AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY

AUSTRALIA

CHEMICAL REVIEW PROGRAM

REVIEW OF THE MAMMALIAN TOXICOLOGY

AND

METABOLISM/TOXICOKINETICS

OF

PARAQUAT

SUMMARY REPORT

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PREFACE

This report was undertaken by the Office of Chemical Safety (OCS) at the request of the Australian Pesticides and Veterinary Medicines Authority (APVMA), under the Chemical Review Program. Paraquat is under review because of concerns over the potential risks to human health and the environment.

A draft toxicology review was submitted to APVMA in 2003 and was subsequently revised and updated in 2009, to address industry responses and to include additional published data. At that stage, the OCS identified published reports of neurotoxicity in mice following treatment with paraquat, where observed neurological lesions had similarities to those observed in patients with Parkinson's disease. In 2010, the APVMA requested that the OCS prepare a supplementary report specifically considering the potential neurotoxicity of paraquat, including relevant published literature. This assessment was extended in 2013 to include new unpublished studies investigating potential neurological effects in mice.

In 2015, the toxicological review of paraquat was completed and the report structured into three parts:

- Summary Report
  - *Comprises an overview of all relevant data available on paraquat relating to human health [this report].*

- Supplement I: Toxicology
  - *Comprises a detailed technical report on paraquat toxicology (excluding neurotoxicity).*

- Supplement II: Neurotoxicity
  - *Comprises a detailed technical report on paraquat neurotoxicity.*

These three reports should be considered together. This 'Summary Report' provides the consolidated hazard characterisation based on the data assessed in the two technical reports, background information on the history of paraquat, Australian health-based guidance values, international status and the advice and recommendations provided to the APVMA by the OCS arising from this Review.

The Occupational Health and Safety (OHS) assessment of paraquat products will be the subject of a separate report.

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1 ABBREVIATIONS

Time		Weight	
d	Day	**bw**	Body weight
h	Hour	**g**	Gram
min	Minute	**kg**	Kilogram
mo	Month	**mg**	Milligram
wk	Week	**µg**	Microgram
s	Second	**ng**	Nanogram
yr	Year	**wt**	Weight

Length		Dosing	
cm	Centimetre	**id**	Intradermal
m	Metre	**im**	Intramuscular
µm	Micrometre	**inh**	Inhalation
mm	Millimetre	**ip**	Intraperitoneal
Nm	Nanometre	**iv**	Intravenous
		po	Oral
		sc	Subcutaneous
		mg/kg bw/d	mg/kg body weight/day

Volume		Concentration	
L	Litre	**M**	Molar
mL	Millilitre	**ppb**	Parts per billion
µL	Microlitre	**ppm**	Parts per million

Haematology

Hb	Haemoglobin
Hct	Haematocrit
RBC	Red blood cell/erythrocyte
WBC	White blood cell/leucocyte

Anatomy

GIT	Gastro-intestinal tract
SN	Substantia nigra
SN pc	Substantia nigra pars compacta

Chemistry

MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP+	Methylphenylpyridinium ion
TH	Tyrosine hydroxylase

Terminology

ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose
F	Female
GLP	Good Laboratory Practice
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
LOEL	Lowest Observed Effect Level
M	Male
MRL	Maximum Residue Limit
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level

NOAEL	No Observed Adverse Effect Level
OHS	Occupational Health & Safety
PPE	Personal Protective Equipment
TGAC	Technical grade active constituent

Organisations & Publications

ACPH	Advisory Committee on Pesticides and Health
APVMA	Australian Pesticides and Veterinary Medicines Authority
CRP	Chemical Review Program
EU	European Union
EC	European Commission
FAISD	First Aid Instructions and Safety Directions
FAO	Food and Agriculture Organization (United Nations)
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety (WHO, FAO)
JMPR	Joint Meeting on Pesticide Residues
NDPSC	National Drugs and Poisons Scheduling Committee
NHMRC	National Health and Medical Research Council
NOHSC	National Occupational Health and Safety Commission
OCS	Office of Chemical Safety
OECD	Organisation for Economic Co-operation and Development
PMRA	Pest Management Regulatory Authority
PubCRIS	Public Chemical Registration Information System
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

2 EXECUTIVE SUMMARY

Paraquat is a non-selective contact herbicide belonging to the bipyridinium class of compounds which also includes the herbicide diquat. Both compounds share a similar mode of herbicidal action which involves the inhibition of photosynthesis (specifically photosystem I) thereby generating superoxide, leading to lipid peroxidation and membrane damage. Plants die rapidly after treatment and exposure to light.

This review considered data submitted by industry both as a response to the announcement of the review by the APVMA in 1997, and subsequently following the neurotoxicity concerns flagged by the Office of Chemical Safety (OCS) in 2009. The review also considered scientific assessments undertaken by pesticide regulators in other countries and the World Health Organisation (WHO) in addition to relevant published studies.

This report discusses both the toxicological and specific neurotoxicity concerns associated with paraquat, with the full assessments contained in separate reports (Supplement I: Toxicology and Supplement II: Neurotoxicity), and provides recommendations to the APVMA.

The toxicological assessment determined that the mechanism of mammalian toxicity of paraquat, like its mode of action in plants, is *via* the generation of highly reactive free radicals and consequent peroxidation of membrane lipids, sulfhydryl groups, proteins, and DNA, leading to membrane damage and cell death. The acute toxicity profile demonstrates that in laboratory animals paraquat is of moderate to high acute oral toxicity and high acute inhalational toxicity but low dermal toxicity, and has been shown to be highly toxic to humans by the oral route. Paraquat is a severe eye irritant, moderate skin irritant but not a skin sensitiser. The review also confirmed that the repeat-dose toxicity of paraquat, when administered by the oral or inhalational routes, is predominantly characterised by pulmonary lesions due to the preferential uptake of paraquat by the lungs, with other effects seen in kidneys and liver.

Potential neurotoxicity was evaluated in a separate supplementary report as paraquat has been implicated as a possible neurotoxicant and potentially a cause of Parkinson's disease. Paraquat is structurally similar to the known dopaminergic neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahdyropyridine (MPTP). For this reason it has been investigated as a possible etiological factor in Parkinson's disease. Neurotoxic effects, specifically death of dopaminergic neurons in the substantia nigra in the mouse brain, were noted when paraquat was administered by intra-peritoneal injection and this type of degeneration is also a pathological hallmark of Parkinson's disease in humans. This report evaluated several studies and noted that these induced neurotoxic effects were not reliable or reproducible in more recent studies. In this regard, some of the original studies reporting a positive association have since been withdrawn due to fraudulent reporting of results. Notwithstanding this, neurotoxicty findings are not supported by oral studies carried out according to Organisation for Economic Co-operation and Development (OECD) guideleines. Importantly, exposure via injection is not considered relevant to human exposure.

Expert opinion on two contemporary epidemiology studies concluded that the strength of association between paraquat exposure and Parkinson's disease cannot be considered robust. In addition, in a recent retrospective worker cohort study, there was no evidence of an increased

risk of Parkinson's disease in workers involved in the manufacture of paraquat, and paraquat poisoning case studies have failed to demonstrate neurotoxic effects.

After consideration of the toxicological data submitted for the purpose of this review, the ongoing approval of this active constituent is supported. This review confirmed the existing health standards. The OHS Assessment of products containing paraquat is the subject of an additional review report which will consider First Aid Instructions, Safety Directions (including the requirement for personal protective equipment) and re-entry intervals.

3 ADVICE & RECOMMENDATIONS TO THE APVMA

3.1 Approval Status

The present review has not identified any data that would impact the approval status of paraquat.

The OCS recommends that the APVMA should be satisfied that the continued approval of the paraquat active constituent would not be likely to have an effect that is harmful to human beings.

3.2 Minimum Compositional Standard

The current APVMA Standard for paraquat dichloride technical concentrate active constituent, including upper limits for toxicologically significant impurities total terpyridines and 4,4'-bipyridyl at 0.001 and 1 g/kg respectively, is considered to remain appropriate from a toxicological perspective.

3.3 HEALTH STANDARDS

3.3.1 Acceptable Daily Intake (ADI)

The present review noted the current Australian ADI of 0.004 mg/kg bw/d established in June 2003. The ADI was established by applying a 100-fold safety factor to the no-observed-effect-level (NOEL) of 0.45 mg/kg bw/d in a 1-year dog study based on pulmonary lesions at the next highest dose.

The present review has not identified a more suitable study or more sensitive toxicological endpoint to warrant changing the ADI.

3.3.2 Acute Reference Dose (ARfD)

An ARfD of 0.004 mg/kg bw was also established in June 2003 by applying a 100-fold safety factor to a NOEL of 0.45 mg/kg bw/d in a 1-year dog study based on pulmonary lesions at the next highest dose. The NOEL for pulmonary lesions in the 1-year dog study is anticipated to be similar for an acute exposure because the formation of lesions occurs after a single exposure and their severity was independent of dosing duration.

The present review has not identified a more suitable study or more sensitive toxicological endpoint to warrant changing the ARfD.

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4 BACKGROUND

4.1 Introduction

Paraquat (1,1'-dimethyl-4,4'-dipyridylium) is a quaternary-nitrogen, non-selective, contact herbicide belonging to the bipyridinium class of compounds. Paraquat's mode of action involves the inhibition of photosynthesis (specifically photosystem I) which generates superoxide, leading to lipid peroxidation and membrane damage. Plants die rapidly after treatment and exposure to light.

Paraquat was first registered for use in Australia in 1964 and is used extensively to control a wide range of grasses and broadleaf weeds among crops and in non-crop situations, and to desiccate seed crops prior to harvest. Formulations of paraquat, sometimes combined with its structural relative, diquat, have been available in Australia since the early 1960s.

Paraquat was one of 80 agricultural and veterinary chemicals originally identified as candidates for priority review under Australia's Chemical Review Program (CRP) administered by the Australian Pesticides and Veterinary Medicines Authority (APVMA). Paraquat was selected as a high priority chemical for review because of its high acute and chronic toxicity. There was also significant public interest in a review.

An initial toxicology assessment from the Office of Chemical Safety (OCS) in the Australian Government Department of Health in 2003 did not identify any issues of major concern regarding the continued availability of the chemical, noting that the existing strict controls in place were adequate to manage the risks of acute poisoning. However, at that time there were concerns in the public domain regarding possible links between long-term or chronic exposure to low doses of paraquat and an increased risk of Parkinson's Disease. In 2009 the APVMA requested the OCS prepare a supplementary report focusing entirely on the potential neurotoxicity of paraquat, which was submitted in 2010. Following this neurotoxicity supplement, additional studies were submitted by holders and assessed by the OCS, including unpublished studies conducted in 2013. This report comprises a summary of the review findings. The toxicological evaluation has been published as two separate technical reports: Supplement I: Toxicology and Supplement II: Neurotoxicity.

4.2 History of Public Health Considerations of Paraquat in Australia

Australian public health standards for agricultural and veterinary chemicals that may enter the food chain include the Poisons Schedule (SUSMP), First Aid and Safety Directions (FAISD), the ADI and ARfD. A further regulatory standard called the maximum residue limit (MRL) is established (by APVMA) and specifies the maximum residue limit for agricultural and veterinary chemicals in agricultural produce, particularly produce entering the food chain.

Maximum Residue Limits (MRLs) for paraquat were first established in 1964. The Australian ADI for paraquat was originally set in 1992, and the current ADI and ARfD were established in 2003. A history of the consideration of the toxicology of paraquat by regulatory committees in Australia is detailed below:

Date	Regulatory activity
July 1964	NDPSC: Recommended that paraquat be placed in Schedule 6. Consideration of scheduling of dilute preparations was deferred.
September 1964	NDPSC: Recommended that paraquat be included in Schedule 6 as follows: Diquat and paraquat except in preparations containing 5% or less of the sum of the two which are labelled and packed in accordance with Appendix A to these Schedules.
February 1969	PACC: Data requested from registrant to enable a tolerance for water to be set as residues of paraquat could constitute a public health risk. The request was based on a submission made by the Victorian Pesticide Review Committee concerning the use of paraquat for the control of aquatic weeds.
June 1969	NDPSC: Scheduling of paraquat and diquat reviewed due to 'numerous poisoning cases'. Committee decides that all preparations containing paraquat or diquat should be labelled with the signal word: 'POISON'.
January 1970	PACC: Noted that there was no reply from registrant regarding the request of February, 1969 meeting. The committee was informed that the Victorian authorities had requested registrant to remove all references to aquatic weed treatment from the labels and literature relating to paraquat.
August 1970	PACC: Received a submission, which indicated that the residues of paraquat that applied to water at recommended usage rate of 1 ppm were quickly inactivated and do not present a hazard to the public or animals. Use of paraquat for the control of aquatic weeds was accepted.
July 1972	NDPSC: The Committee considered that paraquat products should not be available to the general public, because of its unique toxicity insofar as its acute toxicity appeared to be secondary to its capacity to cause mortality. The Committee decided that paraquat be placed in schedule 7.
June 1973	PACC: New Schedule 6 entry: Paraquat in granular preparations containing 3% or less of paraquat was placed in schedule 6 following a request from registrant. (On assessing the data submitted by registrant, the committee considered that the inherent toxicity of paraquat precluded its inclusion in schedule 6 other than in granular preparations containing 3% or less.)
November 1974	NDPSC: Agreed to refer the first aid and safety directions supplied by the company to the working party on first aid instructions.
May 1977	NDPSC: Consideration of an application from registrant on inclusion of an emetic, in paraquat products. The Committee agreed to the proposed inclusion following consideration of existing scheduling status. Also decided that if registrant intended to use this emetic in any other substance, a full submission would be required.
May 1977	PACC: Consideration of an application from registrant for the inclusion in the list of approved adjuvants for AgVet chemicals, and exemption from the requirements of a MRL of the particular emetic. Deferred discussion on this until a Committee member provides a full evaluation of the issue.
August 1977	PACC: Following assessment of the data, the Committee agreed that as a general rule it was not sound preventive medicine to add any emetic to a chemical.
November 1977	NDPSC: Following consideration of a letter from registrant regarding incorporation of the emetic in paraquat formulations, and a letter from a committee member outlining the use of such an ingredient in toxic formulations, the Committee agreed to the proposed inclusion of the particular emetic in liquid paraquat formulations. The Committee felt that this was a unique, one-off situation, where inclusion of the emetic would be beneficial.
February 1978	NDPSC: Recommended that the NH&MRC to adopt the following: The incorporation of an effective emetic in paraquat should be mandatory.

Date	Regulatory activity
August 1978	PACC: Received a submission from registrant regarding incorporation of a particular emetic into granular formulations of paraquat. The submission was supported by data from a study in cynomolgus monkeys.
May 1980	PACC: Requested toxicology data from registrant. Also reaffirmed the NH&MRC policy on the requirement of an emetic in paraquat formulations and paraquat scheduling. A minute from the chairman seeking advice on the requirements for the toxicological data for 'image products' was considered.
November 1980	PACC: Received the data on paraquat toxicology and residue studies from registrant.
March 1981	PACC: Noted a letter from registrant indicating that it acknowledged that the use of the previously discussed emetic, beyond its inclusion in paraquat formulations was not permitted.
August 1982	NDPSC: Recommended that the NH&MRC amend its previous recommendation on the inclusion of an emetic with paraquat by adopting the following: in view of the unique mode of action of paraquat, the Council recommended that all preparations of paraquat should incorporate an approved emetic, which has been demonstrated to be effective when used in a particular formulation. Thus, the phrase 'gastric emptying' that appeared in the previous recommendation was deleted.
May 1984	PACC: Considered 5 studies submitted by registrant. Some of these studies replaced earlier submissions, which were considered to be either flawed or inadequate compared to contemporary standards. Three of these were replacement studies. A further replacement study (2-year rat study) was due in late 1984. The Committee agreed that the data provided a useful addition to the toxicological profile of paraquat and that the current scheduling status was appropriate.
November 1984	PACC: Considered current toxicology database. No outstanding requirements.
February 1985	NDPSC: S7 entry for paraquat was amended to read that 'this substance should be available only to licensed pest control operators, *bona fide* primary producers for approved pesticide purposes and for research purposes. Preparations should contain an effective emetic'.
January 1986	COT: The Committee considered registrant's position regarding mutagenicity of diquat. In their submission, X indicated that positive findings of some mutagenicity studies conducted with paraquat were an experimental artefact caused by antifoam.
August 1986	PACC: Noted that paraquat was to be re-evaluated by the JMPR in 1986. A report from that meeting was to be made available to the committee at a future meeting.
February 1987	PACC: Discussed the requirement of an emetic in paraquat formulations. In light of recent information indicating its ineffectiveness in preventing deaths, the committee felt that this requirement should be removed, and liquid paraquat preparations should contain a dye, and viscosity and stenching agent be added. Requested appropriate safety directions for consideration for FAISD. The committee received additional information from registrant on mutagenicity and inhalation toxicity. Noted that a positive mutagenicity result only occurred in the *in vitro* SCE test in Chinese hamster lung fibroblasts.
May 1987	NDPSC: decided that • the requirement that paraquat contain an effective emetic be removed • paraquat should be coloured blue or green and contain a stenching agent • paraquat be removed from the domestic market and not be available in packs weighing less than 20 kg,

Date	Regulatory activity
	• to accept the proposed signal headings of CAN KILL IF SWALLOWED DO NOT PUT IN DRINK BOTTLES KEEP LOCKED UP • to accept proposed safety directions • to delete S6 entry for paraquat
February 1988	PACC: Rejected a request to reconsider its decision to revoke all S6 entries. The Committee indicated that there was no need for paraquat products to be available in the domestic market, as there are many less toxic alternatives available.
August 1990	NDPSC: Consideration of a letter from the NHMRC representative on the ACAC advising that ACAC was seeking urgent clearance of 2 sources of paraquat. TGAC approvals were holding up clearance of end-use products. The main issue with the clearances was the presence of a contaminant, 2,2':6',2"-terpyridyl. Considered that it was necessary to determine the terpyridyl levels in both sources and relate its content to previous toxicology evaluation, with a view to make an entry in Appendix L. Suggested that the TGA Chemicals Unit review toxicology of terpyridyl for the next meeting. Sought details on the levels of 2,2':6',2"-terpyridyl in paraquat TGAC used in pivotal toxicity studies and any data on terpyridyl itself from the sponsors. TGAC approval was not supported from scheduling aspect.
June 1991	NDPSC: The statement 17, Part 1, Appendix J of SUSDP was amended to read, 'liquid preparations should be coloured blue or green and contain sufficient stenching agent to produce an offensive odour'.
November 1991	PACC: Examined the data on impurity profiles submitted by the sponsors, and approved 3 TGAC sources of paraquat that awaited clearance.
November 1991	NDPSC: Considered the data supplied by the sponsors on the levels and toxicity of the impurity, terpyridyl, in various TGAC sources of paraquat. Recommended a new Appendix L entry for paraquat terpyridyl (2,2':6,2"-terpyridine, 3 mg/kg). No objection to clearance of the 3 TGAC sources from a scheduling aspect.
May 1992	PACC: Considered an application submitted by registrant in support of a new source of TGAC . The Committee decided to consider this at its next meeting as it involves a change in NOEL/ADI listing.
August 1992	PACC: Reconsideration of an application for a new source of TGAC . This application was first considered in November 1991, but the NOEL/ADI was overlooked. A toxicological report prepared by the TGA Chemicals Unit in relation to this submission was considered. The report noted that the lung was the target organ in all species tested via oral, dermal, inhalation routes, resulting in destruction of alveoli, pulmonary fibrosis and death, and dermal absorption was greatly enhanced via damaged skin in humans. A NOEL of 0.38 mg/kg bw/d and an ADI of 0.004 mg/kg bw/d was set, based on a 1-year dog study. Agreed to clearance of the source.
August 1997	NDPSC: Recommended that the APVMA consider including paraquat as part of the ECRP. In addition, it questioned as to why it is not possible to replace paraquat with diquat.
August 1998	NDPSC: Considered data of Victorian and Tasmanian PICs on paraquat/diquat poisoning's. Exposures in Victoria had decreased from 17 in 1993 to 10 in 1997 of which 9 were accidental self-administration, and 1 was work-related. Tasmanian PIC had recorded one information call regarding paraquat. The Committee agreed that this information should be forwarded to the APVMA for consideration in the review.

Date	Regulatory activity
June 2003	ARfD established at 0.004 mg/kg bw based on a NOEL of 0.45 mg/kg bw/d from a 1-year chronic dog study.
June 2005	NDPSC: Considered a request for reconsideration of the scheduling of paraquat for a new formulation containing paraquat. The formulation was claimed to reduce oral poisoning incidents by addition of a 'safening agent' and as such inclusion into Schedule 6 was requested, supported by toxicity studies submitted to the OCS. The product was retained in S7 due to inadequacies in the data provided.
October 2005	cont…Additional data submitted late. Deferred until next meeting.
February 2006	cont…The Committee considered that its concerns relating to the lack of toxicological evidence to support a schedule 6 classification had not been sufficiently addressed to warrant the re-scheduling of paraquat at this time. Accordingly, the Committee agreed that, based on the unique toxicity profile of paraquat, including its capacity to cause mortality, that paraquat continue to be included in Schedule 7 of the SUSDP.
October 2006	NDPSC: Considered another request for reconsideration of the scheduling of paraquat for a new product based on the same technology claiming to provide a 'safening agent'. The Committee concluded that there was still insufficient evidence to support including paraquat in Schedule 6 of the SUSDP. The Committee agreed that the current scheduling of paraquat remained appropriate.

ACPH: Advisory Committee on Pesticides and Health; PACC: Pesticide and Agricultural Chemicals Committee of the NHMRC: National Health and Medical Research Council ; PIC: Poisons Information Centre; ACAC: Agricultural Chemicals Advisory Committee; DPSC: Drugs and Poisons Scheduling Committee; NDPSC: National Drugs and Poisons Scheduling Committee; FAISD: first Aid Instructions and Safety Directions. SCOT: NHMRC Standing Committee on Toxicity. SUSDP: Standard for the Uniform Scheduling of Drugs and Poisons (now known as SUSMP).

4.2 Health Standards

4.2.1 Existing ADI

The existing ADI for paraquat (as cation) of 0.004 mg/kg bw/d was established in 2003 and established by applying a 100-fold safety factor to the NOEL of 0.45 mg/kg bw/d in a 1-year dog study, based on the occurrence of pulmonary lesions at the next highest dose.

4.2.2 Existing ARfD

The existing Australian ARfD for paraquat of 0.004 mg/kg bw/d was established in 2003 by applying a 100-fold safety factor to a NOEL of 0.45 mg/kg bw/d in a 1-year dog study based on pulmonary lesions at the next highest dose. The NOEL for pulmonary lesions in the 1-year dog study is anticipated to be similar for an acute exposure because the formation of lesions occurred after a single exposure and its severity was independent of dosing duration.

4.2.3 Poisons Scheduling

At present, all paraquat formulations are classified as Schedule 7 poisons in the Standard for the Uniform Scheduling of Medicines and Poison (SUSMP) No.6, 2015.

In addition, the SUSMP states that for aqueous solutions of paraquat, the following cautionary statements are required on the product label [s.1(1.3) (1) (f)]:

CAN KILL IF SWALLOWED
DO NOT PUT IN DRINK BOTTLES
KEEP LOCKED UP

and a person must not sell or supply a Schedule 7 poison being a liquid preparation containing paraquat unless it is coloured blue or green and contains sufficient stenching agent to produce an offensive smell [s.6 (2) (b)].

4.3 International Toxicology Assessments

Joint FAO/WHO Meeting o Pesticide Residues (JMPR)

Paraquat has been reviewed by the JMPR in 1970, 1972, 1976, 1978, 1981, 1982, 1985, 1986 and most recently in 2003. In September 2003, the JMPR evaluated a considerable amount of new data generated since 1986 including studies on the absorption, distribution, metabolism and excretion of paraquat and numerous studies of toxicity (acute, reproductive and developmental). Furthermore, a substantial number of papers in the open literature on, *inter alia*, the genotoxicity and neurotoxicity of paraquat were reviewed.

The Meeting concluded that the available mechanistic and other animal studies did not support the hypothesis that paraquat residues in food are a risk factor for Parkinson's disease in humans.

The Meeting established an ADI of 0-0.005 mg paraquat ion/kg bw on the basis of a no-observed-adverse-effect level (NOAEL) of 0.45 mg paraquat ion/kg bw per day in the 1-year study in dogs and using a safety factor of 100. Although a 1-year study in dogs is not considered to be a long-term study, the nature and time-course of the pathogenesis of the lung lesions were such that the application of an additional safety factor was not considered necessary.

The Meeting established an ARfD of 0.006 mg paraquat ion/kg bw based on the NOAEL of 0.55 mg paraquat ion/kg bw per day in the 13-week study in dogs, with a safety factor of 100. Histopathological changes in the lungs were present at higher doses in both studies in dogs.

United States Environemental Protection Agency (US EPA)

Paraquat was first registered in the USA in 1964. It was used preplant or pre-emergence on vegetables, grains, cotton, grasses, sugar cane, peanuts, potatoes, and tree plantation areas; postemergence around fruit crops, vegetables, trees, vines, grains, soybeans, and sugar cane; during the dormant season on clover and other legumes; as a desiccant or harvest aid on cotton, dry beans, soybeans, potatoes, sunflowers, and sugar cane; and as a post-harvest desiccant on staked tomatoes. Paraquat is also applied to pine trees to induce resin soaking as well as being used on non-crop areas such as public airports, electric transformer stations and around commercial buildings to control weeds.

In its 1997 Reregistration Eligibility Decision (RED) (Case 0262), the US EPA (US EPA, 1997) concluded that paraquat dichloride would not pose unreasonable risks or cause adverse

effects to humans or the environment, when used in accordance with the approved label directions. The reference dose (RfD) for chronic dietary intake, including cancer, was established at 0.0045 mg/kg bw/d (expressed as paraquat cation), based on the NOEL of 15 ppm (0.45 mg/kg/d) in a one-year chronic dietary study in dogs, using an uncertainty factor of 100.

Paraquat has been classified as a Group E carcinogen (evidence of non-carcinogenicity for humans), based on the lack of evidence in acceptable animal studies. All paraquat products that have been registered in the USA are classified as Restricted Use pesticides.

The US EPA imposed new measures to mitigate occupational and ecological risks associated with the use of paraquat in the USA following the RED for paraquat in 1997. The maximum rate of application was reduced to 1.0 lb cation/acre with maintenance of the Restricted Use Classification. Additional personal protective equipment (PPE) are required for mixers and loaders. The concentration of paraquat in backpack sprayers was also reduced. Aerial applications were required to include the most current spray drift language. All paraquat products must place a statement in the "Environmental Hazard" section of the label that warns the user about possible adverse effects to non-target and semi-aquatic plants due to drift.

An ARfD of 0.0125 mg/kg bw was established in 2000 using the NOEL of 1.25 mg/kg bw/d[1] (and a uncertainty factor of 100) in a rat reproduction study based on the increased incidence of alveolar histiocytosis in parental animals at the next highest dose (Lindsay 1982 a,b).

In 2006, the total uncertainty factor (used by the US EPA) for the subpopulation of females aged 13-49 was set to 300, comprised of 10x for interspecies variation, 10x for interspecies extrapolation and 3x for uncertainty. The ARfD and APD for females 13-49 is 0.0042 mg/kg bw/d.

[1] The studies by Lindsay (1982 a,b) were evaluated by OCS as part of the current review. The NOEL established in the study was different to that determined by the US EPA because the US EPA's calculation of food consumption was based on the bodyweight of adult rats rather than juveniles.

International Program on Chemical Safety (IPCS)

The IPCS of the WHO published an Environmental Health Criteria (EHC) monograph in 1991 (Health and Safety Guide 51) covering the human health and safety aspects of paraquat.

Joint FAO/WHO Meeting on Pesticide Specifications (JMPS)

In 2003, the JMPS established a revised specification for paraquat technical concentrate under a new FAO/WHO procedure. These specifications promote the manufacture, distribution and use of pesticides that meet basic quality requirements. The specifications provide an international point of reference against which products can be judged, either for regulatory purposes or in commercial dealings, and thus help prevent the trading of inferior products. The FAO specification for paraquat dichloride was updated in 2008, with amendments for SL and SG formulations.

EC (European Commission)

Revocation in the European Union (EU)

Paraquat is not included in Annex 1 (active substances authorised for use in plant protection products within the EU) of the Plant Protection Products Directive (91/414/EEC) following an annulment of its inclusion in 2007.

In December 2003, Directive 2003/112/EC authorised the use of paraquat as a herbicide only, while precluding several use-patterns including knapsack and handheld applications in home gardening, use via broadcast air-assisted application equipment and ultra low volume applications.

Directive 2003/112/EC was annulled in 2007 upon appeal by Sweden (supported by other member nations Denmark, Austria and Finland), after it was ruled that the original decision had not adequately assessed or addressed all available information or addressed potential concerns.

EU health standards are as follows:

Health parameter	Value	Study	NOEL	Safety factor
ADI	0.004 mg/kg bw/d	Dog, 1-year	0.45 mg/kg bw/d	100
Acute RfD	0.005 mg/kg bw	Dog, 90-day	0.5 mg/kg bw/d	100

Canada

A re-evaluation of paraquat was completed in March 2006. It was largely based on the US EPA reregistration eligibility review conducted in 1997. The 1997 US EPA RED was found to address uses of paraquat dichloride that are also registered in Canada, and to address the main

science areas that were necessary for a Canadian regulatory decision. Based on the US EPA RED and Canadian use pattern, the Canadian Pest Management Regulatory Authority (PMRA) concluded that paraquat dichloride was acceptable for continued registration, provided that the required mitigation measures were implemented. Mitigation measures included cancellation of residential uses, increased requirements for protective equipment during handling and the requirement for agricultural buffer zones (PMRA, 2004, 2006).

The registrant notified the PMRA that they did not intend to support uses of paraquat dichloride on aquatic non-food sites, forests and woodlots (for conifer control and control of mixed stands of conifers and deciduous brush), industrial and domestic vegetative control for non-food sites (including chemical mowing) and turf. The PMRA agreed that there should no longer be a restricted use on the end-use product label and that the statement regarding residential areas and bystanders was no longer required.

New or revised label statements for further protection of workers and the environment (including PPE, buffer zones and other statements) were implemented. Specified buffer zones were between the point of direct application and the closest downwind edge of sensitive terrestrial and freshwater habitats. Buffer zones were not required for uses in fruit crops, shelterbelts and for the purposes of post-emergent chemical weeding.

In December 2015, Health Canada, published a Special Review Decision for paraquat to address new occupational health and safety, and environmental concerns. It was concluded that the registration of paraquat containing products can continue provided that certain risk reduction measures are implemented within specified timelines. These conditions included the designation of paraquat products as 'Restricted Class', requiring appropriate licencing of paraquat users. Various label amendments are required including provisions for additional PPE, hazard and environmental warning statements, restraints on backpack and ground boom application and refined mixing and loading instructions. An education program aimed at increasing awareness amongst users is planned for 2016 and 2017 (PMRA, 2015).

Brazil

In October 2015, the Brazillian Health Surveillance Agency, ANVISA, published a technical reassessment of paraquat, inviting public comment on a proposal to prohibit the use of paraquat on human health grounds. The proposed prohibition of paraquat is based on reported evidence of potential mutagenicity and neurotoxicity in humans (specifically Parkinson's disease), risks to workers handling paraquat products, and the lack of an effective antidote – all of which are grounds for prohibition under Brazilian legislation. Public consultation over the technical reassessment expired in November 2015, and as of February 2016, ANVISA are yet to make a final regulatory decision (ANVISA, 2015).

Sri Lanka

In November 2007 the Sri Lankan Department of Agriculture regulated for the need to reduce the concentration of paraquat from 20% to 6.5% from 2008. In addition, the import and use of paraquat was to be phased out completely over 3 years. In September 2010, the Sri Lanka Ministry of Agriculture reverted the phase-out decision and granted the permission to import and market paraquat 65 g/L formulations for use in plantations.

Other Countries

Paraquat is registered for use in many African countries, India, Indonesia, New Zealand, Philippines, Vietnam and Latin American countries.

In Malaysia, after the removal of registration in 2002, the Malaysian government allowed registration in 2006.

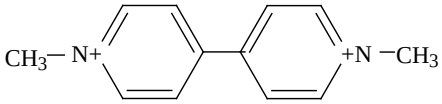
In Switzerland, the registrant decided to not seek re-approval of paraquat.

4.4 Global Registration Status of Paraquat (Gramoxone)

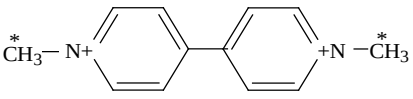
Paraquat is registered and sold in around 90 developed and developing countries around the world as listed below (source http://paraquat.com/safety/regulation, information dated August 2013):

Angola	Indonesia	Rwanda
Antigua & Barbuda	Iran	Samoa
Argentina	Iraq	Sao Tome & Principe
Australia	Israel	Singapore
Bahamas	Jamaica	Solomon Islands
Bangladesh	Japan	South Africa
Barbados	Jordan	Sri Lanka
Belize	Kenya	St Kitts & Nevis
Bolivia	Kiribaiti	St Lucia
Brazil	Madagascar	St Vincent & Grenadines
Cameroon	Malawi	Sudan
Canada	Malaysia	Suriname
Chile	Marshall Islands	Tahiti
China	Mauritius	Taiwan
Colombia	Mexico	Tanzania
Cook Islands	Morocco	Thailand
Costa Rica	Mozambique	Tonga
Cuba	Myanmar	Trinidad & Tobago
Dominica	Namibia	Turkey
Dominican Republic	Nauru	Tuvalu
Ecuador	New Zealand	Uganda
El Salvador	Nicaragua	Uruguay
Ethiopia	Nigeria	USA
Fiji	Niue	Vanuatu
Grenada	Pakistan	Venezuela
Guatemala	Panama	Vietnam
Guyana	Papua New Guinea	Zambia
Haiti	Paraguay	Zimbabwe
Honduras	Peru	
India	Philippines	

4.5 Chemistry: Manufacturing concentrate

Common name:	Paraquat dichloride Paraquat (ISO approved name for the cation)
Chemical name:	1,1'-dimethyl-4,4'-bipyridinium dichloride (IUPAC & CAS)
CAS Registry no:	1910-42-5 (dichloride) 4685-14-7 (cation)
Molecular formula:	$C_{12}H_{14}Cl_2N_2$ (dichloride) $C_{12}H_{14}N_2$ (cation)
Molecular weight:	257.3 (dichloride) 186.3 (cation)
Chemical structure (cation):	

Chemical and physical properties

Colour:	Off-white
Odour:	Slightly ammoniacal.
Physical state:	Hygroscopic crystals.
Melting point:	Approx. 340°C
Vapour pressure at 25°C:	$<<10^{-8}$ kPa
Partition coefficient:	-4.5 at 20°C (log K_{ow})
Density at 20^0C:	1.12-1.15 g/mL as dichloride salt. [At room temperature paraquat dichloride is a solid. The manufacturing concentrate is usually formulated as an aqueous solution
Solubility: in water at 20^0C: in organic solvents:	 620 g/L 143 g/L in methanol, <0.1 g/L in acetone, dichloromethane, toluene, ethyl acetate and hexane.
Stability:	Stable in neutral and acidic media, but readily hydrolysed in alkaline media. Photochemically decomposed by UV irradiation in aqueous solution (75% loss in 96 h in UV light).
^{14}C-methyl labelled paraquat:	(*denotes the position of the radiolabel) 

Paraquat Manufacturing Concentrate:

Declaration of Composition and Batch Analysis

As of February 2016, there are 19 paraquat dichloride manufacturing concentrates approved for use in Australia. Declarations of composition for the paraquat manufacturing concentrate were provided for this review.

Impurities

The impurities in the paraquat manufacturing concentrate, for which compositional standards have been established are 2,2': 6',2"-terpyridine and 4,4'-bipyridyl (Minimum Compositional Standards, APVMA). Free 2,2': 6',2"-terpyridine and 4,4'-bipyridyl have been declared at upper limits of 0.001 g/kg and 1 g/kg. Establishing an upper limit for 2,2': 6',2"-terpyridine can be supported on the grounds of its high acute oral and dermal toxicity (LD_{50} values are 2.17 and 4.31 mg/kg bw, respectively) in rats (Kuhn, 2002 a,b). An inspection of the Declaration of Composition from all registered sources indicates that the existing upper limit of 0.001 g/kg remains appropriate.

The acute oral toxicity of 4,4'-bipyridyl is moderate in rats with an LD_{50} value of 172 mg/kg bw. Following repeat dosing at 5.6 or 25.5 mg/kg bw/d for 3 months, no evidence for its carcinogenicity was observed in rats, except for transitional body weight loss and some renal histopathological abnormalities at the high-dose (Groce & Kimborough, 1982). An epidemiological study involving employees in plants that had been manufacturing this chemical for over 20 years, demonstrated no evidence of 4,4'-bipyridyl-related occupational hazards, including lung cancer (Paddle *et al*, 1991). In the absence of any additional toxicological concerns, the existing upper limit of 1 g/kg for 4,4'-bipyridyl is considered to remain appropriate.

4.6 Products

As at August 2016, there were 110 products containing paraquat registered in Australia. Of the registered products which contain paraquat, 66 contain paraquat only, 41 products contain paraquat in combination with diquat and 3 products in combination with amitrole. In products containing paraquat as the only active constituent, paraquat concentrations were 200, 250, 300, 334 or 360 g/L. In combination products, paraquat concentrations were 135 g/L with 115 g/L diquat or 125 g/L paraquat with 250 g/L amitrole or 250 g/L paraquat with 10 g/L amitrole. Formulation types were comprised mainly of soluble concentrates (SL) but also suspension concentrates (SC), aqueous concentrates (AC), emulsifiable concentrates (EC) and a single liquid product (LD). Product pack sizes range from 5 L to 1000 L.

5 HAZARD CHARACTERISATION

5.1 Toxicology Hazard Profile

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of absorption	Poor; in the rat, approximately 10-18% of an orally administered dose is absorbed.
Dermal absorption	Low; 0.3% in humans
Distribution	Distributes to most organs of the body. The highest initial concentrations were found in the kidney and the lungs.
Potential for accumulation	No evidence of accumulation, other than potential accumulation in the lungs
Rate and extent of excretion	Rapid; in the rat 60-90 % in faeces with 10-20% in urine in 72 h,
Metabolism	Not metabolised by rats. Generation of free radicals due to redox-cycling, primarily in the lung, causing oxidative tissue damage.
Toxicologically significant compounds (animals, plants and environment)	Paraquat and 2,2':6',2"-terpyridine (an impurity)

Acute toxicity (Manufacturing concentrate; approx 34% w/w paraquat cation)	
Note: Unless otherwise indicated, units are expressed as paraquat cation	
Rat oral LD_{50} (mg/kg bw)	100-249
Worst oral LD_{50} in other species (mg/kg bw)	22 (guinea pigs)
Lethal human dose (mg/kg bw)†	50 -80
Rat dermal LD_{50} (mg/kg bw)	>1448 (no deaths)
Worst dermal LD_{50} in other species (mg/kg bw)	No data
Rat inhalation LC_{50} (mg/m^3)	0.5
Worst inhalation LC_{50} in other species	No data
Skin irritation	Moderate irritant (rabbit)
Eye irritation	Severe irritant (rabbit)
Skin sensitisation (No evidence of sensitisation in humans)	Non-sensitiser (Buehler method)

Acute toxicity of 2, 2':6', 2"-terpyridine (impurity)	
Rat oral LD_{50} (mg/kg bw)	2.17 - 2.61
Rat dermal LD_{50} (mg/kg bw)	4.31 - 5.04

Short-term toxicity	
Target/critical effect	Lungs/oxidative tissue damage
Lowest relevant oral NOEL (mg/kg bw/d)	0.5 (13-week dietary study in dogs)
Lowest relevant dermal NOEL (mg/kg bw/d)	Not established – no reliable studies
Lowest relevant inhalation NOEC (mg/m^3)	0.01 (21-day rat whole body exposure)

Genotoxicity	Clastogenic effects at cytotoxic concentrations due to free radical damage. Negative *in vivo*. Some *in vitro* equivocal results.

LOEL (mg/kg bw, single dose applied dermally)	6 (induction of micronuclei at this dose and higher in rat bone marrow micronucleus assay)

Long-term toxicity and carcinogenicity	
Target/critical effect	Lungs/oxidative tissue damage
Lowest relevant NOEL (mg/kg bw/d)	0.45 (pulmonary lesions in male dogs, 1-year study)
Carcinogenicity	No evidence of carcinogenicity

Reproductive toxicity	
Reproduction target/critical effect	No effect on reproductive performance. Toxic effects on offspring only at maternotoxic doses (perivascular inflammatory cell infiltration in the lungs of pups).
Lowest relevant reproductive NOEL (mg/kg bw/d, 3-Generation dietary study in rats)	3.75 in pups (perivascular inflammatory cell infiltration in the lungs) 1.25 for parental animals (focal alveolar histiocytosis)

Developmental toxicity	
Developmental target/critical effect	Minor effects (delayed skeletal development at maternotoxic doses)
Lowest NOEL (mg/kg bw/d, oral gavage in rats)	1 - maternotoxicity (increased mortality, clinical signs and reduced body weight gain) 1 – foetotoxicity (reduced mean fetal and litter weights).
Lowest NOEL (mg/kg bw/d, oral gavage in rabbits)	<1 – maternotoxicity (effects on food consumption and body weight gain at all doses tested) 1 - fetal toxicity (increased incidence of post implantation losses and skeletal variations)

Neurotoxicity	Not neurotoxic by the oral route
Delayed neurotoxicity	No evidence of delayed neurotoxicity
Immunotoxicity	No data available

† Dose level at which there are reports of human deaths (Pond, 1990)

Summary	NOEL (mg/kg bw/d)	Study	Safety factor
ADI (0.004 mg/kg bw/d) (Pulmonary lesions)	0.45	1-year feeding study in dogs	100
ARfD (0.004 mg/kg bw) (Pulmonary lesions)	0.45	1-year feeding study in dogs	100

Note: Unless otherwise indicated 'paraquat' refers specifically to the paraquat cation

5.2 Toxicology studies summary

The toxicological database for paraquat is extensive and consists of unpublished reports generated by industry, in addition to an extensive range of published studies. The database was considered adequate. The following discussion is based on those studies evaluated in the two technical supplements to this review.

Paraquat is a member of the bipyridinium group of chemicals which also includes the herbicide diquat. There are currently two types of paraquat combination products registered in Australia, one containing both paraquat and diquat and the other paraquat and amitrole. Although both paraquat and diquat have similar oral LD_{50} values, paraquat produces lung lesions, while diquat does not. The lungs are the primary target for paraquat toxicity due to the presence of an active uptake mechanism. During its metabolism, paraquat is reduced to form a free radical, which then reacts with molecular oxygen to reform the cation and a superoxide anion. The latter then reacts with cellular H_2O_2 to form two hydroxyl radicals. The intracellular generation of free radicals causes oxidative damage to type I and II pneumocytes, followed by desquamation. This leads to oedema, alveolitis and exudation of granulocytes, all of which usually occurs within a few hours of an acute exposure. A regenerative phase then proceeds approximately 7-14 days after ingestion which is characterised by the proliferation of fibroblasts leading to fibrosis and possibly death. Renal damage is also a feature of paraquat intoxication, while multi-organ failure can also occur at higher doses.

5.2.1 Animal studies

Toxicokinetics and metabolism

In rats, approximately 10-18% of an oral dose of paraquat is absorbed. The concentration of paraquat in the plasma reached peak levels from 15 minutes to 2 hours following oral administration. Paraquat does not appear to bind to plasma proteins. In rabbits treated with large doses of paraquat (eg 30 mg/kg bw), a rebound increase in plasma levels has been noted 72 h after dosing, together with signs of impaired renal function.

Once absorbed, paraquat distributes to most organs of the body. The highest initial concentrations have been found in the kidneys and the lungs. Under *in vivo* conditions, paraquat is not extensively metabolised. In rats, approximately 90-95% of paraquat found in the urine after 72 h was unchanged. Three uncharacterised urinary metabolites, accounting for a small proportion of the administered dose (~0.1-0.8%) have been detected in rats following oral dosing. Intestinal microflora may be responsible for some unidentified faecal metabolites. In rats more than half of the administered dose is excreted in the faeces (60-70%) with smaller amounts in the urine (10%-20%). In rats and monkeys, measurable quantities of paraquat have been detected in the urine for up to 21 days after dosing, although some 45% of the administered dose was excreted in both the urine and faeces within 48 h of treatment. In rats, no major differences were seen in absorption, distribution and excretion following administration of ^{14}C-labelled paraquat by oral gavage regardless of the dose, frequency of dosing or sex of the study animals.

Although paraquat does not appear to accumulate in rat or rabbit lungs, the presence of an active uptake system is indicative of a potential for accumulation in this organ. The rate of

uptake by rabbit and rat lungs is similar suggesting that the same transport mechanism is operational in both species. Following oral dosing, the levels of paraquat in other rat tissues were generally low, except after inhalational or intra-bronchial administration.

Acute toxicity

The acute toxicity profile of paraquat is based on studies that have been conducted using the manufacturing concentrate, which contains approximately 33% paraquat cation. The acute oral toxicity of paraquat is moderate in rodents (LD_{50} range from 100 to 248 mg/kg bw), and high in guinea pigs, rabbits, dogs and monkeys (LD_{50}=22, 40-50 and 50 mg/kg bw, respectively). A range of clinical signs have been observed in laboratory animals following acute oral exposures including hypoactivity, dehydration, hypothermia, irregular breathing, reduced faecal output, piloerection, staining around the mouth and upward curvature of the spine. In humans, vomiting, abdominal pain, nausea, diarrhoea, ulceration of the oral and/or pharyngeal mucosa and gastrointestinal tract, irritability, dyspnoea, and tachycardia have been observed. In rats, the acute dermal toxicity of paraquat is low (LD_{50} > 1448 mg/kg bw) and the acute inhalational toxicity extremely high (LC_{50} = 0.5 mg/$m^{3,}$, whole body exposure, 4-h). The most concentrated aqueous solution of paraquat (33% paraquat cation, w/w was a severe eye irritant in rabbits. A 28.6% (w/w) paraquat solution was a moderate to severe skin irritant in rabbits when tested undiluted or up to 1:25 (v/v) dilution, but a slight irritant from dilutions of 1:50. Paraquat was not a skin sensitiser in guinea pigs.

Percutaneous absorption and dermal toxicity

Numerous studies have shown that percutaneous paraquat absorption is low. *In vitro* studies conducted on the manufacturing concentrate revealed that absorption across rabbit skin was approximately 1% over 10 h, and 2.5% over 55 h for human skin. In addition, human skin was found to be at least 40 times less permeable than animal skin tested *in vitro* (including rat, mouse, rabbit and guinea-pig). A single *in vivo* study conducted in male volunteers determined that approximately 0.3% of an applied dose was absorbed over 120 h.

Absorption across rat skin ranged from 0.003-16.54% of the applied dose and was approximately proportional to the amount applied. Human skin or isolated epidermis showed lower levels of absorption (0.0001-1.43%) and was also proportional to the amount of paraquat applied. In most studies, absorption rates were higher after 10-12 hours of administration, possibly due to tissue degradation. Although the composition of these formulations was largely unknown, a number of studies indicated that the presence of diquat had no effect on percutaneous paraquat absorption.

Consistent with the *in vitro* data indicating that percutaneous paraquat absorption is low, the dermal LD_{50} in rats is relatively low (>1448 mg/kg bw/d). No short-term repeat-dose dermal toxicity studies suitable for regulatory purposes conducted in laboratory animals have been assessed by the OCS.

In humans, there have been relatively few cases of fatality due to dermal paraquat exposure, although it appears that toxicologically-significant absorption can occur via damaged skin or sensitive skin areas such as the scrotum. Five fatalities were reported in Papua New Guinea as a result of occupational accidents or off-label use (to treat head lice or scabies). Exposure in

these cases was via several routes including the skin of the scrotum, back, thighs, scalp, head, face or nose, although in at least one case, oral ingestion was strongly indicated due to ulceration in the mouth and throat. Similar case reports have involved exposure of the scrotum resulting in pulmonary fibrosis, renal and respiratory failure, with eventual recovery of the patients. Other human poisoning cases reported systemic toxicity and death following absorption through scratches and cutaneous lesions (including skin blisters) on the arms and legs.

Most occupational studies have shown that clinical signs or death due to repeated dermal exposure to paraquat are rare. In an occupational setting, the major manifestation of dermal paraquat toxicity appears to be localised skin reactions, rashes, burns and dermatitis at the exposure site/s.

Repeat-dose toxicity

In numerous repeat-dose studies, the toxicological effects of paraquat were dose-related and appeared to be independent of sex, dosing route or duration. Dogs were the most sensitive test species followed by rodents and rabbits. Pulmonary toxicity was the predominant feature of repeated paraquat exposure, while renal damage can also occur. At high enough oral doses (~20 mg/kg bw/d in rodents, ~1 mg/kg bw/d in dogs) decreased body weight gain, clinical signs (ataxia, laboured or rapid breathing, general malaise, lethargy, piloerection, weight loss) and mortalities eventuated.

The types of gross and histopathological lung abnormalities observed in laboratory animals included alveolitis, alveolar wall thickening, congestion, collapse, fibrosis, haemorrhage, macrophage or lymphocyte infiltration, necrosis, oedema, the presence of inflammatory or congestive lesions of various size (a few mm to involvement of most of the lung) and colour (dark red, brown grey or black), and increased lung weight.

Paraquat-induced renal toxicity was evidenced by the occurrence of congestion, tubular degeneration, hydronephrosis and the urinary shedding of renal cells. Renal function was adversely affected as shown by the elevation in plasma urea and creatinine, and urinary glucose, protein and albumin. Several studies also showed elevations in haematocrit (Hct) and erythrocyte counts (RBC) which were probably the result of decreased plasma volume due to dehydration.

Localised tissue damage was apparent following inhalational or dermal exposure. Short-term inhalational studies conducted in rats revealed damage to the airways and throat, manifesting as metaplasia and/or hyperplasia of the epiglottis and arytenoid projections, and ulceration/necrosis and acute inflammatory cell infiltration in the larynx. Lung damage including loss of cilia and clara cells and the presence of mucous, debris or inflammatory cell infiltrates were also detected. Evidence of irritation, mucosal erosion or ulceration of the gastro-intestinal tract (GIT) were also observed in some rat and rabbit studies following oral dosing.

Although secondary to more severe effects such as those manifesting in the lungs, ocular abnormalities including injected retinal vessels and retinal engorgement were detected in some dogs during short-term repeat-dose and subchronic oral toxicity studies at varying doses from

0.175-3 mg/kg bw/d. Similar effects were not detected in a chronic study due possibly to the use of a lower dose range (up to 1.25 mg/kg bw/d). A clear dose-response trend was not apparent and any conclusion that the effects were treatment-related remains equivocal.

More pronounced systemic ocular effects were observed in rats during a chronic toxicity study including opacity in one or both eyes, and cataracts at and above 3.75 mg/kg bw/d, and lenticular degeneration at and above 1.25 mg/kg bw/d. Collectively these studies suggest that relatively high oral doses of paraquat can lead to ocular abnormalities in rats and dogs, however no studies have been performed to elucidate the mechanism of their formation.

Carcinogenicity and genotoxicity

Long-term feeding studies conducted in mice and rats revealed no evidence that paraquat was carcinogenic. Although one study suggested that paraquat induced proliferative lesions in the lung alveolar epithelium in rats at 10.9 mg/kg bw/d, the study did not provide unequivocal evidence of a neoplastic transformation in response to long-term paraquat administration.

The mutagenicity studies of paraquat generally showed little activity. The occasional finding of clastogenicity is weakened by the generally low regulatory standard of the evaluated studies.

The weight-of-evidence indicates that paraquat is non-mutagenic and therefore is not considered to pose a significant genotoxic risk to humans.

Reproductive and developmental toxicity

There was no evidence that paraquat caused reproductive toxicity in rats following dietary administration up to 14.5 mg/kg bw/d, despite evidence of systemic toxicity in parental animals and their offspring. Parental animals exhibited lung lesions, decreased food consumption and body weight, while offspring also showed decreased body weight in addition to hydrourethrosis or perivascular inflammatory cell infiltration in the lungs.

Treatment of male rats with paraquat *via* the dermal route at 0, 6, 15 or 30 mg/kg bw/d demonstrated a weak cytotoxic effect on germ cells, especially on epididymal sperm (day 7) and late spermatids (day 14). This effect was not noted on days 28 and 42 suggesting spermatogonia and spermatocytes present during the treatment period were not affected by treatment because they continued to mature into spermatids and spermatozoa. Although the study describes apparent effects on the morphogenesis of spermatozoa, this lacked a dose response relationship. The significance of a potential weak cytotoxic effect on male germ cells is questionable considering other studies investigating the effect of paraquat on reproduction do not demonstrate an effect on male fertility.

There was no evidence that paraquat had any teratogenic potential based on a range of studies conducted in mice, rats and rabbits. Minor skeletal variations such as delayed or incomplete ossification, reduced fetal weight and viability, were apparent at maternotoxic doses. Post-implantation losses were also observed in one rabbit study at maternotoxic doses. Maternotoxicity was characterised by mortalities, clinical signs, decreased food consumption and body weight loss. Evidence of pulmonary toxicity in maternal mice and rats was also apparent in some studies. The lowest maternal NOELs in mice, rats and rabbits were the same

(1 mg/kg bw/d) consistent with the lowest fetal NOELs in rats and rabbits (1 mg/kg bw/d). In mice, the fetal NOEL appeared to be somewhat higher than in rats and rabbits.

In humans, paraquat has been found to cross the placenta and concentrate to levels 4-6 times greater than in maternal plasma following deliberate ingestion. In a human case report, at maternally fatal doses, all foetuses died following emergency caesarean sections or were still-born. Two women that survived experienced a normal pregnancy, with no evidence of teratogenicity.

Neurotoxicity

The standard toxicological database contains a range of unpublished acute, short-term repeat-dose, subchronic and chronic laboratory studies which do not report any evidence of neurotoxicity in rodents, rabbits or dogs, including any clinical signs (consistent with a proposed neurotoxicant) or neuropathy under the standard suite of pathology tests.

Paraquat is structurally similar to the known dopaminergic neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahdyropyridine (MPTP). For this reason it has been investigated as a possible etiological agent in Parkinson's disease. Numerous published and unpublished studies have been assessed by the OCS in this review, including highly specialised techniques to examine effects, if any, on brain dopaminergic neurons (those neurones that degenerate in Parkinson's disease). Some studies demonstrated that repeat-dose intraperitoneal and/or subcutaneous administration of paraquat (typically 10 mg/kg bw or higher per dose, weekly for 3, 4 or 24 weeks) to mice or rats, causes the selective apoptotic loss of nigrostriatal dopaminergic neurons.
However, more recent well-conducted studies failed to reproduce these findings in the mice by either oral or intraperitoneal administration. No effects were found on the substantia nigra (SN), including the number of tyrosine hydroxylase (TH+) cells or neurotransmitter levels, casting doubt on the reliability of earlier studies. In particular, some of the original studies reporting a positive association have since been withdrawn due to fraudulent reporting of results.

With regard to a link between paraquat exposure and Parkinson's disease, *in vitro* and *in vivo* studies in animals, although supporting a mechanism of toxicity involving intracellular oxidative stress, do not support a mechanism of neurotoxicity consistent with MPTP and the known mode of action associated with Parkinsonism.

Notwithstanding this, the neurotoxicty findings in i.p and s.c studies are not supported by findings in oral studies. Although limited evidence of neurotoxicity was reported from an oral study in neonatal rats, where paraquat was shown to cross the blood brain barrier, pathological damage to neurons was not seen in any oral studies.

Taking into consideration the available database of animal studies, including all studies carried out to OECD guidelines, the overwhelming weight-of-evidence-, is that paraquat does not induce neurotoxicity via the oral, dermal or intranasal exposure routes; routes that are of relevance to human exposure to this pesticide.

5.2.1 Human data

Occupational exposure

Localised skin reactions and damage resulting from unintentional exposure to paraquat have been reported in overseas workers typically as a result of poor work practices such as the use of faulty equipment and/or the lack of suitable PPE. In Australia, workers are expected to be exposed to low levels of paraquat during normal agricultural use, with increased margins of safety due to better work practices and the availability of the appropriate PPE[2]. In Australia, home garden exposure to paraquat is not expected since there are no approved residential uses.

Numerous occupational exposure studies provided no clear indication that paraquat is neurotoxic to humans. There are various epidemiology studies investigating a possible link between paraquat and other pesticides to an increased risk of developing Parkinson's disease. Two contemporary epidemiology studies have been examined in detail in this report. Although the studies lend weight to the suggestion that there is a positive association between adverse health effects and exposure to pesticides, the strength of that association is not considered robust. The studies were weakened to various degrees by issues such as case ascertainment, definition of exposure and determination of outcome. In addition, in a recent retrospective worker cohort study, there was no evidence of an increased risk of Parkinson's disease in a cohort of workers in a series of paraquat production facilities, where workers were exposed to medium to high levels of paraquat in the manufacture of paraquat. The OCS concludes that despite some positive weak trend data, the available epidemiology data is insufficient to conclude any association between paraquat exposure and neurotoxicity (including Parkinson's disease) in the occupational environment.

Poisoning incidents

A large number of human poisoning incidents have been reported in many parts of the world following deliberate ingestion of commercial preparations of paraquat. The prognosis of the intoxicated individuals clearly depended on the amount of paraquat ingested and the time interval between ingestion and commencement of emergency therapy. Complete recovery has been seen in some cases, with no lung damage. In Australia there is no harmonised systematic method for recording paraquat poisonings; these incidents are often classified under the generic category of herbicide or weed killer. Additionally very little information is available on the clinical outcome of patients who made paraquat-related phone inquiries to Poisons Information Centres or who presented at hospital emergency departments. Analysis of the limited data on paraquat poisoning in Australia showed that the majority of hospital admissions or inquiries to Poisons Information Centres relate to occupational accidents involving predominantly young to middle aged adult males. Internationally, several case reports have described cerebral damage in subjects who died following paraquat poisoning, however, this was secondary to more severe effects on other organ systems and may have been indirectly due to hypoxia. Paraquat has been detected in the brains of poisoned humans at levels ranging from 0.08-0.35 μg/g tissue.

Antidotes

[2] Risk mitigation measures for workers using Australian paraquat products will be addressed in the OHS Review report.

Numerous studies have been undertaken in laboratory animals, and in humans who have been admitted to hospital following intentional or accidental poisoning. Collectively these studies have failed to identify an effective antidote or treatment regimen for paraquat poisoning and therefore the current approach used in the treatment for paraquat poisoning is supportive only.

The current treatment for paraquat poisoning involves a combination of gastric lavage (following oral exposure) and/or haemodialysis and/or haemoperfusion. Ventilation with hypoxic breathing mixtures (eg nitric oxide) may be employed in severe cases to reduce lung damage caused by oxygen radicals. However, in severe or late-stage poisoning when breathing becomes difficult, oxygen therapy may be necessary.

A reliable indicator of likelihood of survival following poisoning appears to be the dose, which can be estimated from paraquat concentrations in the plasma and urine Studies have also shown that routine laboratory parameters of renal and hepatic function in addition to acid-base status, and the rate of increase in plasma creatinine can be used to predict patient outcome in paraquat poisoning. The other important determinate of survival is how soon after exposure, treatment is initiated .

5.3 Dose Levels Relevant for HHRA Assessment

A summary of the NOELs determined in those studies considered adequate for regulatory purposes is shown in Table 1 below.

Table 1. Summary of NOELs

Study duration	Species and route	Dose levels tested* (mg/kg bw/d)	NOEL (mg/kg bw/d)	LOEL(mg/kg bw/d) and toxic end point (Reference)
Short-term				
28-day	Mouse, diet	~ 0, 15, 18 and 22.5 paraquat cation (0, 100, 125 or 150 ppm) Pure paraquat or technical paraquat (32.7%)	Not established	15 (100 ppm): histopathological lung abnormalities (alveolar wall thickening, congestion and oedema). Higher mortality with technical paraquat than pure paraquat. (Sotheran *et al*, 1979c)
28-day	Rat, diet	~ 0, 15, 17.5 and 20 paraquat cation, (0, 150, 175 or 200 ppm)	Not established	15 (150 ppm): decreased body weight gain (males), decreased food consumption, macroscopic (red or white spots/patches and congestion) and histopathological lung abnormalities (alveolar wall thickening, oedema and congestion). (Hodge *et al*, 1980)
Subchronic				
13-week	Mouse, diet	M ~ 0, 1.18, 3.65, 11.50 and 35.8 F ~ 0, 1.38, 3.91, 13.8 and 41.9 paraquat cation	11.50 M/ 13.8 F paraquat cation	35.8/41.9 M/F): mortalities, clinical signs (weight loss, rough hair and emaciation) and macroscopic lung abnormalities (consolidation or dark red areas of the lobes of the lung) in 2/20 females, and decreased body weight gain and histopathological lung abnormalities (eosinophilic swelling of alveolar epitheliocytes of the lung in 17/20 surviving males and 12/18 surviving females. (Maita & Saito,1980)
13-week	Rat, diet	M ~ 0, 0.7, 2.0, 6.6, 19.6 F ~ 0, 0.7, 2.1, 7.1 and 21.1 paraquat cation	6.6 and 7.1 mg/kg bw/d paraquat cation in males and females, respectively	19.6/21.1 M/F : decreased body weight gain, lung abnormalities (alveolar epithelial hypertrophy) in males and splenic abnormalities (brown pigmentation) in females. (Maita *et al*, 1980)
13-week	Dog, diet	0, 0.18, 0.5, 1.5, and 3 mg/kg bw/d	0.5 mg/kg bw/d	1.5 : macroscopic lung lesions and histopathological signs of alveolitis. (Sheppard, 1981b)
1-year	Dog, diet	M/F: 0, 0.45/0.48, 0.9/10 or 1.5/1.6	0.45	0.9: pulmonary lesions associated with chronic pneumonitis. (Kalinowski *et al*,1983a, 1983b),
Chronic				
1-year	Dog, diet	M/F: 0, 0.45/0.48, 0.9/10 or 1.5/1.6	0.45	0.9: pulmonary lesions associated with chronic pneumonitis.

Study duration	Species and route	Dose levels tested* (mg/kg bw/d)	NOEL (mg/kg bw/d)	LOEL(mg/kg bw/d) and toxic end point (Reference)
				(Kalinowski *et al*,1983a, 1983b),
104-week	Mouse, diet	M/F: 0, 0.19, 0.95/0.96, 2.84/2.77, 9.48/9.43	2.8	9.4: decreases in haematological parameters (Hct, Hb, RBC, WBC and lymphocyte counts), changes in relative and absolute organ weights (including thyroid, adrenal, lung, heart and liver weights), and reduced body weights. (Toyoshima *et al*,1982)
97-99-week	Mouse, diet	0, 1.9, 5.6, 15/18.8	1.9	5.6: decreased weight gain, increased mortality and non-neoplastic findings (renal tubular degeneration in males, fatty-type vacuolation of the liver in males) (Sotheran *et al*, 1981; Smith, 1986, 1990).
113-122-week	Rat, diet	0, 1.25, 3.75 or 7.5	Not established	1.25: ocular lesions at all doses, both sexes. (Woolsgrove, 1983; Ashby & Finn, 1983; Ishmael & Godley, 1983; Brown & Whitney, 1984; Woolsgrove & Ashby, 1985; Life Sci Res Inst, 1984; Ishmael, 1987)
Reproduction				
2 generation	Rat, diet	~1.5, 7.2, 14.5	Parental: 7.2	14.5: Reduced body weights in F0 and F1 parents.
			Pup: 7.2	14.5: Depression in F0 and F1 pup body weight and increased incidence of hydrourethrosis in F2b pup.
			Reproduction: > 14.5	Not established. No reproductive effects. (Igarashi, 1980)
3 generation	Rat, diet	0, 0, 1.25, 3.75 or 7.5	Parental: 1.25	3.75: Dose related increase in the incidence and severity of focal alveolar histiocytosis.
			Pup: 3.75	7.5: Perivascular inflammatory cell infiltration in the lungs of F1b pups.
			Reproduction:>7.5	Not established. No reproductive effects at doses tested. (Lindsay *et al*, 1982 a,b)
Developmental				
Developmental study (6 – 15 days of gestation)	Mice, gavage	0, 1, 5 and 10	Maternal: 1	5: Reduced body weight gain
			Fetal: >10	Not established. No fetal effects at doses tested.
			Developmental: >10	Not established. No developmental effects at doses tested. (Hodge *et al*, 1978a)
Developmental study (day 6 – 15 gestation)	Mice, gavage	0, 7.5, 15 and 25	Maternal: 15	25: Mortality, clinical signs, reduced food consumption and body weight gain, increased lung and relative kidney weights.

Study duration	Species and route	Dose levels tested* (mg/kg bw/d)	NOEL (mg/kg bw/d)	LOEL(mg/kg bw/d) and toxic end point (Reference)
			Fetal: 15	25: Reduced fetal weight.
			Developmental: 15	25: increased incidences of retarded ossification. (Palmer, 1992b)
Developmental study (day 6 – 15 gestation)	Rat, gavage	0, 1, 5 and 10	Maternal: 1	5: Increased mortality, clinical signs and reduced body weight gain
			Fetal: 1	5: Reduced mean fetal and litter weights
			Developmental: >10	Not established. No developmental effects at doses tested. (Hodge *et al*, 1978b)
Developmental study (day 7 – 16 gestation)	Rat, gavage	0, 1, 3 and 8	Maternal: 3	8: Significant weight loss
			Fetal: > 8	Not established. No fetal effects at doses tested.
			Developmental: >8	Not established. No developmental effects at doses tested. (Hodge, 1992b)
Developmental study (gestation day 7 – 19)	Rabbit, gavage	0, 1, 1.5, 2 and 2.5 mg/kg bw/d	Not established	1: Treatment-related mortalities, clinical signs and bw loss in does at all dose levels.
			Fetal: 1	1.5: minor fetal skeletal variants
			Developmental:1	1.5: Retarded ossification with an increased incidence of developmental variations, only at maternotoxic doses. (Tinston, 1991a,b,c)

* Dose expressed in paraquat cation, unless otherwise indicated.
M – male
F – female
Hb – haematocrit
Hb – haemoglobin
RBC – erythrocyte count
WBC – white blood cell count

5.2 Acceptable Daily Intake (ADI)

The acceptable daily intake (ADI) for humans is an estimate of the amount of a substance in food and drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL from a suitable study by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intraspecies variation, the completeness of the toxicological database and the nature of the potential toxicologically-significant effects.

The current Australian ADI for paraquat is 0.004 mg/kg bw/d. It was established in June 2003 by the application of a 100-fold safety factor to the NOEL of 0.45 mg/kg bw/d in a 1-yr dog study (Kalinowski *et al,* 1983 a,b), based on the occurrence of lung lesions at the next highest dose (0.9 mg/kg bw/d), which was the lowest LOEL established in all oral studies reviewed. A subchronic study in dogs (Sheppard, 1981b) supports the NOEL established in this study with a NOEL of 0.5 mg/kg bw/d, for lung lesions similar to those observed in the 1-year study.

The present review has not identified a more suitable study or toxicological endpoint to warrant changing the ADI and therefore confirms the ADI of 0.004 mg/kg bw/d.

5.3 Acute Reference Dose (ARfD)

The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

The current Australian ARfD for paraquat is 0.004 mg/kg bw. It was established in June 2003 by applying a 100-fold safety factor to the NOEL of 0.45 mg/kg bw/d based on the occurrence of pulmonary lesions in the 1-year dietary study conducted in dogs (Kalinowski *et al,* 1983a & b). The NOEL for pulmonary lesions in the 1-year dog study is anticipated to be similar for an acute exposure because the formation of lesions occurred after a single exposure and its severity was independent of dosing duration.

The present review has not identified a more suitable study or toxicological endpoint to warrant changing the ARfD and therefore confirms the ARfD of 0.004 mg/kg bw.

5.4 Impurity Limits

An integral part of the safety assessment of an active constituent is a consideration of the chemical composition of the material. Technical-grade active constituents will contain measurable levels of impurities, which can arise during manufacture and/or from subsequent degradation during storage. The chemical identity of these impurities is generally well characterised. The impurities present in the technical-grade material are usually of no particular concern since health standards are established on the basis of toxicology studies conducted using the mixture. However, for those which have high acute toxicity, genotoxicity or teratogenic potential, concentration limits need to be set, so that the toxicological profile of the

technical-grade active constituent does not appreciably alter in the event of slight changes in the proportions of the impurities.

The impurities in the paraquat manufacturing concentrate, for which compositional standards have been established by the APVMA are 2,2': 6',2"-terpyridine and 4,4'-bipyridyl (Minimum Compositional Standards for Active Constituents, APVMA). The existing upper limits for these two contaminants are 0.001 g/kg and 1 g/kg respectively, as 2,2': 6',2"-terpyridine is considered to have high acute oral and dermal toxicity (LD_{50} values are 2.17 and 4.3 mg/kg bw, respectively), while 4,4'-bipyridyl is considered to be of moderate acute oral toxicity with an LD_{50} value of 172 mg/kg bw. No additional toxicological concerns have been identified for these impurities, and the current upper limits are considered to remain appropriate

5.5 Poisons Scheduling

Paraquat is listed in Schedule 7 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP No. 6, 2015) with no cut off for lower concentrations.

Under Part 2 of the Poisons Standard, Controls on Medicines and Poisons, s.6 Sale, supply, possession or use: "a person must not sell or supply a liquid preparation containing paraquat unless it is coloured blue or green and contains sufficient stenching agent to produce an offensive smell".

In addition to the Schedule 7 signal heading "Dangerous Poison", s.1 (Labels) indicates that the following cautionary statements are required on paraquat products: 1.3 Primary packs and immediate containers (1) The primary pack and immediate container of a poison must be labelled as follows: (f) if the poison is an aqueous solution of paraquat, with the cautionary statements:

CAN KILL IF SWALLOWED
DO NOT PUT IN DRINK BOTTLES
KEEP LOCKED UP

This assessment confirms that schedule 7 is appropriate for the active constituent paraquat.

5.6 Resolutions of the Advisory Committee on Pesticides and Health

At its 23rd Meeting (2nd May 2002), the Advisory Committee on Pesticides and Health (ACPH) supported the proposed ARfD for paraquat and supported the current ADI. The ACPH also indicated that, based on the available data, paraquat was unlikely to pose a significant neurotoxic risk to humans. This ACPH conclusion was taken into account by the OCS together with a significant amount of new data which was not available to the APCH in 2002. Additional detail available in Appendix I: Extraxt of minutes of the Advisory Committee on Pesticides and Health– 23rd meeting, .

5.7 First Aid Instructions and Safety Directions

First Aid Instructions and Safety Directions have not been reviewed in this report as it considers the toxicity of the active constituent only. The First Aid Instructions and Safety Directions will be reviewed in the OHS review of paraquat products.

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APPENDIX I: EXTRAXT OF MINUTES OF THE ADVISORY COMMITTEE ON PESTICIDES AND HEALTH– 23RD MEETING, 2 MAY 2002

7.4 PARAQUAT – PUBLIC HEALTH ASSESSMENT CHEMICAL REVIEW PROGRAM

PURPOSE

The Committee considered the public health assessment of paraquat performed as part of the Chemical Review Program (CRP).

BACKGROUND

Paraquat is a non-selective contact herbicide belonging to the bipyridinium class of compounds which also includes the herbicide diquat. Both compounds share a similar mode of action which involves the inhibition of photosynthesis (specifically photosystem I) which generates superoxide, leading to lipid peroxidation and membrane damage. Plants die rapidly after treatment and exposure to light. In Australia, paraquat has been registered for use as a contact herbicide and desiccant for over 30 years and there are currently 18 registered products. There are no Australian home garden products containing paraquat.

Paraquat was selected as a high priority chemical for review because of its high acute and chronic toxicity. There was also significant public interest in a review. The toxicological database for paraquat is extensive. The mechanism of its toxicity, like its mode of action in plants, is via the generation of highly reactive free radicals and consequent peroxidation of membrane lipids, leading to membrane damage and cell death. It is well established that the lungs are the target organ of paraquat toxicity due to the presence of an active uptake mechanism.

The current Australian ADI for paraquat (established in 1992) is 0.004 mg/kg bw/d, derived by applying a 100-fold safety factor to the NOEL of 0.45 mg/kg bw/d for lung lesions in a one-year dog study. Paraquat is currently included in Schedule 7 of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP). There are no lower Schedule entries to accommodate dilute preparations.

DISCUSSION

Members noted the main findings of the OCS's toxicological evaluation of paraquat:

- In laboratory animals, approximately 10% of an oral dose of paraquat is absorbed whilst the remainder is eliminated quickly mainly via the faeces.
- Once absorbed, paraquat distributes to most organs of the body, with the highest initial concentrations found in the lungs and kidneys. Paraquat is not extensively metabolised.
- The acute oral toxicity of paraquat is moderate in rodents (LD_{50} = 100-249), and very high in guinea pigs, rabbits, dogs, monkeys and humans. The acute dermal toxicity of paraquat is low and the acute inhalational toxicity extremely high.

- Paraquat is a slight skin irritant, a severe eye irritant and not a skin sensitiser.
- There is no effective antidote for paraquat poisoning.
- Percutaneous paraquat absorption is low, however, toxicologically-significant absorption can occur via damaged skin, or sensitive skin areas such as the scrotum.
- Repeat-dose toxicity studies confirmed that the target organ is the lungs while renal toxicity was also evident. Localised tissue damage was apparent following inhalational or dermal exposure.
- Long-term feeding studies conducted in mice, rats and dogs revealed no evidence that paraquat was carcinogenic. The weight-of-evidence indicates that paraquat is non-genotoxic, however it can damage genetic material at high and/or cytotoxic concentrations due to the generation of reactive oxygen species.
- There was no evidence that paraquat caused reproductive toxicity despite evidence of systemic toxicity in parental animals and their offspring. There was no evidence that paraquat had any teratogenic potential.
- The neurotoxicity of paraquat has not previously been addressed as it has been considered unlikely based on its known mechanism of toxicity. Based on the current data and using a weight-of-evidence approach, paraquat is not considered to pose a significant neurotoxic risk to humans.
- The current Australian ADI for paraquat is 0.004 mg/kg bw/d (set in August 1992) established by the application of a 100-fold safety factor to the NOEL of 0.45 mg/kg bw/d in a one-year dog study, based on the occurrence of lung lesions at the next highest dose.
- An ARfD of 0.004 mg/kg bw was established by applying a 100-fold safety to the same NOEL of 0.45 mg/kg bw/d in the one-year dog study. The rationale for choosing the same endpoint as for the ADI was that acute toxicity testing indicated that lung lesions could develop following a single exposure. Moreover, a range of short and long-term repeat-dose studies indicated that the dose at which lung lesions developed was independent of the duration of exposure. Additionally, there were no suitable acute toxicity studies in the database that would support an alternative figure.

The Committee noted that humans appear to be the most sensitive species to paraquat toxicity, with the estimated lethal dose being 3-5 mg/kg bw (~10-15 mL of a 20% formulation). The committee wondered whether there had been any attempt to compare the toxicity of paraquat in dogs and humans as this would be particularly relevant for the ARfD which was established on the basis of effects in dogs. Members were advised that the data on humans was derived from poisoning cases and it was difficult to accurately determine the dose in such cases.

There was some discussion relating to the upper limit for the impurity 2,2':6,2"-terpyridine (terpyridine) and whether this remained appropriate. The Committee was advised that the sponsor had submitted acute toxicity data for terpyridine (dermal and oral LD_{50} values). The high acute toxicity seen in an early acute dermal toxicity study with paraquat was likely to be due to terpyridine. Members noted that there are 3 sources of the manufacturing concentrate in Australia and only one of these contains this impurity. However, the declaration of composition for this manufacturing concentrate indicates that 2,2':6,2"-terpyridine is below the FAO-specified upper limit. The point was raised that if paraquat can be produced without the impurity and recent toxicology studies are conducted on material that does not have the impurity, why is the manufacturing concentrate with the impurity allowed on the market? The OCS advised that there was usually no data to ascertain the possible effect of an impurity on

the overall toxicity of a chemical and this situation would occur for most review chemicals. The APVMA representative indicated that the issue was not whether an impurity was present but whether the upper limit remained acceptable from a toxicological point of view. If a manufacturing concentrate containing the impurity complies with the standard then its registration should be supported, irrespective of the existence of different manufacturing concentrates that do not contain the impurity.

There was some discussion as to whether 2,2':6,2"-terpyridine would influence the toxicity of paraquat. The Committee noted that there were some equivocal findings regarding the dermal toxicity of paraquat; some of the older studies had very low LD_{50} values (~90 mg/kg bw), almost equivalent to the oral dosing studies, whereas some of the more recent GLP studies gave much higher values (1440 mg/kg bw). The OCS considered that the very low dermal LD_{50} for 2,2':6,2"-terpyridine (0.9-1.8 mg/kg bw) may well have increased the dermal toxicity of earlier paraquat preparations and therefore it is important that an appropriate upper limit for this impurity remain.

The Committee supported the current ADI, and the OCS's proposed ARfD for paraquat. It was recognised that occupational use is clearly the major potential cause of toxicity in humans.

The Committee identified an apparent discrepancy in the current drinking water health guideline value of 0.03 mg/mL for paraquat. This value (established by the NHMRC) is set at approximately 10% of the ADI based on an average adult body weight of 70 kg and an average adult daily water consumption of 2 L. The existing health guideline value did not appear to match the current Australian ADI and therefore the committee suggested that this be investigated. The OCS advised Members that during a recent review of regulatory procedures, it was recognised that there is a need for the OCS to better connect with the NHMRC and possibly set drinking water values for new agvet chemicals which might have some persistence in the environment and mobility in soil. The OCS are looking at a process where Environment Australia would provide advice on those parameters and then the OCS could set a health value and submit it to the NHMRC for incorporation into the Australian Drinking Water Guidelines.

Members discussed the neurotoxicity potential of paraquat and the relevant parts of the OCS's evaluation relating to this issue. The neurotoxicity of paraquat has been of concern because of its structural similarity to the known dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The sponsor had not submitted any neurotoxicity studies, however Members noted that the sponsor had published a rat study showing that paraquat was not neurotoxic. A number of published studies indicated that paraquat can be neurotoxic when instilled directly into the brain of rats (neuropathy, neurochemical effects, behavioural and locomotor effects). Effects on behaviour and neurochemistry (elevations or depressions in striatal dopamine), and the occurrence of lesions/neurological damage were observed following systemic administration in some rodent studies.

Paraquat has been used for almost 40 years throughout many parts of the world; studies conducted in developing countries where very little or no personal PPE was used did not reveal any evidence of neurotoxicity in humans. Numerous poisoning cases have provided no indication that paraquat is neurotoxic in humans. Taking a weight-of-evidence approach, the OCS had concluded that paraquat poses no significant neurotoxic risk to humans. Members agreed that there would be no MPTP-like effects for paraquat under the current use conditions.

The mechanism of MPTP neurotoxicity is also different to that of paraquat. It was recognised that the 2 quaternary nitrogens in paraquat make it behave quite differently to MPTP.

RESOLUTION 23/7

The Committee:

- NOTED the OCS's toxicological evaluation of paraquat conducted as part of the APVMA's Chemical Review Program;

- SUPPORTED the current Australian ADI for paraquat of 0.004 mg/kg bw/d, calculated by applying a 100-fold safety factor to the NOEL of 0.45 mg/kg bw/d in a 1-yr dog study, based on the occurrence of lung lesions at the next highest dose;

- SUPPORTED the OCS proposal for an ARfD of 0.004 mg/kg bw established by applying a 100-fold safety to the same NOEL of 0.45 mg/kg bw/d in the one-year dog study; and

- CONCLUDED that there were unlikely to be any neurotoxicity concerns relating to the current use of this compound.