



Australian Government
**Australian Pesticides and
Veterinary Medicines Authority**



MARCH 2017

**Final regulatory position: Consideration
of the evidence for a formal
reconsideration of glyphosate**

© Australian Pesticides and Veterinary Medicines Authority 2017

ISBN 978-1-925390-67-4 (electronic)

Ownership of intellectual property rights in this publication

Unless otherwise noted, copyright (and any other intellectual property rights, if any) in this publication is owned by the Australian Pesticides and Veterinary Medicines Authority (APVMA).

Creative Commons licence

With the exception of the Coat of Arms and other elements specifically identified, this publication is licensed under a Creative Commons Attribution 3.0 Australia Licence. This is a standard form agreement that allows you to copy, distribute, transmit and adapt this publication provided that you attribute the work.



A summary of the licence terms is available from www.creativecommons.org/licenses/by/3.0/au/deed.en. The full licence terms are available from www.creativecommons.org/licenses/by/3.0/au/legalcode.

The APVMA's preference is that you attribute this publication (and any approved material sourced from it) using the following wording:

Source: Licensed from the Australian Pesticides and Veterinary Medicines Authority (APVMA) under a Creative Commons Attribution 3.0 Australia Licence.

In referencing this document the Australian Pesticides and Veterinary Medicines Authority should be cited as the author, publisher and copyright owner.

Use of the Coat of Arms

The terms under which the Coat of Arms can be used are set out on the Department of the Prime Minister and Cabinet website (see www.dpmc.gov.au/pmc/publication/commonwealth-coat-arms-information-and-guidelines).

Disclaimer

The material in or linking from this report may contain the views or recommendations of third parties. Third party material does not necessarily reflect the views of the APVMA, or indicate a commitment to a particular course of action.

There may be links in this document that will transfer you to external websites. The APVMA does not have responsibility for these websites, nor does linking to or from this document constitute any form of endorsement.

The APVMA is not responsible for any errors, omissions or matters of interpretation in any third-party information contained within this document.

Comments and enquiries regarding copyright:

Director Public Affairs and Communication
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4701

Email: communications@apvma.gov.au

This publication is available from the APVMA website: www.apvma.gov.au.

CONTENTS

FOREWARD	5
EXECUTIVE SUMMARY	8
Introduction	8
Assessment of the carcinogenic potential of glyphosate: a weight-of-evidence approach	8
Consideration of public submissions	9
Final regulatory position	9
<hr/>	
1 INTRODUCTION	10
1.1 Current regulatory status of glyphosate in Australia	10
The Poisons Standard (SUSMP)	11
1.2 Health-based guidance values for glyphosate	11
Acceptable Daily Intake (ADI)	12
Acute Reference Dose (ARfD)	12
Maximum Residue Limits (MRL) and National Residue Survey (NRS)	12
Australian Total Diet Study (ATDS)	13
Drinking water standards	13
1.3 Legislative basis for a reconsideration of glyphosate	14
<hr/>	
2 SUBMISSIONS RECEIVED DURING THE CONSULTATION PERIOD	15
2.1 List of submissions	15
2.2 Assessment of submissions received during the consultation period	21
<hr/>	
3 INTERNATIONAL REGULATORY STATUS	22
3.1 United States	22
3.2 Canada	22
3.3 Europe and the United Kingdom	22
3.4 New Zealand	23
<hr/>	
4 EVALUTATION METHODOLOGY: THE WEIGHT OF SCIENTIFIC EVIDENCE	24

4 FINAL REGULATORY POSITION: CONSIDERATION OF THE EVIDENCE FOR A FORMAL RECONSIDERATION OF GLYPHOSATE

5	SUMMARY OF ASSESSMENTS AND CONCLUSIONS	26
5.1	The IARC glyphosate monograph	26
	Assessment of glyphosate by IARC	26
5.2	Assessment of the IARC monograph	27
	Previous OCS epidemiological review in 2005	28
	Tier 1 assessment of the IARC glyphosate monograph	28
	Tier 2 assessment of the IARC glyphosate monograph	28
5.3	Joint FAO/WHO Meeting on Pesticide Residues (JMPR)	31
5.4	European Food Safety Authority (EFSA)	33
5.5	The European Chemicals Agency (ECHA)	33
5.6	Health Canada	34
5.7	New Zealand Environmental Protection Authority	34
5.8	Adverse Experience Reporting Program (AERP)	35
5.9	Consideration of public submissions	35
6	ASSESSMENT OUTCOMES	36
7	REGULATORY POSITION	38
	ABBREVIATIONS	39
	GLOSSARY	42
	REFERENCES	43

TABLES

Table 1:	List of submissions to the glyphosate Proposed Regulatory Position report	15
----------	---	----

FOREWARD

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, the proposed regulatory decision document including a detailed description of the assessment, 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

6 FINAL REGULATORY POSITION: CONSIDERATION OF THE EVIDENCE FOR A FORMAL RECONSIDERATION OF GLYPHOSATE

<p>1. Nomination</p>	<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>	
<p>2. Prioritisation</p>	<p>Prioritisation. The APVMA (with input from its advisory agencies) determines the priority of the reconsideration.</p>	
<p>3. Scoping and work plan</p>	<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>	
<p>4. Notice of reconsideration</p>	<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>	
<p>5. Assessment</p>	<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. 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>	

6. Draft regulatory measure	<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, the environment and/or trade 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>
7. Consultation	<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>
8. Regulatory decision	<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 and/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>
END OF RECONSIDERATION (regulatory decision)	
9. Implementation	<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

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 previously 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.

Assessment of the carcinogenic potential of glyphosate: 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).

For a detailed description of the methodology used and the outcomes of this assessment, please refer to the proposed regulatory position document on the APVMA's website at www.apvma.gov.au/node/13891.

Consideration of public submissions

The proposed regulatory position report and the Tier 1 and Tier 2 OCS reports were published for public consultation from 30 September 2016 until 30 December 2016. In total, 197 submissions were received during the consultation period. Submissions were received from representatives of growers that use glyphosate (2), representatives of non-governmental organisations (NGOs) (8), a private business (1) and members of the public (186).

The majority of submissions received were beyond the scientific scope of the APVMA's assessment of the nomination for reconsideration of glyphosate. One submission raised concerns about the toxicity of N-nitrosoglyphosate (NNG; synonym N-nitroso-N-phosphonomethylglycine) that is often present as an impurity of glyphosate technical.

No new scientific evidence relating to the possible carcinogenicity of glyphosate that has not already been considered by the APVMA was received during the consultation period.

Final 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 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, thus 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 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. In these registered products, glyphosate is present at varying concentrations and are 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.

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, thus the implementation of any restrictions imposed by the TGA may differ between States and Territories.

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'.

1.2 Health-based guidance values for glyphosate

Health-based guidance values are established by regulatory authorities (and international bodies such as the Joint FAO/WHO Meeting on Pesticide Residues; 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 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. Thus, 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 for enforcement is the sum of glyphosate, *N*-acetyl-glyphosate and aminomethyphosphonic acid (AMPA) metabolite, expressed as glyphosate. For dietary risk assessment, the glyphosate residue definition is the sum of glyphosate, *N*-acetyl-glyphosate, aminomethyphosphonic acid (AMPA) and *N*-acetyl-aminomethyphosphonic acid (*N*-acetyl-AMPA), 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, 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. In the 2015–16 NRS report, glyphosate residues greater than half of the MRL were not detected in any samples of barley, canola, chickpea, cowpea, faba bean, field pea, lentil, linseed, lupin, maize, mung bean, sorghum, soybean, sunflower, triticale, wheat, wheat bran, wheat bran durum, wheat durum, wheat flour, wheat semolina, almonds or macadamias. In 2/35 samples of oats, glyphosate residues above half of the MRL were detected and in 1/35 samples of oats, glyphosate residues above the MRL were detected (NRS 2016).

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 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 SUBMISSIONS RECEIVED DURING THE CONSULTATION PERIOD

2.1 List of submissions

Following the publication of the APVMA's proposed regulatory position on glyphosate in September 2016, 197 submissions were received from representatives of growers that use glyphosate (2), representatives of NGOs (8), a private business (1) and members of the public (186) (Table 1). Of the 186 submissions received from members of the public, 172 were generated from an online petition campaign (submissions 23 to 194 in Table 1).

Table 1: List of submissions to the glyphosate proposed regulatory position report

Order of receipt	Submitter	Issue	Response
1	Seed breeding business, Victoria	Supports the proposed decision. Note importance of glyphosate for controlling weeds that pose a threat to the environment.	The APVMA acknowledges the submission.
2	Chemical sensitivities NGO, SA	Disagrees with proposed decision. Note other countries (Brazil, Portugal) moving towards banning glyphosate. Expressed concern about impacts on soil and to life on earth.	Outside of the scope (carcinogenicity) of the nomination assessment.
3	Private citizen, Victoria	Disagrees with proposed decision due to concerns about glyphosate residues on genetically modified (GM) crops	Outside of the scope (carcinogenicity) of the nomination assessment. The APVMA is not responsible for residue testing in foods.
4	Private citizen, Victoria	Disagrees with proposed decision, requests that the APVMA utilise the precautionary principle and withdraw approval until sufficient independent scientific information is available.	The APVMA utilises the scientific weight-of-evidence risk management approach outlined in the proposed regulatory position document and is confident that sufficient robust scientific information has been assessed.
5	Private citizen, Queensland	Disagrees with proposed decision, concerned that information on the APVMA's website regarding the regulatory status of glyphosate overseas is misleading.	The APVMA will edit the information provided on the webpage to improve clarity.

Order of receipt	Submitter	Issue	Response
6	Agricultural chemical and biotechnology representative, ACT	Supports the proposed decision. Notes that it is crucial that regulatory processes are based on accurate scientific data and independent assessment. Notes that numerous regulatory agencies have reviewed the data relied on by the IARC and have overwhelmingly concluded that glyphosate poses no unreasonable risks to humans or the environment when used according to approved label directions. Notes the substantial resources utilised by the APVMA to reaffirm the existing scientifically and technically robust regulatory position.	The APVMA acknowledges the submission.
7	Cotton grower representative, NSW	Supports the proposed decision. Note importance of glyphosate for weed management in Australian cotton farming systems. Supportive of the methodology utilised by the APVMA. Supportive of the APVMA maintaining close focus on any new scientific evidence that indicates the proposed regulatory position should be revised.	The APVMA acknowledges the submission.
8	Environmental NGO, Victoria	Disagrees with proposed decision. Request full reconsideration of toxicity (including endocrine disruption, genotoxicity, neurotoxicity, liver and kidney damage, ecotoxicity, effects on gut microbiome etc) of glyphosate and glyphosate-based products. Request that the APVMA assess the use of nanomaterials in glyphosate formulations. Request that APVMA commission new data and revise current health standards for glyphosate. Requested extension for public consultation period.	Outside of the scope (carcinogenicity) of the nomination assessment. The APVMA is not aware of any evidence that nanomaterials are used in glyphosate formulations. The APVMA does not commission research. The recent JMPR assessment determined that current health standards were appropriate. Whilst the APVMA acknowledges that the public consultation period concluded during the holiday period, we have no reason to believe that additional scientific information that has not already been assessed would be submitted if the consultation period was extended.
9	Private citizen	Disagrees with proposed decision due to concerns about the effects of glyphosate on human and animal health (reference study about piglet malformations; detections in urine and blood, no reference; toxic at low levels of exposure, no reference), and the environment (reference news article about a NSW DPI study about AMPA; reference permaculture news article about impacts of GMO-crops on biodiversity).	Outside of the scope (carcinogenicity) of the nomination assessment.

Order of receipt	Submitter	Issue	Response
10	Chemical pollutants NGO, NSW	Disagrees with proposed decision. Note glyphosate residue testing in foods by US FDA to begin; EU and Canada implemented risk management measures.	The APVMA is not responsible for residue testing in foods. As described in the proposed regulatory position report, current residue testing of food indicates that Australian consumers are not exposed to unsafe level of glyphosate.
11	GMO-free NGO, Victoria	Disagrees with proposed decision. Does not support the APVMA's evaluation methodology; request use precautionary principle. Request full reconsideration of toxicity of glyphosate and glyphosate-based products, commission research in conjunction with FSANZ to reassess residues in food, offer IARC opportunity to comment on APVMA's assessment, consider the impact of nanomaterials in formulated products, review current exposure levels to glyphosate products, and revise current health standards for glyphosate. Collaborate with FSANZ to determine residues on food.	The APVMA utilises the scientific weight-of-evidence risk management approach outlined in the proposed regulatory position document and is confident that sufficient robust scientific information has been assessed. The scope of the APVMA's assessment was limited to carcinogenicity of glyphosate, as per the IARC categorisation. The APVMA is not aware of any evidence that nanomaterials are used in glyphosate formulations. The APVMA does not commission research. The recent JMPR assessment determined that current health standards were appropriate. The APVMA is not responsible for residue testing in foods.
12	Public and Environmental Health NGO, Tasmania	Disagrees with proposed decision. Request full reconsideration of toxicity (substitution by glyphosate for glycine in vivo, chelating effects of essential metals causing deficiencies in vivo, effects on gut microbes, inhibition of cytochrome P450 enzymes, endocrine disruption, immune modulator, oxidative stress inducers, genotoxicity, antimicrobial resistance) of glyphosate and glyphosate-based products. Request that all industry data be re-analysed. Request re-assess NOEL and ADI (include data for Australian native flora and fauna). Request that any materials used to increase or amplify effects of glyphosate (nanoparticles and POEA) be reviewed. Request full review of carcinogenicity.	Outside of the scope (carcinogenicity) of the nomination assessment. The APVMA routinely analyses data provided by industry and has already done so for the nomination assessment of glyphosate. The recent JMPR assessment determined that current health standards were appropriate. The APVMA is not aware of any evidence that nanomaterials are used in glyphosate formulations. The APVMA assesses the toxicity of complete product formulations (including additional surfactants such as POEA) during the registration process. No new scientific data has been submitted to support the request for the APVMA to conduct a formal reconsideration of the carcinogenicity of glyphosate.
13	Private citizen, Tasmania	Disagrees with proposed decision due to concerns about the effects of glyphosate and adjuvants (particularly POEA) used in formulated products on human health (birth and reproductive defects, endocrine disruption, cancers, genotoxicity, neurotoxicity, respiratory problems, nausea, fever, allergies and skin problems).	Outside of the scope (carcinogenicity) of the nomination assessment. The APVMA assesses the toxicity of complete product formulations (including additional surfactants such as POEA) during the registration process.

18 FINAL REGULATORY POSITION: CONSIDERATION OF THE EVIDENCE FOR A FORMAL RECONSIDERATION OF GLYPHOSATE

Order of receipt	Submitter	Issue	Response
14	Private citizen, Tasmania	Disagrees with proposed decision. Note farming and living in rural areas is associated with poor health. Concerned about the environmental impact of glyphosate.	Outside of the scope (carcinogenicity) of the nomination assessment.
15	Pesticide NGO, WA	Disagrees with proposed decision due to concerns about the effects of glyphosate on human and animal health, and the environment. Concerned that APVMA has ignored the findings of the IARC. Concerned about herbicide resistance; effects of chemical combinations and residues on environment, wildlife and public health; off-label usage; correct use of PPE; independence of APVMA; influence of government policy on APVMA's decisions; carcinogenicity, neurological diseases and autoimmune diseases; soil and foliage testing for glyphosate residues; safety of children in public areas).	Outside of the scope (carcinogenicity) of the nomination assessment. The APVMA has conducted a thorough scientific evaluation of the information relied on by the IARC and has determined that there is not sufficient evidence to warrant placing glyphosate under formal reconsideration. Any concerns about off-label usage should be referred to State and Territory authorities. The APVMA makes regulatory decisions based on the available scientific information and does not have regard to government policy.
16	Environmental NGO, WA	Disagrees with proposed decision due to concerns about the effects of glyphosate on human health (cancer, endocrine disruption, kidney disease etc) and the environment, herbicide resistance under-reporting to the APVMA's AER program, and alleged off-label use.	Outside of the scope (carcinogenicity) of the nomination assessment. Any concerns about off-label usage should be referred to State and Territory authorities.
17	Private citizen, UK	Disagrees with proposed decision due to concerns about the effects of glyphosate on human health (obesity, statistics for disease rates in various populations, not referenced) and the environment (biodiversity in Great Barrier Reef). Provided information about an unpublished observational study of the biodiversity in a small nature reserve exposed to ultra-low dose Roundup. Note that RoundUp is 'banned' in France, Switzerland and Germany.	Outside of the scope (carcinogenicity) of the nomination assessment. The APVMA makes regulatory decisions independently based on the available scientific information. Note that claims that RoundUp is banned in some European countries is not correct.
18	Private citizen, Victoria	Disagrees with proposed decision. Concerned that the APVMA's assessment was incorrectly scoped (based on incorrect interpretation of the APVMA's legislation) and narrowly focussed (IARC also categorised other organophosphates as probably carcinogenic).	Outside of the scope (carcinogenicity) of the nomination assessment. The IARC also categorised malathion and diazinon as 'probably carcinogenic to humans'. These chemicals are currently under reconsideration by the APVMA, so were not addressed here.

Order of receipt	Submitter	Issue	Response
19	Private citizen, Victoria	Petition with signatures (62) attached. Request review all glyphosate formulations for all toxicity (including endocrine disruption and long-term effects on eg immune system).	Outside of the scope (carcinogenicity) of the nomination assessment.
20	Private citizen, WA	Disagrees with proposed decision due to concerns about the effects of glyphosate on human health (endocrine disruption). Notes attendance at the Monsanto Tribunal in the Hague in 2016. Provided report by Food Democracy Now about detections of glyphosate residues in food in the US.	Outside of the scope (carcinogenicity) of the nomination assessment. Current residue testing of food indicates that Australian consumers are not exposed to unsafe level of glyphosate.
21	Private citizen	Disagrees with proposed decision due to concerns about the effects of glyphosate and impurities (NNG) in formulated products on human health.	The Australian standard for glyphosate permits a maximum of 1 mg/kg NNG to be present in glyphosate technical. The toxicity of toxicologically significant impurities is included in the chemistry and toxicology assessments of the active constituent during the registration process.
22	Private citizen, Queensland	Disagrees with proposed decision due to concerns about the effects of glyphosate on human health (Parkinson's disease, foetal abnormalities; glyphosate detected in breast milk and urine), and residues in food (beer and honey). Concerned about off-label use and spray drift.	Outside of the scope (carcinogenicity) of the nomination assessment. Glyphosate has not been detected by validated methods at concentrations that would indicate acceptable health standards have been exceeded. Any concerns about off-label usage and spray drift should be referred to State and Territory authorities.
23	Sustainable agriculture NGO, Victoria	Disagrees with proposed decision due to concerns about the effects of glyphosate on human health (gut health imbalance, birth defects, autism) and the environment (soil ecosystems, GM crops). Concerned that other constituents in formulations contribute to toxicity. Glyphosate reported to be detected in vaccines.	Outside of the scope (carcinogenicity) of the nomination assessment The APVMA assesses the toxicity of complete product formulations (including additional constituents) in whole animal studies during the registration process. The study reporting glyphosate detections in vaccines has been widely criticised for using inappropriate and unreliable methodology.
24	Private citizen, WA	Petition with signatures (12) attached. Request review of toxicity (including endocrine disruption) and effects of long term exposure (particularly for illnesses related to immune system disruption and damage).	Outside of the scope (carcinogenicity) of the nomination assessment.

20 FINAL REGULATORY POSITION: CONSIDERATION OF THE EVIDENCE FOR A FORMAL RECONSIDERATION OF GLYPHOSATE

Order of receipt	Submitter	Issue	Response
25	Private citizen, Victoria	Disagrees with proposed decision due to concerns about the impacts of GM maize on human health.	Outside of the scope (carcinogenicity) of the nomination assessment The responsibility for regulating GM crops lies with the Office of the Gene Technology Regulator.
26-197	Private citizens, campaign submissions	Disagree with proposed decision.	Many of these submissions were outside the scope of the APVMA's assessment of the carcinogenic potential of glyphosate. No new scientific information that has not already been considered by the APVMA was provided.

2.2 Assessment of submissions received during the consultation period

The majority of submissions received were beyond the scope of the APVMA's assessment of the nomination for reconsideration of glyphosate.

One submission raised concerns about the toxicity of NNG that is often present as an impurity of glyphosate technical. The United States EPA concluded that less than 1.0 ppm NNG in glyphosate technical was not toxicologically significant (USEPA 1993). The Australian [standard](#) for glyphosate permits a maximum of 1 mg/kg NNG to be present in glyphosate technical. The toxicity of toxicologically significant impurities is included in the chemistry and toxicology assessments of the active constituent during the registration process.

No new scientific evidence relating to the possible carcinogenicity of glyphosate that has not already been considered by the APVMA was received during the consultation period.

3 INTERNATIONAL REGULATORY STATUS

For a more detailed description of the international regulatory status of glyphosate, refer to the proposed regulatory decision document on the website.

3.1 United States

The registration of glyphosate is currently being reviewed as a part of the US Environmental Protection Agency's (US EPA's) standard re-evaluation process. The [*Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*](#) was published by the US EPA in September 2016.

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.

3.2 Canada

In 2010 Health Canada's Pest Management Regulatory Agency (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. These included a restricted-entry period of 12 hours for agricultural uses, directions to apply when potential for drift into areas of human activity is minimised, environmental hazard statements, spray buffer zones, precautionary statements and use restrictions to reduce runoff to aquatic areas.

3.3 Europe and the United Kingdom

Glyphosate is registered for use throughout the European Union (EU) and the UK and in August 2014 was subjected to a re-assessment by the Rapporteur Member State (RMS), Germany, as mandated by the European Commission (EC) and coordinated by the European Food Safety Authority (EFSA). For more details about this assessment, please refer to the APVMA's proposed regulatory decision on glyphosate on the website.

The initial registration of glyphosate was scheduled to expire on 31 December 2015 (EC 2015). The EFSA recommended that a renewal of the registration of glyphosate be granted, and to accommodate a thorough peer review by the competent authorities of the EU Member States, 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 EU Standing Committee on Plants, Animals, Food and Feed (hereafter referred to as the Standing Committee) held a series of meetings to discuss the re-registration for glyphosate in the EU; however, the EU Environment Committee Members of the European Parliament (MEPs) were unable to reach a qualified majority regarding a decision.

Subsequently, on 29 June 2016, the EC extended the approval of glyphosate in the EU to allow the European Chemicals Agency (ECHA) to complete an assessment of glyphosate (expected by 31 December 2017). 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. These restrictions included:

- an EU-wide ban on polyethoxylated tallowamines (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.

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.

3.4 New Zealand

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.

4 EVALUTATION 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 international (eg Organisation for Economic Co-operation and Development; OECD) 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 International Programme on Chemical Safety (IPCS) (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 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. Thus, 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.

For more detailed information about the methodology used by the APVMA to conduct the nomination assessment of glyphosate, refer to the [proposed regulatory position](#) document on the website.

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

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

5 SUMMARY OF ASSESSMENTS AND CONCLUSIONS

For a detailed description of the APVMA's assessment outcomes, refer to the [proposed regulatory position](#) document on the website. Please note that the US EPA's assessment of the carcinogenicity of glyphosate was not available during the APVMA's assessment.

5.1 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 appoints a working group to evaluate carcinogenic risks to humans, which is guided by the [Preamble](#) (IARC 2006). 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.

The IARC Monographs evaluate cancer hazards (as opposed to cancer risks evaluated by regulatory bodies) and the Preamble cautions that cancer hazards may be identified even when the risks are very low at current exposure levels (IARC 2006). 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'.

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.

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 non-Hodgkin's lymphoma (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 good laboratory practice; 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), which concluded that exposure to glyphosate was not associated with all cancers combined or any cancer at a specific anatomical site (De Roos et al. 2005), 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 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.

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.

5.2 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). Thus, 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 in the proposed regulatory position document.

Tier 1 assessment of the IARC glyphosate monograph

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 (19; Tier 2, Part 1)
- relevance for the carcinogenicity classification for humans unclear and to be determined internationally (71; the APVMA will rely on international assessment of these studies)
- not relevant to the classification and excluded (174).

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 (see www.apvma.gov.au/node/14181).

Tier 2 assessment of the IARC glyphosate monograph

The Tier 2 assessment involved:

- Evaluation of 19 studies relevant to the carcinogenicity classification of glyphosate
 - 12 genotoxicity studies
 - five oxidative stress studies
 - one epidemiology study
 - one 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 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.

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. However, as no dose-response was observed, these were not considered to be treatment-related.

Greim et al. (2015) evaluated nine chronic toxicity/carcinogenicity (24 to 29 months) studies in rats submitted by industry. 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. Thus, the authors 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.

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

Genotoxicity

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

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.

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).

In addition to the chromosome aberration assay, two studies 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) (Li & Long (1988); Rank et al. (1993)).

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). 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. 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). 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.

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.

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).

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).

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.

5.3 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. 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 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.

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).

The 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 Meeting considered prospective epidemiological 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 10 appropriate combined chronic toxicity and carcinogenicity studies in rats (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. Thus, 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. Thus, 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 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).

5.4 European Food Safety Authority (EFSA)

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. The German Federal Institute for Risk Assessment (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).

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

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.

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.

5.5 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 (i.e. toxicity) of the chemical and does not take into account exposure; thus, 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 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). The ECHA held a 45 day [public consultation of the CLH proposal](#) for glyphosate between 2 June and 18 July 2016; comments are available on the ECHA's [website](#). The Committee for Risk Assessment (RAC) held the first [preparatory discussion](#) on the harmonised classification and labelling of glyphosate in December 2016. A second meeting is scheduled for March 2017 and the deadline for the RAC to adopt its opinion is the end of November 2017. Once it has been finalised, ECHA will submit the RAC's scientific opinion to the European Commission.

5.6 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.

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, the increased incidence was only observed at the highest tested doses and historical control data were not available. Thus, 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.

5.7 New Zealand Environmental Protection Authority

The New Zealand Environmental Protection Authority commissioned a review of the evidence relating to the carcinogenicity of glyphosate.

The 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 (Temple 2016).

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, thus the overall weight-of-evidence does not indicate that glyphosate is carcinogenic (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).

5.8 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 the use of glyphosate and 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.

5.9 Consideration of public submissions

During the public consultation period (30 September 2016 until 30 December 2016), 197 submissions were received from representatives of growers that use glyphosate (2), representatives of NGOs (8), a private business (1) and members of the public (186).

No new scientific evidence relating to the possible carcinogenicity of glyphosate that has not already been considered by the APVMA was received during the consultation period.

6 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, 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. The remaining 71 references were considered to require further review to determine their relevance to the carcinogenicity classification. 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 the use of glyphosate and 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.

No new scientific evidence relating to the possible carcinogenicity of glyphosate that has not already been considered by the APVMA was received during the public consultation period following the publication of the proposed regulatory decision.

7 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.

ABBREVIATIONS

ACT	Australian Capital Territory
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 Agricultural and Veterinary Chemicals Code Act 1994
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
CLP criteria	Classification, Labelling and Packaging of Substances and Mixtures
DNA	Deoxyribonucleic acid
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
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

40 FINAL REGULATORY POSITION: CONSIDERATION OF THE EVIDENCE FOR A FORMAL RECONSIDERATION OF GLYPHOSATE

GLP	Good laboratory practice
GMO	Genetically modified organism
GSH	Glutathione
GST	Glutathione-S-transferase
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
MEPs	Members of the European Parliament
mg/kg bw/day	Milligrams per kilogram of bodyweight per day
mg/L	Milligrams per litre
MOA	mode-of-action
MRL	Maximum residue limit
NGO	Non-governmental organisation
NHL	Non-Hodgkin's lymphoma
NHMRC	National Health and Medical Research Centre
NNG	N-nitrosoglyphosate (synonym N-nitroso-N-phosphonomethylglycine)
NOAEL	No observed adverse effect level
NRS	National Residue Survey
NSW	New South Wales
OCS	Office of Chemical Safety
OECD	The Organisation for Economic Co-operation and Development
OECD TGs	OECD Testing guidelines
PMRA	Pest Management Regulatory Agency
POEA	Polyethoxylated tallow amine (or polyoxyethylated tallow amine and various synonyms)

RAC	Committee for Risk Assessment (ECHA)
RAR	Renewal assessment rapport
RMS	Rapporteur member state
ROS	Reactive oxygen species
SCE	Sister chromatic exchange
SCGE	single cell gel electrophoresis
SOD	Superoxide dismutase
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
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
WA	Western Australia
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
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

REFERENCES

- Alvarez-Moya, C, Silva, MR, Ramirez, CV, Gallardo, DG, Sanchez, RL, Aguirre, AC & Velasco, AF 2014, 'Comparison of the in vivo and in vitro genotoxicity of glyphosate isopropylamine salt in three different organisms', *Genetics and Molecular Biology*, vol. 37, pp. 105–10.
- Astiz, M, de Alaniz, MJ & Marra, CA 2009, 'Effect of pesticides on cell survival in liver and brain rat tissues', *Ecotoxicology and Environmental Safety*, vol. 72, pp. 2025–32.
- Bolognesi, C, Bonatti, S, Degan, P, Gallerani, E, Peluso, M, Rabboni, R, Roggeri, P & Abbondandolo, A 1997, 'Genotoxic Activity of Glyphosate and Its Technical Formulation Roundup', *Journal of Agricultural and Food Chemistry*, vol. 45, pp. 1957–62.
- Chaufan, G, Coalova, I & Rios de Molina Mdel, C 2014, 'Glyphosate commercial formulation causes cytotoxicity, oxidative effects, and apoptosis on human cells: differences with its active ingredient', *International Journal of Toxicology*, vol. 33, pp. 29–38.
- De Roos, AJ, Blair, A, Rusiecki, JA, Hoppin, JA, Svec, M, Dosemeci, M, Sandler, DP & Alavanja, MC 2005, 'Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study', *Environmental Health Perspectives*, vol. 113, pp. 49–54.
- EC 2015, 'Commission Implementing Regulation (EU) 2015/1885 of 20 October 2015 amending Implementing Regulation (EU) No 540/2009 as regards the extension of the approval periods of the active substances, 2,4-D, acibenzolar-s-methyl, amitrole, bentazone, cyhalofop butyl, diquat, esfenvalerate, famoxadone, flumioxazine, DPX KE 459 (flupyrsulfuron-methyl), glyphosate, iprovalicarb, isoproturon, lambda-cyhalothrin, metalaxyl-M, metsulfuron methyl, picolinafen, prosulfuron, pymetrozine, pyraflufen-ethyl, thiabendazole, thifensulfuron-methyl and triasulfuron', *Official Journal of the European Union*, vol. L276, pp. 48–51.
- ECHA 2016, *CLH Report: Proposal for Harmonised Classification and Labelling: Substance name: N-(phosphonomethyl)glycine; Glyphosate (ISO)*, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, ECHA, Helsinki, available at <http://echa.europa.eu/documents/10162/9fb5d873-2034-42d9-9e53-e09e479e2612>.
- EFSA 2015, 'Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate', *European Food Safety Authority Journal*, vol. 13, pp. 107.
- Elie-Caille, C, Heu, C, Guyon, C & Nicod, L 2010, 'Morphological damages of a glyphosate-treated human keratinocyte cell line revealed by a micro- to nanoscale microscopic investigation', *Cell Biology and Toxicology*, vol. 26, pp. 331–9.
- FSANZ 2011a, *The 23rd Australian Total Diet Survey*, Food Standards Australia New Zealand, Canberra, available at www.foodstandards.gov.au/publications/documents/FSANZ%2023rd%20ATDS_v8_.pdf.
- FSANZ 2011b, *The 23rd Australian Total Diet Survey - Appendices*, The 23rd Australian Total Diet Survey, Food Standards Australia New Zealand, Canberra, available at www.foodstandards.gov.au/publications/pages/23rdaustraliantotald5367.aspx.
- Gasnier, C, Dumont, C, Benachour, N, Clair, E, Chagnon, MC & Seralini, GE 2009, 'Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines', *Toxicology*, vol. 262, pp. 184–91.
- Germany 2015, *Final addendum to the renewal assessment report: risk assessment provided by the rapporteur Member State Germany and co-rapporteur Member State Slovakia for the active substance glyphosate according to the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC laid down in Commission Regulation (EU) No. 1141/2010*, EFSA, Geneva, Switzerland, available at www.efsa.europa.eu.
- Greim, H, Saltmiras, D, Mostert, V & Strupp, C 2015, 'Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies', *Critical Reviews in Toxicology*, vol. 45, pp. 185–208.
- Hardell, L & Eriksson, M 1999, 'A case-control study of non-Hodgkin lymphoma and exposure to pesticides', *Cancer*, vol. 85, pp. 1353–60.

Hardell, L, Eriksson, M & Nordstrom, M 2002, 'Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies', *Leukemia & Lymphoma*, vol. 43, pp. 1043–9.

IARC 2006, *Preamble: IARC monographs on the evaluation of carcinogenic risks to humans*, International Agency for Research on Cancer, Lyon, France, available at <http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf>.

IARC 2015, *IARC monographs on the evaluation of carcinogenic risks to humans: Glyphosate*, International Agency for Research on Cancer, Lyon, France, available at <http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf>.

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

JMPR 2016, Report of the special session of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. FAO Plant Production and Protection Paper 227, Geneva, Switzerland, Joint FAO/WHO Meeting on Pesticide Residues.

Kier, LD & Kirkland, DJ 2013, 'Review of genotoxicity studies of glyphosate and glyphosate-based formulations', *Critical Reviews in Toxicology*, vol. 43, pp. 283–315.

Kwiatkowska, M, Huras, B & Bukowska, B 2014, 'The effect of metabolites and impurities of glyphosate on human erythrocytes (in vitro)', *Pesticide Biochemistry and Physiology*, vol. 109, pp. 34–43.

Li, AP & Long, TJ 1988, 'An evaluation of the genotoxic potential of glyphosate', *Fundamental and Applied Toxicology: Official Journal of the Society of Toxicology*, vol. 10, pp. 537–46.

Manas, F, Peralta, L, Raviolo, J, Ovando, HG, Weyers, A, Ugnia, L, Cid, MG, Larripa, I & Gorla, N 2009, 'Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests', *Environmental Toxicology and Pharmacology*, vol. 28, pp. 37–41.

McDuffie, HH, Pahwa, P, McLaughlin, JR, Spinelli, JJ, Fincham, S, Dosman, JA, Robson, D, Skinnider, LF & Choi, NW 2001, 'Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health', *Cancer Epidemiology, Biomarkers & Prevention*, vol. 10, pp. 1155–63.

Mink, PJ, Mandel, JS, Scurman, BK & Lundin, JI 2012, 'Epidemiologic studies of glyphosate and cancer: a review', *Regulatory Toxicology and Pharmacology*, vol. 63, pp. 440–52.

Mladinic, M, Berend, S, Vrdoljak, AL, Kopjar, N, Radic, B & Zeljezic, D 2009a, 'Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro', *Environmental and Molecular Mutagenesis*, vol. 50, pp. 800–7.

Mladinic, M, Perkovic, P & Zeljezic, D 2009b, 'Characterization of chromatin instabilities induced by glyphosate, terbuthylazine and carbofuran using cytome FISH assay', *Toxicology Letters*, vol. 189, pp. 130–7.

Monroy, CM, Cortes, AC, Sicard, DM & de Restrepo, HG 2005, '[Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate]', *Biomedica: revista del Instituto Nacional de Salud*, vol. 25, pp. 335–45.

Nordstrom, M, Hardell, L, Magnuson, A, Hagberg, H & Rask-Andersen, A 1998, 'Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study', *British Journal of Cancer*, vol. 77, pp. 2048–52.

NRS 2014a, *Almond Annual Report 2013-2014*, National Residue Survey, Canberra, available at www.agriculture.gov.au/SiteCollectionDocuments/agriculture-food/nrs/2013-14-results/almond.pdf.

NRS 2014b, *Oat Annual Report 2013-2014*, National Residues Survey, Canberra, available at www.agriculture.gov.au/SiteCollectionDocuments/agriculture-food/nrs/2013-14-results/oat.pdf.

NRS 2015, *Oat residue testing annual datasets 2014-15*, National Residues Survey, Canberra, available at www.agriculture.gov.au/SiteCollectionDocuments/agriculture-food/nrs/oat-residue-testing-datasets-2014-15.pdf.

NRS 2016, *Oat residue testing annual datasets 2015-16*, National Residues Survey, Canberra, available at www.agriculture.gov.au/SiteCollectionDocuments/agriculture-food/nrs/oat-residue-testing-datasets-2015-16.pdf.

Prasad, S, Srivastava, S, Singh, M & Shukla, Y 2009, 'Clastogenic effects of glyphosate in bone marrow cells of swiss albino mice', *Journal of Toxicology*, vol. 2009, pp. 308985.

Rank, J, Jensen, AG, Skov, B, Pedersen, LH & Jensen, K 1993, '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*, vol. 300, pp. 29-36.

Temple, W 2016, *Review of the evidence relating to glyphosate and carcinogenicity*, New Zealand Environmental Protection Authority, Wellington, available at www.epa.govt.nz/Publications/EPA_glyphosate_review.pdf.

USEPA 1993, *Reregistration eligibility decision (RED): Glyphosate*, United States Environmental Protection Agency, Washington, D.C., available at https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf.

WHO 2015, *Main findings and recommendations of the WHO Core Assessment Group on Pesticides Expert Task Force on diazinon, glyphosate and malathion*, World Health Organization, Geneva, Switzerland, available at www.who.int/foodsafety/areas_work/chemical-risks/main_findings_and_recommendations.pdf.