new risk assessment methodologies for pesticides and setting international scientific policy on the interpretation of toxicological studies. Participation in the JMPR is not representational but based on expertise in toxicology and pesticide risk assessment.

The relationship between the WHO, JMPR and IARC

The WHO was established in 1948 to direct and coordinate international health within the UN's system. The IARC is the specialised cancer agency of the WHO, but has its own Governing Council and Scientific Council. While the JMPR also works under the banner of the WHO, its role is to conduct risk assessments for pesticide residues in food, which includes the potential for pesticide residues in food to adversely affect human health in many ways, not just the potential to cause cancer.

The IARC classifies various chemicals, substances and situations in terms of their carcinogenic hazard, which indicates that some level of exposure could increase the risk to cancer. On the basis of this hazard identification and classification process, the JMPR may determine that it is necessary to evaluate or re-evaluate the safety of residues of that chemical in food, following its use in agriculture. Therefore, the two processes are complementary: the IARC determines whether a chemical may potentially cause cancer, while the JMPR determines whether it is likely humans will develop cancer following exposure to realistic residues of that chemical in food.

Assessment process

The process used by JMPR to assess potential risks associated with pesticide residues in food is described in detail in the [International Programme on Chemical Safety \(IPCS\) Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food](#), which is a joint publication of the FAO and WHO. The IPCS has developed definitions of hazard and risk, which are adopted by JMPR for its risk analyses (IPCS 2009):

- hazard—inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent
- risk—the probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent.

Therefore, a risk assessment of food chemicals involves characterising the potential hazards associated with the chemical, as well as the potential risks to life and health resulting from exposure to those chemicals present in food over a specified period of time. This means that as well as looking at the potential for a chemical to cause harm, a risk assessment also considers the probability of that harm occurring as a result of realistic exposure scenarios. A risk assessment conducted by JMPR comprises four steps (IPCS 2009):

- Hazard identification—identification of the type and nature of adverse effects that a chemical is able to cause, taking into account the nature of the health hazard and the circumstances under which a hazard may be expressed.
- Hazard characterisation—assessment of the relationship between the administered dose of or exposure to a chemical and the incidence of the observed adverse health effect, including where possible, a dose-response relationship between increasing dose and health hazard incidence.
- Exposure assessment—evaluation of the exposure of for example, a human to a chemical and its derivatives, taking into account the occurrence and concentrations of the chemical in the diet, consumption patterns of foods containing the chemical, the likelihood of people consuming large amounts of those foods and the likelihood of high concentrations of the chemical being present in those foods. There are usually a range of intake or exposure estimates, which may be broken down by subgroups of the population.
- Risk characterisation—the information from the hazard characterisation and exposure assessment is integrated into suitable advice for risk-based decision making, by providing estimates of the potential risk to human health under various exposure scenarios, as well as the nature, relevance and magnitude of these risks.

The information generated from a risk characterisation may be either qualitative or quantitative, as defined by IPCS (2009) (Table 3). Any areas of uncertainty that result from gaps in the scientific evidence or any information on particularly susceptible subpopulations (eg young children, people with predisposing physiological conditions or people using the chemical as part of their occupation etc.) should be clearly outlined in the risk characterisation.

Table 3: Examples of qualitative and quantitative information outlined by the International Programme on Chemical Safety

Qualitative information	Quantitative information
Statements or evidence that demonstrates an absence	A comparison of dietary exposures with health-based

of toxicity even at high exposure levels	guidance values
Statements or evidence of safety in the context of specified uses	Estimates of risks at different levels of dietary exposure
Recommendations to avoid, minimise or reduce exposure	Risks at minimum and maximum dietary intakes
	Margins of exposure

The IPCS describes the general principles of toxicological study design, which should include compliance with GLP and adherence to internationally recognised organisations that provide guidance for standards of design and conduct of toxicological studies, such as the OECD. The IPCS outlines acceptable study design principles for determining absorption, distribution, metabolism and excretion, as well as general systemic toxicity, acute toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, food allergies/hypersensitivities and effects on the gastrointestinal tract and gut flora. There are also specific guidelines on designing and conducting studies in humans.

The IPCS goes on to provide guidance on the conduct of dose-response assessments, stating that where there is 'sufficient plausibility' for the presence of a cause-effect relationship, dose-response data are essential (IPCS 2009). Guidance is provided for setting health-based guidance values for substances present in food and drinking water, which are used to quantitate the range of acute or chronic oral exposure that presents no appreciable health risk. The ADI is generally set on the basis of the lowest NOAEL in the most sensitive species; however, a benchmark dose may also be used to determine the ADI. Where appropriate, an ARfD is also developed. Generally, a 100-fold uncertainty factor is used to convert the NOAEL obtained from a study using experimental animals into a health-based guidance value in humans; however, additional uncertainty factors may also be applied in certain circumstances (described by IPCS) (IPCS 2009). The default 100-fold uncertainty factor represents two 10-fold factors that allow for:

- differences between average responses in animals and average responses in humans
- variability in responses between average humans and highly sensitive humans.

Guidance is provided by IPCS on how to perform and interpret acute and chronic dietary exposure assessments for chemicals present in food. This assessment combines data about food consumption patterns with data about the concentration of chemicals in food to provide a dietary exposure estimate, which can be compared with the relevant health-based guidance value available for that chemical. The assessment should include the general population, as well as more vulnerable groups, or people expected to have different exposures from the general public, such as infants, pregnant women etc (IPCS 2009).

Pesticide residue data is evaluated by JMPR according to the IPCS guidelines, using data generated from pesticide use that was conducted according to Good Agricultural Practice, which stipulates that effective pest control be achieved while leaving the smallest residue amount practicable. National legislation stipulates MRLs, which are the maximum concentrations of pesticide (or veterinary drug) residues permitted in or on a food.

Importantly, the IPCS provides guidance on how to perform a risk characterisation as a part of the risk assessment process, which integrates the information obtained during the hazard characterisation process and the exposure assessment to provide advice to risk managers (IPCS 2009).

Assessment of glyphosate

Glyphosate has been assessed by JMPR in 2003, 2006 and most recently, in 2011. Following the IARC decision in March 2015 to reclassify glyphosate as 'probably carcinogenic to humans' and noting that new data may have been generated since the JMPR's most previous assessment of glyphosate in 2011, the WHO established an ad hoc expert taskforce to evaluate the available data relating to glyphosate and report its findings to JMPR. The task force completed its assessment of the IARC monograph in September 2015 and recommended that JMPR conduct a full re-evaluation of glyphosate, as the IARC assessment included a number of peer reviewed scientific publications that had not been available during the JMPR's 2011 assessment (WHO 2015).

In October 2015, the WHO issued a data call for a number of substances, including glyphosate. This evaluation of glyphosate was discussed at an extraordinary meeting of the JMPR at WHO headquarters in Geneva, Switzerland on 9 to 13 May 2016. The Meeting [summary report](#) was published online in May 2016.

The summary report contained a description of how the Meeting evaluated genotoxicity and epidemiological evidence for the active constituent glyphosate, glyphosate-based formulated products and metabolites (JMPR 2016). The Meeting evaluated a large number of genotoxicity studies that were identified via various means: direct submission to JMPR, searches of publicly available literature, requests to the IARC Monographs Secretariat, or requests to industry groups. The Meeting also searched databases for any relevant articles published after the studies cited in the IARC Monograph, using defined search terms. These studies were either unpublished studies that had been submitted by a sponsor to support an application for registration (the majority of which adhered to internationally accepted guidelines) or peer-reviewed studies published in the scientific literature. The studies were separated into categories that reflected their phylogenetic relevance and the significance of the genetic end-point measured: human biomonitoring studies, *in vivo* mammalian studies, *in vitro* mammalian cell culture models, *in vitro* bacterial models, phylogenetically distant organisms, metabolites *in vivo* and finally, metabolites *in vitro*. Overall, mammalian *in vivo* studies were given more weight than *in vitro* cell culture studies or studies using phylogenetically distant organisms, and studies of gene mutations and chromosomal alterations were given more weight than studies measuring less serious or transient types of genotoxic damage. Studies that measured the effects of oral exposure were considered to be more relevant for determining dietary exposure. Human biomonitoring studies were most likely to be confounded by exposure to other pesticides or other limitations. An overall weight-of-evidence assessment approach was used to reach conclusions about the genotoxicity of glyphosate, based on an evaluation of the studies using the criteria described above as well as an assessment of the overall quality of each study.

The meeting used a pre-agreed evaluation process, as described in the JMPR (2016) Meeting summary, to:

- select glyphosate/cancer site combinations for inclusion in the evaluation
- screen papers for inclusion or exclusion in the evaluation
- evaluate the information for risk assessment.

Glyphosate/cancer site combinations were included if IARC identified positive associations from the evidence it assessed and all studies cited by IARC, published since the IARC assessment was completed or identified from reference lists of already identified papers were screened for inclusion in the evaluation. Papers were included if they were the most recent publication with the longest follow-up period for that glyphosate/cancer site combination and/or the most complete analysis of that glyphosate/cancer site combination with the largest sample size/number

of participants, providing that the exposure assessment was specific to glyphosate and quantitative (ie exposure was expressed on a ratio scale), and that the paper was relevant and could contribute to a quantitative risk assessment for that glyphosate/cancer site combination.

As described in the JMPR (2016) Meeting summary, for each paper that was included in the assessment:

- the quantitative exposure units were determined
- the magnitude of effect or uncertainty was described
- the quality of the study was reviewed
- the exposure assessment was described
- the manner in which exposure levels compared or translated to glyphosate residue levels or pathways was described.

As described in the JMPR (2016) Meeting summary, for each glyphosate/cancer site included in the assessment:

- the hazard from all studies contributing to the quantitative risk assessment was characterised
- the strength-of-evidence was summarised.

When evaluating the evidence for glyphosate/cancer site associations, the Meeting considered factors that would decrease the level of confidence in the body of evidence (including the risk of bias, unexplained inconsistencies and imprecision) as well as factors that would increase the level of confidence in the body of evidence (including a large magnitude of effect, dose-response and consistency) (JMPR 2016). When evaluating the information available for risk assessment and hazard characterisation, the Meeting evaluated the overall evidence for dose-response relationships, by comparing risk estimates with quantitative exposure measures (eg days of use per year) (JMPR 2016).

The Meeting considered prospective cohort studies to be a more powerful study design than case-control studies, as case-control studies are usually retrospective and are therefore more prone to recall and selection biases (JMPR 2016). The one large, prospective cohort study (the AHS cohort) found no evidence of a positive association between glyphosate exposure and NHL incidence. Various case-control studies reported varying results, with some reporting elevated risks (both significant and non-significant) and others not observing an association. The Meeting concluded that there was some evidence of a positive association between glyphosate exposure and the risk of NHL; however, the AHS—a large, high-quality prospective cohort study found no evidence of an association at any exposure level (JMPR 2016).

The Meeting identified nine carcinogenicity studies in mice, two of which were considered to be of insufficient quality for inclusion in the assessment (JMPR 2016). Equivocal evidence of lymphoma induction was apparent in 3/7 studies in male mice and 1/7 studies in female mice at high doses (5000–40 000 ppm or 814–4348 mg/kg bw/day). In contrast, higher doses (up to 50 000 ppm or 7470 mg/kg bw/day) in the remaining three studies did not cause an effect. In 4/7 studies, there was a trend for a marginal increase in induction of kidney adenomas in male mice at the highest dose tested; however, again, higher doses failed to illicit a response.

The Meeting identified 11 combined chronic toxicity and carcinogenicity studies in rats; however, one was considered inadequate for carcinogenicity assessment (short exposure duration of only 12 months) (JMPR 2016).

An increased incidence of various tumours (interstitial cell tumours of the testes, pancreatic islet cell adenoma, thyroid C-cell tumours, skin keratoma) was observed in 1/10 or (in one case) 2/10 studies. However, in all cases, higher doses used in other studies did not illicit a response. The Meeting also reported a lack of dose-response relationship for some tumour types. There was no evidence for spleen or kidney lymphoma induction in any of the studies. Therefore, the Meeting concluded that there was no reliable evidence for treatment-related tumours in rats at doses of up to 32 000 ppm (or 1750 mg/kg bw/day).

The Meeting concluded that glyphosate is not carcinogenic in rats, but was unable to exclude the possibility that glyphosate is carcinogenic in mice at very high doses (JMPR 2016).

The overall weight-of-evidence suggested that oral doses of up to 2000 mg/kg bw/day glyphosate (either alone or in a formulated product) are not associated with genotoxic effects in the majority of studies in mammals. In cell culture models and organisms that are phylogenetically different to humans, DNA damage and chromosomal effects have been observed following exposure to glyphosate. However, these effects have not been replicated in oral *in vivo* mammalian model studies. Therefore, the Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures (JMPR 2016).

The Meeting's overall conclusion relating to the carcinogenic potential of glyphosate was that, the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity in mammals following oral exposure, along with the epidemiological evidence from occupational exposure indicated that glyphosate is unlikely to pose a carcinogenic risk to humans via exposure from the diet (JMPR 2016).

The Meeting also concluded that there was no evidence from seven studies in rats that up to 30 000 ppm (or 1983 mg/kg bw/day) glyphosate resulted in reproductive toxicity. There was also no evidence for teratogenicity or developmental toxicity in rats (up to 3500 mg/kg bw/day; four studies) or rabbits (low-incidence fetal effects were observed in 3/7 studies at doses that exceeded maternal toxicity). There was no evidence of endocrine disruption, with a range of *in vitro* and *in vivo* assays demonstrating no interaction with oestrogen or androgen receptor pathways or thyroid pathways. There was no evidence of neurotoxicity in rats (up to 2000 mg/kg bw/day) or immunotoxicity in female mice (up to 500 ppm, or 1448 mg/kg bw/day) (JMPR 2016).

Finally, the Meeting concluded that the extent to which glyphosate adversely effects the microbiota of the human or mammalian GIT is unclear, as this is an emerging area of scientific research. However, the available information on minimum inhibitory concentration values suggest that it is unlikely that dietary glyphosate residues would be capable of adverse effects on normal GIT microbiota function (JMPR 2016).

The Meeting further concluded that the glyphosate metabolite, AMPA, is unlikely to be genotoxic following oral exposure in mammals and there was no evidence for embryo or fetal toxicity. Similarly, two other metabolites, *N*-Acetyl-glyphosate and *N*-Acetyl-AMPA are unlikely to be genotoxic in mammals (JMPR 2016).

4.4 European Food Safety Authority (EFSA)

Assessment process

The European Food Safety Authority requires scientific information that has adhered to OECD guidelines on toxicological testing of chemicals and the [EU Test Method Regulation No. 440/2008](#), which stipulates in detail how the studies must be conducted. By European law, all required studies must be conducted according to the

principles of GLP. Scientific information that does not meet these standards but has been published in peer-reviewed journals are also included in the assessment.

When evaluating the carcinogenic effects of a chemical, the RMS delegated to conduct the assessment must follow the classification criteria outlined in EU Regulation (EC) No 1272/2008 on CLP criteria. The CLP criteria for establishing the level of evidence (eg sufficient, limited evidence etc.) for a carcinogenic effect are similar to those used by IARC; however, additional factors that influence the overall likelihood that a substance may be carcinogenic to humans must be taken into account. The emphasis placed on each individual factor is dependent on the amount and coherence of available evidence. Generally, more complete evidence is required to decrease the level of concern than is required to increase the level of concern. Some examples of factors to be taken into account include:

- tumour type and background incidence
- multi-site responses
- progression of lesions to malignancy
- reduced tumour latency
- whether responses are in single or both sexes
- whether responses are in single or multiple species
- structural similarity of the chemical to another substance for which there is good evidence of carcinogenicity
- routes of exposure
- comparison of absorption, distribution, metabolism and excretion between experimental animals and humans
- the possibility of a confounding effect of excessive toxicity at experimental doses
- mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression or mutagenicity.

Assessment of glyphosate

Glyphosate is registered for use throughout Europe and the UK and in 2010 was subjected to a re-assessment by the RMS, Germany, as mandated by the EC and coordinated by EFSA (See Section 2.3).

The BfR concluded that glyphosate was 'unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential' (EFSA 2015).

During the re-evaluation process, the BfR evaluated more than 150 new toxicology studies and re-assessed nearly 300 toxicological studies, as well as considering around 900 scientific publications and reviewing more than 200 in detail. The BfR concluded that the available data do not demonstrate that glyphosate exhibits carcinogenic or mutagenic properties or that it has adverse effects on fertility, reproduction or embryonal/fetal development in laboratory animals. The BfR concluded that there was convincing evidence that the toxicity associated with some glyphosate-containing products was attributable to co-formulants, such as tallowamines used as surfactants.

In July 2015, the BfR was commissioned to review the IARC monograph on the re-classification of glyphosate.

The BfR agreed with the conclusion that there is 'limited evidence in humans for the carcinogenicity of glyphosate' and its assessment of the epidemiological studies was comparable to that of the IARC Working Group. However, the BfR also noted that no consistent positive association between glyphosate exposure and the development of cancer was demonstrated and the most statistically highly-powered study detected no effect. The BfR further noted that it was not possible to differentiate between the effects of glyphosate and the co-formulants from the epidemiology studies discussed in the IACR monograph (Germany 2015).

The BfR disagreed with the conclusion by the IARC Working Group that there is 'sufficient evidence in animals for the carcinogenicity of glyphosate', which was based on a positive trend in the incidence of rare renal tumours, a positive trend for haemangiosarcoma in male mice and increased pancreatic islet-cell adenoma in male rats. The BfR assessed the studies relied on by the IARC Working Group and concluded that the weight-of-evidence suggests that there is no carcinogenic risk related to the use of glyphosate and that no hazard classification for carcinogenicity is warranted according to the CLP criteria (Germany 2015). Three studies conducted in mice reported a significant positive trend for renal tumours following glyphosate exposure, when data were analysed using the Cochran-Armitage test for linear trend; however, the analysis by pair-wise comparisons did not demonstrate a significant difference between the groups and the incidences of tumours were within the historical control range (up to 6% for adenoma and carcinoma combined). Similarly, two studies conducted in mice reported a significant positive trend for haemangiosarcoma following glyphosate exposure, when data were analysed using the Cochran-Armitage test for linear trend; however, analysis by pair-wise comparisons did not demonstrate a significant difference between the groups. Furthermore, the background incidence for haemangiosarcoma in male mice is up to 12%. Two of three studies conducted in mice reported a significant positive trend for malignant lymphoma following glyphosate exposure, when data were analysed using the Cochran-Armitage test for linear trend; however, the analysis by pair-wise comparisons did not demonstrate a significant difference between the groups in all three studies. Again, the incidences of malignant lymphoma were within the historical control range (up to 12%). The BfR determined that a significant difference to the incidence of pancreatic islet cell adenomas in rats occurred in the low dose group only, therefore was considered incidental (ie there was no dose-response effect). Therefore, the BfR concluded that the observed incidences of renal tumours, haemangiosarcoma and malignant lymphoma were spontaneous and not related to glyphosate exposure.

The BfR also disagreed with the IARC's conclusion that there 'is mechanistic evidence for genotoxicity, oxidative stress, inflammation, immunosuppression, receptor-mediated effects, and cell proliferation or death of glyphosate'. The BfR concluded that a weight-of-evidence assessment approach indicates that neither glyphosate nor AMPA induce mutations *in vivo* and no hazard classification for mutagenicity was warranted according to CLP criteria (Germany 2015). It further concluded that the mechanistic and other studies do not provide evidence for a carcinogenic mechanism. Consistently negative results were observed in *in vitro* bacterial assays and mammalian cell gene mutation assays and the majority (all of the GLP-compliant studies) of the *in vitro* chromosomal aberration tests and micronucleus tests were also negative. *In vitro* studies produced negative results for induction of DNA repair but positive results for induction of SCE and DNA strand breaks. *In vivo*, 14 somatic cell tests for induction of chromosomal aberrations or micronuclei were negative even at extremely high intraperitoneal doses and there was no evidence for mutagenic activity in germ cells. Two publications reported significant increases in micronuclei following ip administration; however, in both studies the dose tested was in the range of the ip LD₅₀ of glyphosate in mice and one study was fundamentally flawed in design. Two publications reported induction of DNA strand breaks following exposure to very high ip doses or repeated oral doses, which were close to or exceeded the ip LD₅₀ of glyphosate in mice; therefore, the observed positive results may be the result of secondary effects of cytotoxicity. However, the BfR noted that no firm conclusions can be drawn with regard to a need for classification according to the CLP criteria, regarding specific glyphosate-based formulations, for which there was some

evidence for *in vivo* mammalian chromosomal damage. The BfR recommended that further genotoxicity studies be conducted according to OECD test guidelines.

The BfR agreed with the IARC Working Group that glyphosate does not appear to exhibit endocrine disrupting properties (Germany 2015).

The BfR agreed with the IARC Working Group that there is some indication of induction of oxidative stress, based on *in vitro* studies using human cells and *in vivo* mammalian studies, particularly in blood plasma, liver, brain and kidney of rats; however, it was not indicative of genotoxic or carcinogenic activity in humans. Furthermore, the majority of this work was conducted using a glyphosate-based formulation rather than glyphosate alone. There was no indication of induction of oxidative stress by AMPA.

While the IARC Working Group concluded that there was 'weak evidence that glyphosate may affect the immune system, both the humoral and cellular response', the BfR concluded that the available data do not indicate that glyphosate or glyphosate formulations adversely affect the immune system (Germany 2015). However, it noted that the small number of available studies had methodological limitations and therefore no robust information was available to conclusively determine the possible immunomodulatory action of glyphosate. The BfR mostly agreed with the reporting of the studies relied on by IARC; however expanded on a number of points. For example, the IARC Working Group concluded that one study demonstrated 'pathological effects of glyphosate on the immune system' in rats (Chan & Mahler 1992). However, the only finding reported was a reduction in absolute/relative thymus weight in male rats at the highest dose of glyphosate tested. The BfR concluded that this reduction in thymus weight in male rats was likely related to non-specific toxicity, as evidenced by a lower weight gain and a lower final bodyweight (18%) in male rats, which was not observed in females.

4.5 The European Chemicals Agency (ECHA)

The ECHA is responsible for managing the harmonised classification (CLH) process for active constituent chemicals within plant protection products in the EU. The CLH is based solely on the hazardous properties (ie toxicity) of the chemical and does not take into account exposure; therefore, the CLH procedure conducted by ECHA is not a risk assessment. In that respect, the CLH procedure undertaken by ECHA is similar to the scope of the IARC assessment process.

As a part of the procedure for the renewal of the glyphosate registration in the EU, Germany submitted a proposal for CLH to ECHA. The ECHA launched a 45 day [public consultation of the CLH proposal](#) for glyphosate on 2 June 2016 (deadline for comment 18 July 2016). In addition to the existing CLH (eye irritation and aquatic toxicity), a new classification was [proposed](#) (ECHA 2016):

- STOT RE 2: May cause damage to organs through prolonged or repeated exposure.

This proposed classification was based solely on the results obtained from developmental studies conducted in rabbits (which appear to be the most sensitive laboratory animal species), where adverse effects (maternal toxicity; NOAEL = 50 mg/kg bw/day) occurred at doses lower than those occurring in the very large number of studies conducted in mice, rats and dogs over longer durations of exposure. Based on CLP hazard criteria, the NOAEL of 50 mg/kg bw/day is lower than the 28-day guidance value in rats (< 300 mg/kg bw/day) and therefore glyphosate technically qualifies for this statement.

The ECHA concluded that a weight-of-evidence approach indicated that glyphosate is not mutagenic and that no hazard classification for mutagenicity was warranted according to the CLP criteria (ECHA 2016). The ECHA considered that standard mutagenicity tests (eg cytogenetic tests or micronucleus assays) were more reliable and carried greater weight than 'indicator tests' (eg comet assays or DNA damage assessed via sister chromatid exchange or DNA strand breaks). Generally, these indicator tests are regarded as useful follow-up tests for confirmation of positive or equivocal standard *in vitro* test results.

Consistently negative results were obtained from *in vitro* bacterial assays and mammalian cell gene mutation assays. Guideline *in vitro* mammalian chromosome aberration tests and micronucleus tests also produced negative results. In contrast, positive results were reported in *in vitro* indicator tests for SCE and DNA strand breaks. Negative results were reported from 11 *in vivo* micronucleus tests or cytogenetic studies in somatic cells that followed international guidelines, while one study reported a weak positive effect in female mice receiving a very high (likely cytotoxic) dose. Inconsistent results were obtained in a number of published studies that did not adhere to international guidelines and generally tested low doses via the ip route. As for *in vitro* studies, positive results for DNA damage (eg strand breaks) were observed in a number of published indicator tests following high ip or repeated oral (via drinking water) administration, while a study assessing unscheduled DNA synthesis produced negative results. There was no evidence of mutagenic activity in germ cells of mice and rats following oral doses of up to 2000 mg/kg bw.

The ECHA concluded that a weight-of-evidence assessment of epidemiological data and data from long-term studies in both rats and mice indicate that no hazard classification for carcinogenicity was warranted for glyphosate according to the CLP criteria (ECHA 2016). In the discussion relating to carcinogenicity, the ECHA addressed the differing assessments of the available information by IARC and EFSA. The ECHA also noted that glyphosate differed from most other pesticides in that a number of comprehensive and high quality studies are available for nearly all toxicological endpoints.

A total of 5/8 long-term, guideline-compliant studies conducted in mice were considered by ECHA. The ECHA took into account the known very large variability of the incidence of spontaneous malignant lymphoma in both Swiss and CD-1 mice, the consistent lack of any dose-response relationship between tumour incidence and glyphosate exposure and the excessively high concentrations that elicited increased incidences of tumours in some studies and concluded that, overall, there was inconsistent evidence for the occurrence of malignant lymphoma, renal tumours and haemangiosarcoma in males but not females.

The ECHA evaluated a total of 7/11 studies conducted in rats, the majority of which (6/7) were guideline-compliant. The non-guideline study (Lankas 1981) was not considered suitable for regulatory purposes due to study design and reporting limitations. The ECHA took into consideration the consistent lack of statistical significance using pairwise analyses, the consistent lack of any dose-response relationships and the lack of reproducibility across multiple studies and concluded that there was no evidence for an association between glyphosate exposure and pancreatic islet cell adenomas, hepatocellular adenomas, C-cell thyroid adenomas or interstitial testicular tumours.

The ECHA also assessed human data on the potential carcinogenicity of glyphosate noting that the value of this data had limitations for regulatory assessments, as it was exclusively derived from epidemiological studies. Firstly, it is difficult to distinguish between the effects of the active constituent and co-formulants, because humans are never exposed to the active constituent alone. As the co-formulants are not only contained in glyphosate-based products, but are also contained within other formulated products, an assessment of the entire formulated product is not indicative of the safety of the active constituent or glyphosate-based products specifically. Secondly, humans

are exposed to a great number of environmental chemicals, making it difficult to attribute health effects to one specific chemical.

The ECHA described the results of the AHS study that analysed data from approximately 57 000 pesticide applicators. Analysis of this data did not identify an association between glyphosate and various forms of cancer, including leukaemia, melanoma, all lymphohaematopoietic cancers, NHL, or cancer of the lung, prostate, breast, colon, rectum, oral cavity, pancreas, kidney or bladder (De Roos et al. 2005; Blair & Freeman 2009). Some papers relied on by the IARC assessment reported positive associations between glyphosate exposure and NHL; however, this association was based on very small sample populations with low numbers of exposed subjects, relied on reported use (and was therefore susceptible to recall bias) by either primary or secondary (eg relatives) sources and was not statistically significant in one study (Nordstrom et al. 1998; Hardell & Eriksson 1999; McDuffie et al. 2001; De Roos et al. 2003; Hardell & Eriksson 2003; Eriksson et al. 2008). In contrast, the ECHA also described 18 papers that did not identify a risk between glyphosate exposure and various specific cancer types (Alavanja & Bonner 2012): prostate cancer (Alavanja et al. 2003; Band et al. 2011; Koutros et al. 2011), stomach and oesophageal adenocarcinomas (Lee et al. 2004), gliomas (Carreon et al. 2005), breast cancer (Engel et al. 2005; El-Zaemey et al. 2013), childhood cancer (following parental exposure) (Flower et al. 2004), pancreatic cancer (Andreotti et al. 2009), monoclonal gammopathy (Landgren et al. 2009), Hodgkin's lymphoma (Karunanayake et al. 2012), multiple myeloma (Pahwa et al. 2012; Kachuri et al. 2013), NHL (Schinasi & Leon 2014), lymphomas in general (including B cell lymphoma) (Cocco et al. 2013) or soft tissue sarcoma (Pahwa et al. 2011).

The ECHA concluded that, while epidemiological data is of limited value for detecting the carcinogenic potential of a pesticide, the data do not provide convincing evidence for an association between glyphosate exposure in humans and any cancer type and no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria (ECHA 2016).

Following the public consultation, any received comments will be provided to the Committee for Risk Assessment (RAC), which will form an opinion on the hazard classes that were open for consultation only. For glyphosate, these include: all health hazards except respiratory sensitisation and aspiration hazard (carcinogenicity, germ cell mutagenicity and reproductive toxicity) and all environmental hazards except ozone layer hazards. In addition, ECHA may request further clarification and contact some of those who commented to discuss specific issues. From there, any opinion of the CLH proposal must be adopted by RAC within 18 months from the receipt of that proposal by ECHA and the 'background document', which contains the CLH report with RAC evaluations inserted will be published on the ECHA website. The ECHA will then forward the RAC opinion to the EC, which will determine whether the CLH is appropriate.

4.6 Health Canada

In 2010, Health Canada's PMRA commenced a re-evaluation of glyphosate in collaboration with the US EPA's re-evaluation of glyphosate. In April 2015, the PMRA published its Proposed Re-evaluation Decision (PRVD2015-01) for glyphosate, as discussed above in Section 2.2. In conducting re-evaluations of registered products, the PMRA utilises data from holders of product registrations, as well as published scientific reports, information from other regulatory agencies and any other information considered relevant to the evaluation. The PMRA evaluation of the available scientific information concluded that there were no unacceptable risks to human health or the

environment as a result of using glyphosate according to the proposed label directions and no additional data were requested.

The re-evaluation report describes how the potential risks to human health are assessed, which is similar to the method employed by the APVMA. The PMRA re-evaluation of glyphosate determined that adverse effects observed in animals occurred at doses more than 100 times higher than levels to which humans are normally exposed when using glyphosate according to label directions. The re-evaluation reported that glyphosate has low acute oral, dermal and inhalational toxicity, does not irritate the skin or cause allergic skin reactions in laboratory animals; however, it was a severe eye irritant.

The PMRA determined that acute dietary exposure represented between 12% and 45% of the ARfD for all of the population subgroups. The chronic dietary exposure estimate for the general population represented 30% of the ADI, with a range of 20% to 70% of the ADI for the various population subgroups. As a result, the PMRA concluded that acute and chronic dietary risks were not of concern when glyphosate is used according to the label directions.

The re-evaluation also assessed residential handler exposure from mixing, loading and applying glyphosate product to residential lawns and turf (primarily dermal) as well as incidental oral exposure of children playing in treated areas. Bystander exposure was estimated for scenarios where people enter non-cropland areas, such as parks or hiking areas that had recently been treated with glyphosate. For all of these assessments, assessed either alone or in combination with background chronic dietary exposure (discussed above), no evidence of health risk was determined. Similarly, the risk estimates associated with mixing, loading and applying glyphosate in an agricultural scenario or re-entering treated agricultural sites did not demonstrate any health risks, based on the current directions for use and agricultural use patterns.

The PMRA re-evaluation report addressed the IARC conclusions, emphasising that a hazard classification is not a health risk assessment. They also stressed that the level of human exposure is the factor that determines the risk and that this was not taken into account in the IARC classification of glyphosate. The PMRA considered the epidemiological information included in the IARC assessment and concluded that the majority lacked adequate characterisation of glyphosate exposure, which limited their suitability for assessing the hazard of glyphosate.

The PMRA concluded that the available *in vitro* and *in vivo* tests demonstrated that glyphosate is not genotoxic in rats or mice and that glyphosate is not carcinogenic in rats. While there was some evidence for a marginal increase in the incidence of ovarian tumours in mice, no dose-response was evident and the increased incidence was only observed at the highest tested doses and historical control data were not available. Therefore, the PMRA concluded that these results were of low concern for human health risk assessment.

Overall, the PMRA concluded that the weight-of-evidence obtained from both acute and chronic animal toxicity studies, genotoxicity assays and epidemiology studies indicates that glyphosate is unlikely to pose a human cancer risk.

4.7 New Zealand Environmental Protection Authority

The New Zealand Environmental Protection Authority commissioned a review of the evidence relating to the carcinogenicity of glyphosate. The scope of the review covered the basis on which the IARC Working Group classified glyphosate as a probable human carcinogen, which involved reviewing the quality of the evidence for

carcinogenicity in humans and animal models, as well as the data used to support mechanistic arguments (Temple 2016).

The review concluded that a possible dose-response relationship in humans could not be evaluated, as the epidemiological evidence did not indicate whether any internal exposure was measured or, if there was, the extent of that exposure. The review also agreed with conclusions by WHO in 2006, which reported that weak, rarely statistically significant associations between glyphosate exposure and lymphopietic cancers do not generally meet the criteria for determining causal relationships from epidemiology data.

The review discussed each epidemiological study relied on by the IARC Working Group in its assessment that there was 'limited evidence' for carcinogenicity in humans, following exposure to glyphosate, as well as a review conducted by Mink et al. (2012) and the assessment conducted by the BfR for EFSA. As with other assessments, the review placed more weight on the prospective AHS cohort study, which did not identify an association between glyphosate and NHL, or a number of other cancer types, even though exposure was higher than that presented in the case-control studies. The review highlighted the fact that only two of the case-control cohort studies cited by the IARC Working Group reported statistically significant increased ORs at the 95% confidence level (Temple 2016).

The review noted that a small, non-significant increased risk of multiple myeloma was identified in the AHS cohort (De Roos et al. 2005), but described in detail the reassessment of that data, which questioned that result (Temple 2016). This re-assessment argued that the reported elevated risk ratio (RR) for multiple myeloma were not relevant, as they resulted from a restricted data set that (most likely by chance) were not actually representative of the population (Sorahan 2015). That is, a number of cases of multiple myeloma in the group of pesticide applicators who had never used glyphosate were excluded from the original analysis because they did not have data about the use of alcohol, smoking etc. This resulted in a false impression of increased risk in ever users, compared with those who had never used glyphosate. The re-analysis resulted in a RR of 1.1 (Sorahan 2015), compared with the original estimated rate ratio of 2.6, reported by De Roos et al. (2005).

One Swedish case-control study reported an association between glyphosate exposure and cancer risk after more than 10 years of exposure (OR 2.26, 95% CI 1.16–4.4) using 29 exposed cases and 18 unexposed controls (Eriksson et al. 2008) and was considered by the IARC Working Group to be a large study. In contrast, Temple (2016) concluded that 29 cases and 18 controls could not be considered a large study and had limited power to detect an effect. The significant effect reported in this study was only significant using a univariate evaluation and there was the possibility that results could have been confounded by earlier exposure to MCPA (2-methyl-4-chlorophenoxyacetic acid), which is associated with an increased risk of NHL.

The review highlighted that the key studies cited in support of 'sufficient evidence' for carcinogenicity in experimental animals consisted of three studies in mice: a positive trend for increased renal tubule carcinoma in one oral study; a positive trend for increased incidence of haemangiosarcoma in one oral study; and tumour promotion in a skin study. The review also highlighted that the IARC Working Group used different statistical tests (trend analysis) to assess the data in those studies, compared with the original analysis (pairwise comparisons). In the original pairwise comparisons, none of the studies produced positive associations. The IARC Working Group also did not take into account historical incidence data or the presence of a viral infection which may have affected survival rates and lymphoma incidence in one study. In addition, a number of studies that have been used by other regulators (which did not support an association between glyphosate and carcinogenicity) were not considered by the IARC Working Group noting that this is consistent with the scope of IARC. The New Zealand

review concluded that the total database of long-term carcinogenicity bioassays were consistently negative and the positive findings reported by the IARC Working Group are not considered supportive of carcinogenicity by other reputable scientific bodies, therefore the overall weight-of-evidence does not indicate that glyphosate is carcinogenic (Temple 2016).

The review concluded that the studies relied on by the IARC Working Group as 'strong evidence' for genotoxicity and oxidative stress primarily utilised *in vitro* mammalian cell studies, in which mammalian cells are directly exposed to glyphosate (or a formulated product) at high concentrations that are not realistic to *in vivo* exposure in animals or humans. The review highlighted that all studies that followed internationally accepted guidelines produced negative results, while all positive associations were achieved in studies that used unvalidated test methods or species, glyphosate formulations, or high intraperitoneal doses that are widely considered inappropriate for assessing genotoxicity in humans (Temple 2016).

The overall conclusion of the review was that, based on a weight-of-evidence approach that considered the quality and reliability of the available data, glyphosate is unlikely to be genotoxic or carcinogenic to humans and does not require classification as either a carcinogen or a mutagen (Temple 2016).

4.8 Adverse Experience Reporting Program (AERP)

The AERP is a post-registration program that assesses reports of adverse experiences associated with the use of agricultural and veterinary products, when the product has been used according to the approved label instructions.

Between 1996 and 2013, a total of four AERs relating to human safety were submitted to the AERP. All were classified as 'possible' or 'probable' by the AERP. Of the four AERs, one related to skin irritation while the remaining three were reports of eye irritation.

5 ASSESSMENT OUTCOMES

In the Tier 1 assessment, the OCS examined the reference list from the IARC Monograph 112 for glyphosate, which included 264 publisher papers. Following analysis of the study abstracts, 174 references were excluded from requiring further review (Table 6), mostly because the study utilised non-conventional species or methodology for evaluating human toxicity (eg fish). A total of 19 references were considered relevant to the carcinogenicity classification of glyphosate, requiring further in-depth revision (Table 4). The remaining 71 references were considered to require further review to determine their relevance to the carcinogenicity classification (Table 5). The APVMA will rely on international assessments of these papers.

The OCS concluded that, based on the results of the critical appraisal and the limited number of studies reviewed by the OCS in the Tier 2 assessment, there did not appear to be any additional information to indicate that glyphosate poses a carcinogenic risk to humans, on the basis of the following:

- a carcinogenic mechanism of action via genotoxicity or oxidative stress is not evident
- the level of cytotoxicity associated with *in vitro* genotoxicity testing of glyphosate was significant, limiting the ability of *in vitro* tests to determine the genotoxicity potential of glyphosate.

The OCS noted that there is some evidence that *in vitro*, glyphosate-based formulated products are more toxic to cells than glyphosate; however, this effect has not been confirmed *in vivo*. Furthermore, many of the studies exhibited significant methodological limitations, reducing the usefulness of the data.

No definitive conclusions could be drawn on the ability of glyphosate-based formulations to induce oxidative stress as there is limited information regarding the involvement of an oxidative stress mechanism for inducing cytotoxicity.

The OCS concluded that glyphosate was unlikely to pose a carcinogenic or genotoxic risk to humans.

The APVMA evaluated a number of recent assessments of glyphosate conducted by international organisations and regulatory agencies (JMPR, EFSA, ECHA, Health Canada and the NZ Environmental Protection Authority), which considered the publicly available data that was considered in the IARC monograph, as well as other published and unpublished data using a weight-of-evidence approach.

The APVMA agreed with the international assessments of the available epidemiological data that, while epidemiological data is of limited value for detecting carcinogenic potential of a pesticide, the weight-of-evidence does not provide convincing evidence for an association between glyphosate exposure in humans and any cancer type, as there was no consistent pattern of statistical associations that would suggest a causal relationship between glyphosate exposure and the development of cancer in adults or children (total or site-specific).

The APVMA agreed with the international assessments that the weight-of-evidence in experimental animals indicates that glyphosate does not pose a carcinogenic risk at realistic exposure levels, as no consistent dose-response relationship was evident in mice or rats and many of the reported tumours are common age-related tumours in rats and mice.

The APVMA agreed with the international assessments that glyphosate is not likely to be genotoxic, as well-designed *in vitro* tests consistently reported negative results. While some *in vitro* studies reported positive

results for, these were generally observed following very high intraperitoneal doses and most likely a secondary effect of cytotoxicity.

Between 1996 and 2013, a total of four 'possible' or probable' AERs relating to human safety (skin or eye irritation) were submitted to the AERP. The APVMA is confident that the current safety and use directions included on approved labels for products containing glyphosate are sufficient to mitigate these known adverse effects.

6 PROPOSED REGULATORY POSITION

On the basis of the evaluation of the scientific information and assessments, the APVMA concludes that the scientific weight-of-evidence indicates that:

- exposure to glyphosate does not pose a carcinogenic risk to humans
- there is no scientific basis for revising the APVMA's satisfaction that glyphosate or products containing glyphosate:
 - would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
 - would not be likely to have an effect that is harmful to human beings
 - would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment
 - would be effective according to criteria determined by the APVMA by legislative instrument, and
 - would not unduly prejudice trade or commerce between Australia and places outside Australia.
- **there are no scientific grounds for placing glyphosate and products containing glyphosate under formal reconsideration**
- the APVMA will continue to maintain a close focus on any new assessment reports or studies that indicate that any of the above conclusions may need revising.

APPENDIX A – LIST OF KEY STUDIES REFERENCED IN THE IARC MONOGRAPH 112 REQUIRING FURTHER REVIEW BY OCS (TIER 2, PART 1)

The studies referenced in the IARC monograph that the OCS recommended for review are presented below in Table 4. These studies were selected according to the criteria outlined in Section 0 to be assessed in Tier 2, Part 1 of the OCS evaluation to determine whether glyphosate should be placed under formal reconsideration.

Table 4: 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 Ramirez, 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	http://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), 2025–32	Liver and brain rat cell survival; MOA for oxidative stress seen in previous study	http://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), 1957–62	Uses roundup and glyphosate alone; positive results seen in both	http://pubs.acs.org/doi/abs/10.1021/jf9606518
Chan, P & Mahler, J	1992	genotoxicity	glyphosate	F344/N rats and B6C3F1	NTP technical report on the toxicity studies of Glyphosate (CAS No.	Effects in rats and mice; no mutagenicity in	http://europepmc.org/abstract/med/12209170

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
				mice	1071-83-6) Administered In Dosed Feed To F344/N Rats And B6C3F1 Mice. Toxicity report series, 16, 1-D3	salmonella; negative for LLNA	
*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	http://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), 331–39	Shows the timeline of membrane damage and ROS production in human keratinocytes	http://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), 184–91	Shows effects are dependent on formulation not glyphosate concentration	http://www.sciencedirect.com/science/article/pii/S0300483X09003047
*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	Shows effects are due to formulation; uses human keratinocyte cell	http://www.sciencedirect.com/science/article/pii/S0378517304005733

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
					journal of pharmaceuticals, 288(2), 219–26	line	
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	http://www.tandfonline.com/doi/abs/10.3109/10408444.2014.1003423#.Vf9hMvk0VcY
JMPR	2006	classification					http://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	http://www.ncbi.nlm.nih.gov/pubmed/23480780
*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	http://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), 537–46	Multiple genotoxicity tests; shows no genotoxic	http://toxsci.oxfordjournals.org/content/10/3/537.short

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
						potential	
*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	http://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), 800–7	Shows no clear dose dependent effect	http://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 carbofuran using cytome FISH assay. Toxicology letters, 189(2), 130–7	Cytome FISH assay; shows no hazardous effect on DNA at low concentrations	http://www.sciencedirect.com/science/article/pii/S0378427409002616
*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), 335–45	Suggests MOA not limited to plants	http://www.scielo.org.co/scielo.php?pid=S0120-41572005000300009&script=sci_arttext&lng=pt
Prasad, S, Srivastava, S, Singh, M &	2009	genotoxicity	glyphosate	swiss albino mice	Clastogenic effects of glyphosate in bone marrow cells of Swiss albino mice. Journal of toxicology,	Shows positive clastogenic and cytotoxic effects in mouse bone	http://www.hindawi.com/journals/jt/2009/308985/abs/

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
Shukla, Y					2009	marrow	
*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	http://www.sciencedirect.com/science/article/pii/0165121893901362

*Considered by EFSA (2015)

APPENDIX B – LIST OF KEY STUDIES REFERENCED IN THE IARC MONOGRAPH 112 THAT REQUIRE FURTHER REVIEW TO DETERMINE RELEVANCE TO THE CARCINOGENICITY CLASSIFICATION

The studies that were referenced in the IARC monograph that the OCS concluded required further assessment to determine their relevance to the carcinogenicity classification of glyphosate are presented below in Table 5. These studies were selected according to the criteria outlined in Section 0. The APVMA will rely on international assessments of these studies to determine whether glyphosate should be placed under formal reconsideration.

Table 5: 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	weblink
*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), 800–14	No direct reference to glyphosate in abstract, increased risk to 'other pesticides' only seen in subjects with a FHx of prostate cancer	http://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), 465–73	Glyphosate administered alone and in combo with other a.i.'s; unclear if results are for combo; in vivo rat model	http://www.sciencedirect.com/science/article/pii/S1382668909001392
Astiz, M, Hurtado de Catalfo, GE., García, MN, Galletti, SM,	2013	oxidative stress	glyphosate	wistar rat	Pesticide-induced decrease in rat testicular steroidogenesis is differentially prevented by	Oxidative stress seen in testicular cells; investigates	http://www.sciencedirect.com/science/article/pii/S0147651313000389

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
Errecalde, AL, de Alaniz, MJ, & Marra, CA.					lipoate and tocopherol. Ecotoxicology and environmental safety, 91, 129–38	antioxidant treatment after administration; 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	http://pubs.acs.org/doi/abs/10.1021/tx800218n
Benachour, N, Sipahutar, H, Moslemi, S, Gasnier, C, Traver, 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), 126–33	Uses glyphosate formulations, investigates toxicity and endocrine-disruption	http://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), 986–97	Columbian aerial spray program; uses formulation as exposure to glyphosate; measurement of binucleated lymphocytes with micronuclei as DNA damage	http://www.tandfonline.com/doi/abs/10.1080/15287390902929741#.Ve0iNfk0VcY
Brewster, DW, Warren, J, & Hopkings, WE.	1991	metabolism	glyphosate	SD rat	Metabolism of glyphosate in Sprague-Dawley rats: tissue distribution, identification, and	Tissue distribution study, shows no persistence in	http://toxsci.oxfordjournals.org/content/17/1/43.short

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
					quantitation of glyphosate-derived materials following a single oral dose. <i>Toxicological Sciences</i> , 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. <i>Cancer Causes & Control</i> , 4(2), 153–56	No direct reference to glyphosate or roundup; shows little evidence of association between pesticides and multiple myeloma	http://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. <i>Toxicology</i> , 320, 34–45	Uses formulation; neurotoxic effects on rat hippocampus	http://www.sciencedirect.com/science/article/pii/S030483X14000493
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. <i>Journal of medicinal food</i> , 14(10), 1263–72	Uses formulation; ip to mice; studies the effect of Ginkgo against effects seen	http://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. <i>Pestycydy</i> , 3	Chronic toxicity study review	

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
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), 1306–11	Uses formulation and adjuvant on Hep-2 cell line; shows toxicity and ROS	http://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	http://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), 1499–510	Apoptosis induced by glyphosate, neurodevelopmental study; uses human and mouse neural cells	http://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 health study. Environmental Health Perspectives, 118(6), 812–	Uses formulation; no results relating to glyphosate	http://www.ladep.es/ficheros/documentos/10(35).pdf

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
17							
*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	http://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), 375–82	Comparative study using glyphosate formulation; negative results	http://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), 121–35	Uses formulation; glyphosate not directly referenced in the abstract; no clear association with breast cancer	http://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), 1657–63	Uses formulation; results were not adjusted for multiple exposures; shows increased risk of NHL for glyphosate	http://onlinelibrary.wiley.com/doi/10.1002/ijc.23589/pdf

*Considered by EFSA (2015)

APPENDIX C – LIST OF KEY STUDIES REFERENCED IN THE IARC MONOGRAPH 112 REVIEWED BY THE EU IN 2013 THAT WERE NOT CONSIDERED BY THE OCS

Table 6 below lists the studies referenced in the IARC Monograph 112 for glyphosate that were not considered to require further evaluation by the OCS, as well as the reasons for exclusion.

Table 6: List of excluded studies based on criteria outlined in Section 4.2

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 fetal exposure to pesticides associated with GM foods	No	No
Band	2011	carcinogenicity		No direct reference to glyphosate, refrence 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
Chen	2012			DNA damage in cyanobacteria	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
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
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

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
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
US EPA	1980a	teratology		Not relevant to carcinogenicity endpoint	No	No
US EPA	1980b	teratology		Not relevant to carcinogenicity endpoint	No	No
US EPA	1992			Glyphosate in drinking water	No	No
US EPA	1997			Pesticides sales and usage	No	No
US EPA	2015			Tox database	No	No
US EPA	1991c			Peer review of glyphosate	No	No
US EPA	1993a			Glyphosate RED	No	No
US EPA	1993b			Glyphosate RED factsheet	No	No
US EPA	2011			Pesticides sales and usage	No	No
Eustis	1994			Multiple-section histo sampling	No	No
FAO	2000			Review	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
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
Gluszczuk	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
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

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Guilherme	2014a	oxidative stress		Not a relevant human model—fish	No	No
Guilherme	2014b	genotoxicity		Not a relevant human mode—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
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

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
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
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

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
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			Measurement of 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
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		Not relevant to carcinogenicity classification	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
		response				
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
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

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
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
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

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
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
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		Not relevant to carcinogenicity classification, not a relevant human	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
		disruption		model—fish		
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

ADI	Acceptable daily intake (for humans)
ADME	Absorption, distribution, metabolism and excretion
AER	Adverse Experience Report
AERP	Adverse Experience Reporting Program
Agvet Code	Agricultural and Veterinary Chemicals Code, Schedule to the <i>Agricultural and Veterinary Chemicals Code Act 1994</i>
AHS	Agricultural Health Survey
AMPA	Aminomethylphosphonic acid
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute reference dose
ATDS	Australian Total Diet Survey
BfR	Federal Institute for Risk Assessment
CAT	Catalase
CHO-HGPRT	Chinese Hamster Ovary-Hypoxanthine-Guanine Phosphoribosyl Transferase
CLH	Harmonised classification
CI	Confidence Interval
CLP criteria	Classification, Labelling and Packaging of Substances and Mixtures
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EOS	Earth Open Source
EP	European Parliament
EPSPS	Enzyme 5-enolpyruvylshikimate-3-phosphate synthase
EU	European Union
FAO	Food and Agriculture Organisation

FRAP	Ferric-inducing ability of plasma
FSANZ	Food Standards Australia New Zealand
GLP	Good laboratory practice
GSH	Glutathione
GST	Glutathione-S-transferase
HIV	human immunodeficiency virus
hOGG1	Human 8-oxoguanine DNA N-glycosylase 1
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	Kilogram
L	Litre
LD ₅₀	Lethal dose
MCPA	2-methyl-4-chlorophenoxyacetic acid
MEPs	Members of the European Parliament
mg/kg bw/day	Milligrams per kilogram of bodyweight per day
mg/L	Milligrams per litre
MRL	Maximum residue limit
NHL	Non-Hodgkin's lymphoma
NHMRC	National Health and Medical Research Centre
NOAEL	No observed adverse effect level
NRA	National Registration Authority
NRS	National Residue Survey
OCS	Office of Chemical Safety
OECD	The Organisation for Economic Co-operation and Development
OECD TGs	OECD Testing guidelines
8-OHdG	8-hydroxy-2'-deoxyguanosine

OR	Odds Ratio
PMRA	Pest Management Regulatory Agency
POEA	Polyethoxylated tallow amine (or polyoxyethylated tallow amine and various synonyms)
RAR	Renewal assessment rapport
RMS	Rapporteur member state
ROS	Reactive oxygen species
RR	Risk ratio
SCE	Sister chromatic exchange
SCGE	single cell gel electrophoresis
SOD	Superoxide dismutase
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
TBARS	Thiobarbituric acid reactive substances
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States
US EPA	US Environmental Protection Agency
US FDA	US Food and Drug Administration
WHO	World Health Organization

GLOSSARY

Acceptable daily intake	A level of intake of a chemical that can be ingested daily over an entire lifetime without any appreciable risk to health
Acute reference dose	The estimated amount of a substance in food or drinking-water, (expressed on a body weight basis), that can be ingested or absorbed over 24 hours or less, without appreciable health risk
Benchmark dose	A dose of a substance associated with a specified low incidence of risk, generally in the range of 1–10%, of a health effect; the dose associated with a specified measure or change of
Lethal dose	The amount of an ingested substance that kills 50 per cent of a test sample
Maximum residue limit	The highest concentration of a chemical residue that is legally permitted in a food
No observed adverse effect level	Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organism under defined conditions of exposure

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