Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the Propylene Oxide in the Product

Dibbs Progas Fumigant

APVMA Product Number 55095

MAY 2012

This document is published by the APVMA. In referencing this document the APVMA should be cited as both author and publisher.

ISBN: 978-0-9873041-0-0

ISSN: 1443-1335

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

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing, Office of Chemical Safety (OCS), Department of Sustainability, Environment, Water, Populations and Communities (DSEWPaC), and State Departments of Primary Industries.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of public release summaries for all products containing new active ingredients.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's publications *Ag MORAG: Manual of Requirements and Guidelines* and *Vet MORAG: Manual of Requirements and Guidelines*.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the APVMA and its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Comment is sought from interested persons on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **DIBBS PROGAS FUMIGANT**

should be granted. Submissions should relate only to matters that the APVMA is required by legislation to take into account in deciding whether to grant the application. These grounds include **occupational health and safety, chemistry and manufacture, residues, safety and first aid, environmental fate and toxicity, trade** and **efficacy**. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **6 June 2012** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- Contact name
- Company or Group name (if relevant)
- Postal Address
- Email Address (if available)
- The date you made the submission.

All personal and ***confidential commercial information (CCI)***[1] material contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the **grounds for registration** should be addressed in writing to:

Contact Officer
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Phone: + 61 2 6210 4748
Fax: + 61 2 6210 4776
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[1] A full definition of "confidential commercial information" is contained in the Agvet Code.

Further information

Further information can be obtained via the contact details provided above.

Copies of full technical evaluation reports covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on public release summaries can be found on the APVMA website:
http://www.apvma.gov.au

1 INTRODUCTION

Applicant

R. A. Dibbs & sons PTY LTD

Details of Product

It is proposed to register Dibbs Progas Fumigant containing 830 g/L propylene oxide as a liquid for the control of microbiological spoilage caused *Salmonella enteritiditis, Salmonella typhimurium and Eschericia coli* in shelled almonds. Dibbs Progas Fumigant is intended to be used at the rate of 0.5 – 2.4 kg/m^3 in a fumigation chamber under vacuum at a temperature of 50±1°C.

Microbiological spoilage of shelled almonds is a problem for the Australian almond industry. The Australian almond crop is predominantly planted to soft shell varieties that are vulnerable to contamination during ground harvesting and storage, and elevated moisture levels in the nuts if rain occurs during harvest.

Methyl bromide (MeBr) has traditionally been the fumigant used for the fumigation of almonds to control both insect and microbiological spoilage; however under the Montreal Protocol on Substances that Deplete the Ozone Layer, uses of the fumigant methyl bromide are being phased out. Propylene oxide (PPO) has been identified as an alternative to methyl bromide for the fumigation of some tree nuts. PPO has also been used historically to reduce bacteria, mould and yeast contamination on processed spices, cocoa and processed nutmeats except peanuts (Bond 1984). It is currently registered to treat several dried food commodities in the USA and was approved by the United States Food and Drug Administration for the pasteurization of raw almonds in September 2007. Japan and Canada have propylene oxide Maximum residue Levels (MRLs) in place for almonds.

PPO is a liquid at atmospheric pressure with a boiling point of 33.9°C and has a noticeable ether odour. As PPO is flammable from 3% to 37% in air, it should be applied under low pressure or in a CO_2-enriched atmosphere to avoid flammability. Under the conditions of fumigation proposed (vacuum of -92kPa and temperature of 60°C), the product volatilises to a gas and behaves as a true fumigant under those conditions.

PPO is an alkylating agent that is widely used for industrial applications and has found a niche application in the disinfestation and sterilization of agricultural products, including spices and nuts. The biocidal mode of action of propylene oxide is the alkylation of DNA guanines, which results in single-strand breaks. Propylene oxide hydrolyses in the presence of moisture to form nontoxic propylene glycol.

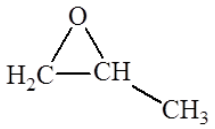
This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Dibbs Progas Fumigant.

2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

The chemical active constituent PROPYLENE OXIDE has previously been approved by the APVMA.

COMMON NAME:	Propylene Oxide
APVMA APPROVAL NO.	55106
APPROVAL HOLDER	R A Dibbs & Sons Pty Ltd
MANUFACTURE SITE	Aberco Inc. 270 Miller St Newark New Jersey 07114 USA

CHEMICAL NAME:	1,2-Epoxypropane
CAS NUMBER:	75-56-9
MINIMUM PURITY:	997 g/kg
MOLECULAR FORMULA:	C3H6O
MOLECULAR WEIGHT:	58.08
STRUCTURE:	
CHEMICAL FAMILY:	Epoxides

APVMA STANDARD	
CONSTITUENT	Propylene Oxide
SPECIFICATION	Propylene Oxide
LEVEL	Not less than 997 g/kg

2.2 Product

DISTINGUISHING NAME	Dibbs Progas Fumigant
FORMULATION TYPE	Liquid
ACTIVE CONSTITUENT CONCENTRATION	830 g/L

PHYSICAL AND CHEMICAL PROPERTIES OF THE PRODUCT

COLOUR AND PHYSICAL STATE	Colourless liquid
ODOUR	Ether-like odour
FLASH POINT OF LIQUIDS (CONTAINING FLAMMABLE SOLVENTS)	-37°C
EVAPORATION POINT	33.7°C
BOILING POINT	33.9°C
MELTING PONT	-112°C
RELATIVE DENSITY	0.83 g/mL at 20°C
SOLUBILITY	59g/100mL (water)
AUTO-IGNITION TEMPERATURE	449°C
pH	8.1
VAPOUR PRESSURE	445 mmHg at 20°C
OCTANOL/WATER PARTITION COEFFICIENT	Log K_{ow}=0.03
HENRY'S LAW CONSTANT	6.96 x 10^{-5} atm -m^3.mol^{-1}

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

The product Dibbs Progas Fumigant is a liquid (vapour producing) formulation containing the active ingredient propylene oxide at 830 g/L. It will be used in fumigation of almonds for the control of microbiological spoilage. It is new to the Australian market and is intended as a replacement for the fumigant methyl bromide in specific situations.

In animal studies, propylene oxide is of moderate acute oral and dermal toxicity, and low inhalational toxicity. However, acute exposure to 400 ppm is likely to be immediately dangerous to life and health in humans. Propylene oxide is a moderate to severe irritant to skin and eyes, and may cause allergic contact dermatitis in humans.

In addition to reduced body weight gain, repeated oral dosing produced hyperplasia, hyperkeratosis, papillomas and squamous-cell carcinomas in the forestomach of rats; inhalation produced local tissue irritation and inflammation, hyperplasia, metaplasia, adenomas and squamous cell carcinoma, haemangiosarcomas and haemangiomas in the respiratory epithelium and nasal turbinates in rats and/or in mice. Tumours occurred only at the site of first contact with propylene oxide. Propylene oxide was genotoxic in a wide range of in vitro studies. In contrast, in vivo studies were generally negative with the exception of a micronuclei test in mice and a specific locus test in *Drosophila melanogaster*. Embryotoxicity and foetotoxicity were observed in rats exposed to propylene oxide at concentrations which caused maternal toxicity. An increased incidence of misaligned, fused or bipartite sternebrae was observed in treated rabbits.

Analyses of fumigated foodstuffs revealed that the principal residues are propylene oxide, propylene glycol, and propylene halohydrins. The metabolites occur at relatively low levels and have low toxicity compared to the parent compound.

Based on an assessment of the toxicology and occupational health and safety, it was considered that there should be no adverse effects on human health from the use of this product when used in accordance with the label directions.

3.2 Summary of the Evaluation of Toxicological Studies (Propylene Oxide)

The toxicological database for propylene oxide is quite extensive and primarily consists of toxicity tests conducted using animals. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate that such effects might occur in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available.

Where possible, considerations of the species-specific mechanisms of adverse effects are given strong weight in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to

human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

There are no data on the absorption of oral doses of propylene oxide but, as the compound is highly soluble in water, absorption from the lungs and gastrointestinal tract is likely to occur rapidly. Studies in rats suggest that propylene oxide is widely distributed in tissues, and the main route of detoxification in rats is via glutathione conjugation and excretion in the urine. It may also undergo enzymatic hydrolysis, and this may be an important route of detoxification in humans. Propylene oxide is hydrolysed in water to form propylene glycol (1,2-propanediol). The rate of hydrolysis to propylene glycol at neutral pH is slow (half-life about 1-3 days); however, in acid conditions, it proceeds rapidly. When ^{14}C-labelled propylene oxide was incubated with human gastric juice (pH 1.5), propylene oxide was completely converted to propylene glycol within 20 minutes, with a half-life of approximately 2 minutes. On incubation with rat forestomach juice (pH 5.0), the half-life was approximately 46 hours. The only metabolite produced during incubation in gastric juice was propylene glycol. From *in vitro* data, a half-life of approximately 40 minutes was calculated for the elimination of propylene oxide from rat tissues, assuming 100% alveolar absorption and first order kinetics. Propylene glycol may be excreted unchanged via the kidneys or be oxidised to lactic acid and pyruvic acid.

Acute Studies

Propylene oxide has moderate acute oral toxicity in mice, rats and guinea pigs with lowest LD_{50}s in these species of 440, 380 and 660 mg/kg, respectively. It has moderate dermal toxicity in rabbits (LD_{50} 1245 mg/kg) and low inhalational toxicity in mice, rats, guinea pigs and dogs, with LC_{50}s of 1740, 4000, 4000 and 1930 ppm/4h, respectively. However, acute inhalation exposure to 400 ppm of propylene oxide or above is likely to be immediately dangerous to life and health.

Application to the skin of propylene oxide in water may produce inflammation (hyperaemia, oedema and perivasular infiltrates of mononuclear cells), and prolonged contact may lead to scarring. Application of propylene oxide to the eye produces chemical burns that may heal rapidly without sequelae or, if severe, may lead to corneal necrosis. There is limited evidence that propylene oxide may cause allergic contact dermatitis in humans, but no skin sensitisation studies in animals are available.

Short-Term Studies

Rats administered 18 oral doses of 10% propylene oxide in olive oil by gavage had slightly reduced body weight gain, gastric irritation and slight liver damage at 300 mg/kg bw/day, but there were no observable toxic effects at 200 mg/kg bw/day.

Mice exposed by inhalation to propylene oxide at 0, 23, 46, 97, 194 or 485 ppm for 6 h per day, 5 days per week, during a 2-week exposure period showed only dyspnoea at 194 and 485 ppm and hypoactivity at 485 ppm.

Rats exposed by inhalation to propylene oxide at 0, 46, 97, 194, 485 or 1435 ppm for 6 h per day, 5 days per week, during a 2-week exposure period showed dyspnoea, gasping, irregular limb movements and diarrhoea at 1435 ppm; one rat at 1435 ppm died.

Rats and mice exposed to 500 ppm propylene oxide vapour for 6 h per day for 63 days showed weight loss but no histopathologic changes were observed.

Subchronic Studies

Rats and mice were exposed by inhalation to 0, 31, 63, 125, 250 and 500 ppm propylene oxide for 6 hours/day, 5 days/week for 13 weeks. Final mean body weights of rats and mice exposed at 500 ppm were lower but there were no treatment-related pathological effects in any group.

Rats, guinea pigs, rabbits and 1 monkey were exposed by inhalation to propylene oxide at 0, 100, 195 or 460 ppm propylene oxide vapour for 7 hours/day, 5 days/week for up to 218 days. At 460 ppm, rats had eye and nasal irritation and increased mortality due to pneumonia, and guinea-pigs showed irritation of the eyes and respiratory passages and reduced growth rate. Histological findings in guinea pigs included slight fatty degeneration of the liver and pulmonary irritation (alveolar haemorrhages and oedema, and interstitial oedema and hyperaemia in the lungs). These histopathological effects were also observed in rats after 37-39 days of exposure to 460 ppm, but there were no effects after 128-154 exposures at 195 ppm. Rabbits and monkeys did not show any adverse effects.

Chronic / Carcinogenicity Studies

Rats received 0, 15 or 60 mg/kg propylene oxide in oil, by gavage, twice weekly for a total of 112 weeks. There were increased incidences of hyperkeratosis, hyperplasia, papillomas, and squamous cell carcinoma of the forestomach at 15 and 60 mg/kg. At 60 mg/kg, one adenocarcinoma of the pylorus was also observed.

Mice were exposed to propylene oxide vapour concentrations of 0, 200 or 400 ppm for 6 h/day, 5 d/week, for 103 weeks. The survival rate was decreased at 400 ppm from week 60 onwards and growth was slightly reduced from week 29 onwards. In the nasal turbinates, a dose-related increased incidence of inflammation occurred. Squamous cell metaplasia was observed in 1 male at 200 ppm and 2 females at 400 ppm. Female mice at 400 ppm had an increased incidence of ovarian atrophy. At 400 ppm, the incidence of haemangiomas and haemangiosarcomas were increased. One squamous cell carcinoma and one papilloma were induced in the nasal cavity of male mice at 400 ppm and two adenocarcinomas were induced in the nasal cavity of females at 400 ppm.

Rats were exposed by inhalation to propylene oxide vapour concentrations of 0, 200 or 400 ppm, for 6 h/day, 5 d/week, for 103 weeks. Growth was slightly reduced from week 20 onwards. The respiratory epithelium of the nasal turbinates showed a dose-related increase in the incidence of suppurative inflammation of the mucosae, hyperplasia, and squamous cell metaplasia. At 400 ppm, there was an increased incidence of papillary adenomas involving the respiratory epithelium and the underlying submucosal glands of the nasal turbinates and, in the males, an increase in skin keratoacanthomas. Rats at 200 and 400 ppm had an increased incidence of testicular atrophy.

In an inhalation toxicity and carcinogenic study, rats were exposed to propylene oxide concentrations of 0, 30, 100 or 300 ppm, for 6 h/day, 5 d/week, for 123-124 weeks. The mortality rate was increased in females at 100 ppm and both sexes at 300 ppm. At 300 ppm, body weight gain was reduced and the weights of adrenals, spleen, liver, and lungs of males were increased. In both sexes, the incidences of basal cell hyperplasia, atrophy of the olfactory epithelium and the incidence of nest-like infolds of the respiratory epithelium were increased, mainly at the 2 highest exposure levels. One rat had squamous cell carcinoma of the nose. In female rats, the incidence of benign tumours of the mammary glands, mostly fibroadenomas, was increased at 300 ppm.

In a chronic inhalation toxicity and carcinogenicity study, rats were exposed to propylene oxide at 100 or 300 ppm for 7 h/day, 5 d/week for 104 weeks. In all groups of exposed rats, body weights were significantly reduced and mortality was increased. Skeletal muscle atrophy in the absence of any sciatic nerve neuropathology was found in rats exposed 300 ppm propylene oxide. Rats exposed to propylene oxide had a dose-dependent increase in the incidence and severity of inflammatory lesions in the lungs, nasal cavity, trachea, and middle ear, and male rats at 100 and 300 ppm had decreased testes weights. At 300 ppm propylene oxide, there was an increased incidence of complex epithelial hyperplasia of the nasal passages and 2 rats had nasal-cavity adenomas.

Mice received weekly subcutaneous injections of 0, 0.1, 0.3, 1, or 2.5 mg propylene oxide for 106 weeks. At the injection site, an increase in the incidence of sarcomas (mainly fibrosarcomas) occurred at 1 and 2.5 mg. The first tumour appeared in week 38.

In a study to assess the effect of propylene oxide on spermatogenic function, monkeys were exposed to 100 or 300 ppm propylene oxide, for 7 h/day, 5 d/week, for 2 years. At both exposure levels, sperm counts and sperm motility were reduced, and the sperm drive range (time to traverse a linear path) was increased.

Reproduction and Developmental Studies

In a two generation reproductive study, rats were exposed to propylene oxide by inhalation at 0, 30, 100 or 300 ppm for 6 hours/day, 5 days/week for 14 weeks prior to mating. F_1 pups were then exposed to the same concentrations of propylene oxide for 17 weeks after weaning and subsequently mated to produce the F_2 generation. Body weight was significantly lower in F_0 and F_1 rats exposed to 300 ppm propylene oxide, but there were no effects on reproductive parameters and no pathological effects were observed in the adults or their offspring. Reproduction was not affected at the highest dose, 300 ppm (713 mg/m^3).

Pregnant rats were exposed to propylene oxide by inhalation at 0 or 500 ppm, for 7 h per day, during days 7-16 of gestation, days 1-16 of gestation, or for 3 weeks before mating and on days 1-16 of gestation. In all exposed groups, dams had decreased body weight gains and food consumption, increased kidney weights and pulmonary inflammation, and the body weights and lengths of foetuses were decreased. In the group exposed during gestation days 7-16, the number of resorptions was increased. In the group exposed from days 1-16 of gestation, increases in wavy rib and in reduced ossification, primarily of the vertebrae and ribs, were observed. The numbers of corpora lutea, implantations per dam, and live foetuses were lower in the group exposed for 3 weeks before mating and on days 1-16 of gestation, but the pregnancy rate was unchanged.

Pregnant rats were administered propylene oxide by inhalation at 0, 100, 300 or 500 ppm from days 6-15 of gestation. Maternal weight gain and food consumption were reduced at 500 ppm throughout the treatment period. There was no evidence of foetotoxicity with the exception of increased frequency of 7th cervical ribs in foetuses at 500 ppm.

Rabbits were exposed to 500 ppm (1190 mg/m^3) propylene oxide, for 7 h per day, on days 1-19 or days 7-19 of gestation. Food consumption was reduced during the treatment period but there was no evidence of maternal toxicity. In females that were treated on days 1-19, resorptions were increased and, in the foetuses, an increased incidence of misaligned, fused or bipartite sternebrae was observed, but malformations were not increased in any group.

Genotoxicity

Propylene oxide was genotoxic in a wide range of in vitro assays in bacteria (*Salmonella typhimurium* strains TA 100 and TA 1535, and *Eschericia coli* WP2 and WP2 uvrA), yeast and fungi. Vapour exposure to propylene oxide caused increased lethal mutations in *Drosophila melanogaster*, with spermatocytes and mature sperm apparently being sensitive stages. In mammalian cells (rat hepatocytes and human lymphocytes, in vitro) chromatid gaps, single strand DNA breaks and chromosomal gaps, breaks and fragments were increased following propylene oxide exposure.

Two oral doses of 100, 250 or 500 mg/kg propylene oxide did not induce micronuclei in the polychromatic erythrocytes in mice. When given to mice by i.p. injection, 2 doses of 300 mg/kg, administered within 24 h, gave a 5-fold increase over controls, but 2 doses of 75 or 150 mg/kg were negative.

The results of the dominant-lethal assay were negative when male mice received 14 daily doses of propylene oxide at 0, 50, or 250 mg/kg, by gavage, for 2 weeks prior to mating, and when male rats were exposed by inhalation to propylene oxide vapour at a concentration of 300 ppm for 5 days, prior to mating with 2 females per week for 6 weeks following exposure.

No increased frequency of abnormal sperm heads was observed, 1 - 9 weeks after exposure of mice to propylene oxide vapour at a concentration of 300 ppm, for 7 h per day for 5 days, or in monkeys exposed to 0, 100 or 300 ppm for 2 years.

No increases in chromosome aberrations or sister-chromatid exchanges were found in peripheral lymphocytes of monkeys, after inhalation exposure to 0, 100 or 300 ppm propylene oxide, for 7 h per day, 5 days per week, for 2 years.

In humans, increased levels of haemoglobin and DNA adducts, and sister chromatid exchanges (SCE) have been detected in a small group of workers occupationally exposed to propylene oxide. Lymphocytes from individuals occupationally exposed to propylene oxide (<12 ppm for 1-20 y) had a reduced capacity for unscheduled DNA synthesis (UDS). Induction of UDS by N-acetoxy-2-acetylaminofluorine (NA-AAF) was inhibited by about 25% in lymphocytes from propylene oxide-exposed workers.

Special Studies

Neurotoxicity

Rats exposed by inhalation to 0, 100 or 300 ppm propylene oxide for 6 hours/day, 5 days/week for approximately 24 weeks, had no treatment-related signs of neurotoxicity and no gross pathology or microscopic changes attributable to treatment. Slight axonal degeneration in the spinal cord and neuroaxonal dystrophy in the nucleus gracilis were observed at equivalent incidences in the treated and control groups.

Axonal dystrophy was observed in the brains of monkeys exposed to propylene oxide by inhalation at 237 and 717 mg /m3 (7 h/day, 5 days/week) for 2 years. Two monkeys examined from each group had lesions in the nucleus gracilis but there was no apparent dose-relationship in severity and one of two untreated monkeys also showed such changes.

Toxicity of metabolites and degradation products

The main metabolite in animals is propylene glycol. In fumigated foods, the major residues are propylene oxide and the halohydrins, propylene chlorohydrin and propylene bromohydrin. Two propylene chlorohydrin isomers have been identified in fumigated foods, but the 1-chloro-2-propanol isomer constitutes the major proportion of chlorohydrin residues. Propylene oxide is stable in lipids and does not off-gas readily, and high levels may be found in lipid-rich foods following fumigation.

Propylene glycol has very low acute toxicity in mammals (oral LD_{50} about 20 g/kg in rats, rabbits and dogs and dermal LD_{50} 20.8 g/kg in rabbits). It is a slight skin irritant in rabbits and humans, and a slight eye irritant in rabbits. In rats and mice, no reproductive toxicity was observed following oral administration of 10,000 mg/kg/day during gestation or inhalation exposure to 112 ppm for 18 months. Propylene glycol was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation, and was not clastogenic in Chinese hamster cells or human fibroblasts. There is no evidence that propylene glycol is carcinogenic in animals or humans.

Propylene chlorohydrin has moderate acute oral toxicity in rats and dogs, with LD_{50}s of 218 and 200-250 mg/kg, respectively.

Rats fed propylene chlorohydrin (ratio of 1-chloro to 2-chloro isomer approx. 2:1) in the diet at approximately 0, 100, 250, 500 or 1000 ppm for 25 weeks had a slight to moderate reduction in bodyweight gain and food consumption in both sexes at 500 and 1000 ppm, but food efficiency was normal. The liver and kidney weights of males and the liver weight of females at 1000 ppm were decreased, but there were no other treatment-related effects.

Propylene chlorohydrin was administered to rats by gavage at 0, 25, 50, 75, and 100/150/200/250 mg/kg/day for 22 weeks. The highest dose was increased in increments from 100 mg/kg to 250 mg/kg during weeks 11-16. At 250 mg/kg, all the rats died. There was a slight to moderate reduction in body weight gain at 100 and 150 mg/kg, and animals lost weight when the dose was increased to 200 mg/kg. Food consumption was slightly decreased in the males at 100 mg/kg and decreased to a greater extent in both sexes when the dose was increased. The liver weights of males at 25 mg/kg and both sexes at 75 mg/kg were increased, but there were no gross or microscopic alterations in the liver. Tissues were not examined from the highest dose group.

1-chloro-2-propanol has acute oral LD50s in rats, guinea pigs and dogs of 100-300, 720 and 200 mg/kg, respectively, and a dermal LD50 of about 500 mg/kg in rabbits. The inhalation LC_{50} in rats was 1000 ppm/4h. It was not a skin irritant in rabbits but produced marked corneal injury in rabbits.

Mice were administered 1-chloro-2-propanol in the drinking water at concentrations of 0, 100, 330, 1,000, 3,300, or 10,000 ppm for 14 days, or 0, 33, 100, 330, 1,000, or 3,300 ppm for 14 weeks. Mean body weight gains of 10,000 ppm mice were reduced and water consumption at 3,300 and 10,000 ppm was reduced throughout the study. Males at 3,300 ppm had slight anaemia, and kidney and epididymis weights were increased. Liver weights were increased in males at ≥1,000 ppm and in females at all doses. Thymus weights were increased in females at 1,000 and 3,300 ppm and decreased in both sexes at 10,000 ppm. The incidences of pancreatic acinar cell degeneration and fatty change were increased in 3,300 ppm males and females and cytoplasmic vacuolization of hepatocytes in all groups of exposed females were significantly increased. The severity of renal tubule cytoplasmic vacuolization was increased in the 1,000 and 3,300 ppm males.

Rats were administered 1-chloro-2-propanol in drinking water at concentrations of 0, 100, 330, 1,000, 3,300 or 10,000 ppm for 14 days, or 0, 33, 100, 330, 1,000 or 3,300 ppm for 14 weeks. Two 10,000 ppm females died. The bodyweight gains at 3,300 were reduced and rats at 10,000 ppm lost weight. Water consumption at 3,300 and 10,000 ppm was significantly reduced throughout the study. Slight anaemia was observed in exposed female rats. The thymus weights of 10,000 ppm rats were significantly decreased. The cauda epididymis and epididymis weights of 3,300 ppm males were decreased and the percentage of abnormal sperm at 3,300 ppm and the concentration of epididymal sperm at 330 ppm were significantly increased. Kidney and liver weights of males and females exposed to 100 ppm or more were generally greater than those of the controls. There were increased incidences of acinar cell degeneration and fatty change of the pancreas in both sexes at 1,000 and 3,300 ppm, hepatocytic metaplasia of the pancreatic islets in females at 3,300 ppm, cytoplasmic vacuolization of the hepatocytes in males at ≥100 ppm, and renal tubule epithelium regeneration in females at 3,300 ppm.

There was no effect of treatment in rats administered 1-chloro-2-propanol in the drinking water at 0, 150, 325, or 650 ppm, or in mice at 0, 250, 500, or 1,000 ppm for up to 105 weeks, and no treatment-related neoplasms or non-neoplastic lesions were observed in these studies.

1-chloro-2-propanol produced slight reproductive toxicity in rats exposed to concentrations of 0, 0.03, 0.065, and 0.13% in drinking water throughout 2 generations. Toxicity was seen only at the high dose, and included significantly reduced water consumption, reduced body weight gain and increased kidney weights in both sexes. In the males, epididymis weights were increased, testis weights were decreased, and there was a slight increase in the proportion of abnormal sperm, but there was no effect on fertility or on any other reproductive parameters.

1-Chloro-2-propanol was weakly mutagenic in *S. typhimurium* strain TA100 and was positive in TA1535. It was positive in cytogenetic tests with CHO cells in vitro, but did not induce chromosomal effects in vivo. Sex-linked recessive lethal mutations were induced in *D. melanogaster* when 1-chloro-2-propanol was administered via injection, but negative results were obtained when it was administered in feed. 1-Chloro-2-propanol was negative in a germ cell reciprocal translocation test *in D. melanogaster*, and in a mouse micronucleus test in which mice were administered 1-chloro-2-propanol via the drinking water for 14 weeks.

2-Chloro-1-propanol had moderate acute oral toxicity in rats (LD50 240 mg/kg), low acute oral toxicity in guinea pigs (LD50 720 mg/kg), and moderate acute dermal toxicity in rabbits (LD50 530 mg/kg). It was a slight skin irritant and a severe eye irritant in rabbits. 2-Chloro-1-propanol was weakly mutagenic in *S. typhimurium* strain TA100 and was positive in strain TA1535 (both without S9).

Propylene bromohydrin may be a skin, eye and respiratory irritant. 1-Bromo-2-propanol was positive in *S. typhimurium* at 155 µg/plate and a DNA repair test in *E. coli* at 620 µg/plate.

3.3 Public Health Standards

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

On the basis of its toxicity, the NDPSC has included propylene oxide in schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) with an inclusion in Appendix J. There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

The Acceptable Daily Intake is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for propylene oxide was established at 0.006 mg/kg bw/day based on a NOEL of 2.9 mg/kg bw/day (30 ppm) in a 123 – 124 week rat inhalational study and using a 500-fold safety factor.

Acute Reference Dose (ARfD)

The acute reference dose is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event. The ARfD is derived from the lowest single or short term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The highest acute dose of propylene oxide at which no evidence of toxicity was detected was 205 mg/kg bw/day in a rat inhalational developmental study. The ARfD was established at 0.4 mg/kg bw/day on the basis of this NOEL and using a 500-fold safety factor.

4 RESIDUES ASSESSMENT

4.1 Introduction

Dibbs Progas fumigant contains 830 g/L propylene oxide as active constituent and is to be used as a fumigant for almonds to control microbiological spoilage. As part of the residues assessment for propylene oxide, the fate of residues in treated commodities and animals, supervised residue trials and trade aspects were considered. Details are provided below.

4.2 Metabolism

No data were available describing the pre- or post-harvest metabolism of propylene oxide by plants. Information in the literature and the residue studies provided indicate that propylene oxide can react with inorganic chlorine or bromine to form halo-hydrins. The available data suggest that the halo-hydrins are not formed in animals where the main metabolite is propylene glycol.

4.3 Analytical methods

The method for the determination of propylene oxide involved heating the sample in a sealed vial and the quantitation of propylene oxide via automated headspace analysis using GC-FID. The LOQ for the method was 0.1 mg/kg. Recoveries of propylene oxide from fortified samples of almond nutmeat were acceptable as tabulated below.

Table 1: Analytical recoveries of propylene oxide from fortified almond nutmeat.

FORTIFICATION LEVEL (mg/kg)	RECOVERY %
0.1	94, 111
5.0	89, 99
10.0	92, 97
52.6	93, 93
105	88, 89
946	96, 98

For later studies and analysis of commercial samples in the USA, ground samples were boiled in a flask with water. The propylene oxide was collected in a boiling flask as it distilled off and kept on ice until analyis by GC-FID. The LOD was 1.9 mg/kg for shelled almonds and 3.5 mg/kg for in-shell almonds.

A US EPA review indicated that propylene oxide is stable in water for 14 days at -10°C. In general samples analysis occurred on the day of collection. Where this was not indicated, study protocols stated that distilled

samples were good for 24 hours if refrigerated, suggesting it is unlikely samples would have been stored for significant periods prior to analysis.

4.4 Residue Definition

The main metabolite in animals is propylene glycol. Propylene glycol has low toxicity and is an approved food additive in Australia. Inclusion of this material in the residue definition is therefore not required.

In fumigated foods, the major residues are propylene oxide and the halohydrins, propylene chlorohydrin and propylene bromohydrin. With respect to the halohydrins, the Office of Chemical Safety (OCS) considered it unnecessary to include them in the residue definition or establish an ADI or ARfD. The halohydrins are present in nutmeats at several orders of magnitude below propylene oxide.

The recommended residue definition for propylene oxide is parent only.

4.5 Residue Trials

Dibbs & Sons supplied a residue study on almonds treated at the required fumigation rate and residue data for commercially treated almonds from the USA. In the almond residue study, residues in nutmeats after fumigation at 0.5 kg/m^3 and 15 days after treatment (DAT) with storage at ambient temperature were 5.4 and 6 mg/kg. Residues in inshell almonds at 15 DAT with storage at ambient temperature were 57 and 66 mg/kg. In commercial samples of almond nutmeats, residues approximately 15 DAT at 0.5 kg/m^3 were 17.7, 18, 19.2, <25, 26.2, 30.9, 66, 71 and 73 mg/kg. Based on this data an MRL of 100 mg/kg is recommended for propylene oxide on TN 0660 Almonds in conjunction with a 15 day WHP.

4.6 Processing studies

Processing studies have not been provided and are not required.

4.7 Animal commodity MRLs

Almond hulls may be fed to livestock. However, label specifies the situation as shelled almonds only. It is appropriate to include a restraint on the label prohibiting treatment of almonds prior to removal of the hull. It is therefore not necessary to establish animal commodity MRLs for propylene oxide.

4.8 Estimated dietary intake

The chronic dietary exposure to propylene oxide is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is

made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for propylene oxide is equivalent to 30% of the ADI.

It is concluded that the chronic dietary exposure of propylene oxide is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food.

The acute exposure to propylene oxide residues in almonds is considered acceptable being 8.4% of the acute reference dose for the general population and 13.3% for children (2-6 years).

4.9 Bioaccumulation potential

The octanol/water partition coefficient (Kow) of propylene oxide is 0.03 at 25°C. Propylene oxide is unlikely to bioaccumulate in fat.

4.10 Recommendations

Upon granting of the application the following amendments are recommended to the MRL Standard:

Table 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
Propylene oxide	TN 0660	Almonds	100

Table 3

COMPOUND	RESIDUE
ADD:	
Propylene oxide	Propylene Oxide

[2] *Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.*

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Almonds are the commodities exported. Almonds are not considered major export commodities.[3]

5.2 Destination and Value of Exports

In 2002/03 Australia exported 1,205 tonnes of almonds (in shell), valued at $5.65 million. The major export markets for almonds are summarised below. [4]

Table 2: Destination and value of Australian exports in almonds (nut-in-shell) in 2002/03.

DESTINATION	QUANTITY (TONNES)	VALUE ($'000)
India	1,056	4,776
France	50	287
United Kingdom	39	157
Kuwait	17	140
United Arab Emirates	17	139
New Zealand	9	72
Indonesia	3	27
Italy	10	22
China	2	19
Papua New Guinea	1	7
Other	1	5
Total	1,205	5,651

[3] Part 5B of the Vet Requirements Series and Ag Requirements Series, Overseas Trade Aspects of Residues in Food Commodities, August 2004.

[4] The Australian Horticulture Statistics Handbook 2004.

5.3 Proposed Australian use-pattern

Dibbs Progas Fumigant (830 g/L propylene oxide)

Situation	Pest	Rate	Critical Comments
Shelled Almonds	Bacteria, Yeasts, Moulds and Fungi	0.5 to 0.7 kg/m^3	Apply in accordance with the Standard Operating Procedure for Pasteurization Using Propylene Oxide set out below. Where nuts are packed in impermeable packaging, either pierce packaging prior to fumigation and then reseal with tape before shipping, or remove from packaging to treat and then replace in packaging after treatment.

WITHHOLDING PERIOD:

DO NOT apply to nuts within 15 days of shipment for use for human consumption.

5.4 Overseas registration and approved label instructions

Propylene oxide products are registered for use on tree nuts in the USA. The proposed use pattern for Australia is based on commercial procedures used in the USA.

5.5 Comparison of Australian MRLs with Codex and overseas MRLs.

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Propylene oxide has not been considered by Codex.

The following overseas residue MRLs/ tolerances have been established:

COMPOUND	COUNTRY/STATUS	COMMODITY	TOLERANCE (mg/kg)
Propylene oxide	USA	Nut, tree, group 14	300
Propylene chlorohydrin	USA	Nut, tree, group 14	10

COMPOUND	COUNTRY/STATUS	COMMODITY	TOLERANCE (mg/kg)
Propylene oxide	Canada	Almonds	300

No overseas animal commodity MRLs/tolerances have been established for propylene oxide.

5.6 Potential risk to trade

Export of treated produce containing finite (measurable) residues of propylene oxide may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

The use of propylene oxide on tree nuts will be restricted to almonds as data for other nuts treated at the proposed rate are not available. As almonds are not considered to be a major export commodity the risk to trade is considered to be low. However, only the USA and Canada have established relevant tree nut MRLs. As use of propylene oxide may result in detectable residues in nutmeats, the label should include advice that tolerances may not be established in all export markets and that users should determine the requirements of export markets before use.

The overall risk to export trade in animal commodities is considered to be low as nutmeats are not considered to be an animal feed, and treatment of almonds before the hull is removed is prohibited.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Dibbs Progas Fumigant containing 830 g/L propylene oxide is proposed for use in chamber fumigation of tree nuts (almonds) for the control of microbiological spoilage caused by fungi, yeasts, moulds and bacteria. A use rate of 0.5 – 0.7 kg/m^3 is proposed to be used on this purpose.

The product will only be used by licensed fumigators in a nominated fumigation operation plant which is located in a large warehouse. Fumigation pre-treatment (pre-warm the goods and chamber, negative vacuum of the chamber) and treatment (inject product vapour, exposure for 4 hours, aeration cycles for ventilation) are carried out inside of the fumigation chamber, followed by off-gassing in an area outside the chamber for 15 days or longer before off-site transportation.

Exposure to propylene oxide in the workplace including fumigation facilities is required to be minimised by hazardous substances legislation. Based on science-based risk assessment, it is important to use engineering controls and personal protection equipment to minimise worker exposure to the lowest practicable level, i.e. below 5 ppm propylene oxide for short term exposure, and below 1 ppm for long term exposure.

A worker exposure study has been submitted and assessed in the present application. This study, together with the toxicology data and other information on the product provided and considered justify the First Aid Instructions, Warning Statement, Safety Directions, Precaution Statements and Re-handling statement established for workers.

Safety Directions:

When handling propylene oxide drums/cylinders, and when entering areas where exposure to propylene oxide vapour above 1 ppm is likely, wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length butyl rubber gloves, impervious footwear (not steel capped) and full-face respirator with organic vapour cartridge.

Precautions Statement:

DO NOT enter the chamber, where full fumigation concentrations are present.

In cases of extreme emergency, self-contained breathing apparatus (SCBA) or ambient air breathing apparatus must be employed.

DO NOT open chamber door until measured levels of propylene oxide are below 5 ppm (12 mg/m^3).

Re-handling Statement:

Do not allow handling the fumigated goods for off-site transportation until propylene oxide residues / emissions are below 2 mg/kg / 4.8 mg/m^3 (2 ppm).

In addition, there is no public access to the fumigation operation plant; the levels of propylene oxide measurement at boundary of the warehouse were negligibly low (according to the exposure study); all exhaust gases (air purges and off-gassing) from fumigation are vented to the atmosphere through a wet scrubber system which removes 99% of the propylene oxide. Hence, risk of exposure to the general public is minimal.

Based on worker exposure data, the toxicology data and other information on the product provided and considered in the risk assessment, the First Aid Instructions, Warning Statement, Safety Directions, Precaution Statements and Re-handling statement have been established to minimise worker exposure to the lowest practicable level, i.e. below 5 ppm propylene oxide for short term exposure, and below 1 ppm for long term exposure.

Hence, the proposed use of Dibbs Progas Fumigant will not be an undue health hazard to humans according to the criteria stipulated in Section 14 of the Ag/Vet Code Act of 1994.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

R A Dibbs & Sons Pty Ltd have applied for the registration of DIBBS PROGAS FUMIGANT to be used to prevent microbial spoilage caused by fungi, yeasts, moulds and bacteria, and for the control of insects, in food commodities including herbs and spices, tree nuts and cocoa powder. DIBBS PROGAS FUMIGANT contains the active constituent propylene oxide (830 g/L).

Propylene oxide is not currently registered in Australia for use as a fumigant in food commodities or as an Agvet chemical. However, it is a widely used industrial chemical, used mainly as a chemical intermediate in the production of synthetic polymers and propylene glycol. Propylene oxide is registered for use as a fumigant of food commodities in the USA.

Propylene oxide is applied to food commodities in an enclosed fumigation chamber. The proposed label recommends adding rates up to 2.5 kg/m^3 Progas under vacuum to a fumigation chamber and treating the produce for 4-6 h. Very detailed directions for use and operational requirements are specified on the label to minimise environmental release as well as achieving safe and effective treatment of the produce and ensuring operator safety.

7.2 Environmental Fate

Propylene oxide is widely used in industry and data are available in existing reports and the published literature. The pertinent information is summarized below.

Atmospheric Fate

With the present application, it is proposed that the product will be only used in fumigation chambers fitted with scrubbers and mist eliminators to ensure environmental release of the exhaust gas is negligible. It is possible that low levels may be released from fumigated product by desorption post fumigation.

Propylene oxide is expected to have limited stability in the atmosphere. It does not absorb solar radiation appreciably at wavelengths greater than 300 nm (it has a maximum absorption at 199.5 nm). Thus direct photolysis does not occur. Its main degradation pathway is expected to be through reaction with photochemically produced hydroxyl radicals.

The rate of the reaction with hydroxyl radicals has been estimated in a number of publications to range between 6.6 and 32.3 days. The calculated half-life in air based on the OECD methods is 26 days. These data indicate relatively slow degradation in air.

Reactions with hydroxyl radicals are expected to form acetyl formyl oxide, formaldehyde, formanhydride and methyl glyoxal, which are expected to degrade further. Propylene oxide is not expected to react significantly with ozone. It is not considered an important cause of photochemical air pollution, and is expected to eventually transform into carbon dioxide and water.

Aquatic Fate

Propylene oxide is highly soluble in water (590 g/L). If released to water it is expected to hydrolyze to form 1,2-propylene glycol by cleavage of a carbon-oxygen bond of the cyclic ether. Propylene glycol relatively rapidly degrades in water.

Propylene oxide may also react with halogen ions in water. For example, it reacts with chlorine in water to form 90% 1-chloro-2-propanol and 10% 2-chloro-1-propanol under neutral pH. The estimated half-life time in surface water with a pH 7-9 is 11.6 days, and in water with a pH of 5 is 6.6 days (25ºC). Hydrolysis is accelerated in the presence of chloride ions, with half-life times in seawater of between 1.5-4.1 days. With these half-life times, propylene oxide is classified as readily hydrolysable.

Propylene oxide is highly volatile. The vapour pressure and Henry's Law constant suggest that volatilization from surface water could be significant. The half-life times for volatilization from a river and an oligotrophic lake were estimated to be 3 days and 18 days, respectively, based on computer simulations using the vapour pressure and water solubility. Partitioning from water to sediment is not expected to occur given the high water solubility and low calculated Koc of 4.2.

Terrestrial Fate

Data on the fate of propylene oxide in soil is limited. Hydrolysis in moist soil is expected to occur, based on the results of aquatic hydrolysis. Evaporation from dry soil is indicated from the high vapor pressure, while propylene oxide is expected to be mobile in soils based on the low Koc.

Biodegradation

Evidence for the biodegradation of propylene oxide is variable. One study was reported where the bacterium, *Nocardia* A60, was able to utilize propylene oxide as a carbon source for growth. *Pseudomonas graveoleus* and *P. fluorescens* are also reported to be capable of slowly biodegrading propylene oxide at concentrations of <700 ppm in industrial wastewaters using aeration tanks.

Data from some studies indicate that propylene oxide is readily biodegraded by microorganisms, while in other studies it is not. It appears that microbial degradation of propylene oxide is favoured in the presence of acclimated microorganisms. Therefore, propylene oxide is assumed to be inherently biodegradable.

Bioaccumulation

The high water solubility and low octanol-water partition coefficient of propylene oxide predict that bioaccumulation will not be significant. A Bio-Concentration Factor (BCF) of between 0.0 and 0.6 was estimated by equations from the water solubility or the log Kow of 0.03.

7.3 Environmental Effects

Aquatic toxicity data indicate that propylene oxide is slightly to very slightly toxic to fish, with the most sensitive species being rainbow trout having a 96 h LC50 of 52 mg/L.

The only studies available for the toxicity of propylene oxide in the terrestrial compartment dealt with its sterilising effects on soil. These studies were intended to assess the suitability of propylene oxide to sterilise soil prior to its use in other experiments and hence involved relatively high exposure levels of around 200 g/kg wet weight for 115 days. Fumigation of soil rich in organic carbon with propylene oxide eliminated protozoa and nematodes, as well as microbial populations from the soil. Propylene oxide also caused a strong increase in soil respiration throughout the incubation experiment, and resulted in almost total immobilisation of nitrate within the first 14 days of the incubation experiment.

Another study found that propylene oxide not only sterilised soil (initial concentration 0.8 and 1.7 g propylene oxide for 25 g dry soil, i.e. 32 and 68 g/kg dry weight respectively), but retarded plant growth as well. Germination and growth of wheat and alfalfa were retarded by 50-60% in propylene oxide-treated soil, and plant stems were twisted and distorted, with alfalfa appearing to be more resistant than wheat. Therefore, propylene oxide residues in soil could hinder subsequent plant growth. However, when propylene oxide was used as a fumigant against the soil borne fungus *Waitea circinea*, which causes root rot of coniferous seedlings, the seedlings appeared healthy in appearance.

7.4 Risk Assessment

The applicant estimates maximum usage volumes of propylene oxide < 50 t per year. The amount of propylene oxide used by industry in Australia each year is significantly higher (said to be in the order of 100s of thousand tonnes). The world production for 1990 was over 3.5 million tonnes with an increasing trend.

Environmental release and exposure to the chemical is expected to be limited in the proposed application. The applicant has indicated that fumigation of commodities will occur in gas tight chambers by licensed and trained fumigators. During use, the propylene oxide is transferred from 200 L drum under vacuum into a fully sealed fumigation chamber. Detailed instructions are provided on the label for injecting the gas and treating the produce, then for purging the chamber with carbon dioxide and then air, followed by transfer of the produce to a room for post-ventilation treatment. The exhaust gas is vented to air via scrubbers so that propylene oxide is removed prior to release. The removal of propylene oxide from the exhaust gas is via hydrolysis to propylene glycol in acidic aqueous solutions comprising 3% sulphuric acid solutions. The applicant noted that the scrubbers are designed to remove 99% of propylene oxide, with the remaining 1% off-gassed from the tank through a duct pipe. The propylene glycol formed in the scrubbers is drained out of the tank as necessary.

Data provided by the applicant indicated a total of 0.083 grams of propylene oxide would be discharged to the atmosphere over a 40-minute degassing cycle, based on the proposed operating conditions (i.e. 4 metre packing height, and a mass of propylene oxide filling the autoclave chamber of 72.65 kg). This discharge equates to a theoretical scrubber removal efficiency of over 99.99%. Propylene oxide entering the atmosphere is expected to be destroyed by reacting with hydroxyl radicals and water.

The applicant has indicated that the only possible source of contamination is through transport accidents or malfunction of the fumigation equipment. The combined total capacity of fumigation chambers currently in existence in Australia is 300 kg. Therefore, if all chambers suffered simultaneous ruptures, the maximum amount of propylene oxide released is 300 kg.

DSEWPaC concludes that on the basis of the limited potential for exposure and the low toxicity to aquatic organisms, propylene oxide poses a negligible risk to the aquatic environment from the intended use.

Limited data are available for assessing the effects of propylene oxide on terrestrial organisms. Soil organisms and vegetation in particular could be exposed to propylene oxide in the wash water from drum washings or residues in empty drums if the contaminated rinse water or empty 200 L drums are disposed of to land. However, DSEWPaC considers the risk will be negligible. The concentration in drum washings is expected to be low, as significant dilution by the rinsing water would occur. The chemical would also be expected to hydrolyse once released to soil. If the soil is dry, some evaporation is also expected to occur.

No toxicity data are available for terrestrial organisms exposed to propylene oxide vapours in air. DSEWPaC expects the risk to organisms from exposure to propylene oxide in air will be low, owing to the low expected atmospheric discharge and environmental exposure from the intended use pattern. It is also noted that propylene oxide is emitted to the atmosphere during fuel combustion including in motor vehicle exhaust.

The proposed use of Dibbs Progas Fumigant is limited to fumigation chambers fitted with scrubbers and mist eliminators to ensure environmental release of the exhaust gas is negligible.

There are sufficient data available in literature sources to perform an adequate risk assessment. DSEWPaC concludes that use of propylene oxide as a fumigant of commodities to control microbial contamination does not present a hazard to the environment, provided that, the label recommendations are followed when using the product and fumigation occurs in airtight chambers fitted with efficient scrubbers to remove propylene oxide.

8 EFFICACY AND SAFETY ASSESSMENT

The applicant submitted a number of scientific papers and reports on overseas studies to demonstrate the efficacy of propylene oxide against a range of biological spoilage organisms. The data included those arising from trials undertaken on almonds in commercial situations. Laboratory studies on a range of organisms in pure culture and reports on trials undertaken on other dried foods were presented as supporting data. The applicants premise was that efficacy data from California was applicable to the Australian situation because the spoilage organisms for almonds in Australia were substantially the same as those in California.

Trials were specifically undertaken to validate the use of propylene oxide to reduce a specific food-borne pathogen, *Salmonella enteritiditis*, on bulk whole almonds (Danyluk et al. 2005). The experiments included fumigation of bulk 900kg bins and 22.7kg boxes of almonds that included almonds inoculated with *S. enteritiditis*. Fumigation was performed at a minimum of 0.5 g/L, 48°C under a vacuum maintained at 84.3 kPa, resulting in a concentration x time product (CT product) of more than 2 g.h/L. The data showed a 5-log or greater reduction in populations of *S. enteritiditi,* 5 days post treatment. This data demonstrated that propylene oxide was efficacious in controlling the food-borne pathogen *S. enteritiditis*. This research was relied upon by the Almond Board of California to establish "Almond Pasteurization Using Propylene Oxide (PPO) Standard Operating Procedure (SOP)", http://www.almondboard.com/Handlers/Documents/Pasteurization-Using-PPO-SOP.pdf.

Data from small scale trials on dried commodities (red peppers, cocoa and almonds) were also submitted. These trials specifically tested the level of control achieved for *Eschericia coli* and *S. typhimurium* using the same fumigation parameters as Danyluk et al. 2005 (above). A 99.9%reduction in colony growth post treatment was observed for both organisms.

A range of data from laboratory studies was submitted to demonstrate the general effectiveness of propylene oxide against a broad range of microorganisms. Organisms tested were *Acerobacter aerogenes, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhaosa, Serratia marcescens, Shigella sonnei, Micrococcus flavus, Sarcina lutea, Staphylococcus aureus, Streptococcus faecalis, Lactobacillus plantarum, Streptococcus lactis, Bacillus stearothermophilus and Bacillus subtillus* and *Escherichia coli.* Cultures of the microorganisms were fumigated with 1cm^3/L (8.3g/L) propylene oxide at atmospheric pressure, 35°C for up to 3 hours at 65% Relative Humidity. The results indicated 90% reduction was achieved within 30 minutes (CT product 4.2 g.h/L) for all but spores of *Bacillus stearothermophilus* and *Bacillus subtillus* (which required approximately 30 minutes and 2 hour fumigations respectively to achieve a greater than 90% kill under the laboratory fumigation conditions). The above findings provide support that the proposed fumigation conditions are likely to be effective against other bacteria. The higher CT product required in this instance to achieve control is a likely to be a reflection of the change in fumigation parameters used in the trials, namely atmospheric pressure and 35°C compared to a vacuum maintained at 84.3 kPa and 48°C.

The data provided demonstrated that under the proposed fumigation conditions the spoilage organisms: *E.Coli, S. enteritiditis* and *S. typhimurium* would be effectively controlled.

Trials undertaken at fumigation facilities in Australia demonstrated the ability of the local facility to achieve the conditions (temperature, vacuum and concentrations) proposed which were shown to be effective in the overseas trials.

The overall conclusion that can be drawn from the applicant's submission is that the scientific data showed general efficacy of propylene oxide as a fumigant for control of a range of microorganisms and efficacy against specific spoilage microorganisms in tree nuts found in the USA. These data support that the proposed product should be efficacious in the control of microbiological spoilage in almonds and as the variety of almonds is similar to that grown in California, are expected to be relevant and applicable to the proposed use pattern.

9 LABELLING REQUIREMENTS

Proposed Label

DANGEROUS POISON

KEEP OUT OF REACH OF CHILDREN

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

DIBBS

PROGAS

Fumigant

ACTIVE CONSTITUENT: 830 g/L PROPYLENE OXIDE

For the control of microbiological spoilage caused by fungi, yeasts, moulds, and bacteria

in shelled almonds as per the directions for use.

NET CONTENTS 200L

R.A. DIBBS PTY LTD
76 PENTEX STREET
SALISBURY QLD 4107
TEL: 07 3274 5709
A C N: 009 669 854

DIRECTIONS FOR USE

Restraints:

DO NOT use on almonds prior to removal of the hull
DO NOT use this product unless trained in the proper use of required respirator equipment and detection devices, emergency procedures and safe use and handling of the fumigant. Fumigators must hold the relevant State/Territory license for propylene oxide fumigation.
DO NOT use this product on goods whilst being transported.
DO NOT use this product in premises and/or plants that have not been approved for such use by relevant local authorities.
DO NOT exceed the maximum rate (chamber charge dose) specified on this label.

Situation	**Pest**	**Rate**	**WHP (days)**	**Critical Comments**
Shelled Almonds	Microbiological spoilage organisms (*Eschericia coli, Salmonella enteriditis & Salmonella typhimurium*)	0.5 to 0.7 kg/m^3	15	Apply in accordance with the Standard Operating Procedure for Pasteurisation Using Propylene Oxide set out below. This procedure is only applicable for pasteurisation of bulk-packed almonds on double or single stacked pallets. The procedure is not applicable for retail packed bags. Where bulk almonds are packed in impermeable packaging, either pierce packaging prior to fumigation and then reseal with tape before shipping, or remove from packaging to treat and then replace in packaging after treatment.

NOT TO BE USED FOR ANY PURPOSE OR IN ANY MANNER CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION.

WITHHOLDING PERIOD:
DO NOT APPLY TO NUTS WITHIN 15 DAYS OF SHIPMENT FOR USE FOR HUMAN CONSUMPTION

GENERAL INSTRUCTIONS

Standard Operating Procedure for Pasteurisation Using Propylene Oxide:

1. Pre-warm product to at least 30ºC at the coldest point in the container. The product temperature should not exceed 40ºC during this step due to product quality concerns. The pre-warm temperature area can be in the range of 38 - 49ºC to achieve the 30ºC minimum product temperature.
2. Measure product temperature from the centre of every bin or pallet to assure that the product achieves a minimum temperature of 30ºC.
3. Pre-heat the PPO chamber to 49-51ºC.
4. Load the conditioned product into the pre-heated PPO chamber and close all doors and vents.
5. Maintain a chamber temperature of 49-51ºC throughout .
6. Apply a vacuum until the chamber reaches a minimum of –92 kPa. Check that vacuum holds steady to ensure that the chamber is completely sealed.
7. Turn on PPO vaporiser to achieve a temperature of at least 60ºC, but not in excess of 63ºC.
8. Inject a sufficient amount of PPO through the vaporiser to assure that PPO vapour in the chamber reaches at least 0.5 kg/m3. (The absolute amount of PPO will depend upon the chamber size.) The vacuum in the chamber will decrease slightly upon addition of the PPO.
9. Inject an inert gas to decrease chamber vacuum to between –17 and –20 kPa.
10. Treat product for 4 hours. (The pasteurisation time begins after completion of inert gas injection.)
11. After 4 hours of exposure, increase the vacuum to between –92 and –95 kPa.
12. To ensure effective off-gassing, a minimum of two (2) carbon dioxide purges, followed by a minimum of four (4) air purges must be completed. The purge cycle is: Vacuum (–96 kPa); CO2 purge back to –10 kPa (x2), followed by Vacuum (–96 kPa); air to atmospheric pressure (x4). Each air-wash should be held under vacuum for 15 – 20 minutes to facilitate desorption of gases.
13. The number of cycles varies with chamber size and should allow air surrounding the product being transferred from the chamber to contain no more than 5 mg/kg (12 mg/m3) PPO.
14. After completion of aeration cycles, transfer the product to a room for post-ventilation treatment. The temperature recommended for post-ventilation is 38-43ºC for at least two days or at ambient temperature above 15°C for five days. A higher temperature speeds up dissipation of PPO.
15. Release the product after 15 days.
16. Record all measurements and document all recordings for each PPO pasteurisation treatment.
17. Good manufacturing practices must be followed to assure that recontamination of the treated almonds does not occur.

PPO Pasteurisation Operating Parameters:

Parameters	***Operational Level***
Initial product temperature	Not less than 30ºC
Chamber temperature at start and during Sterilisation	49-51ºC
Chamber vacuum before PPO injection	At least –92 kPa vacuum
PPO vaporiser temperature	60-63ºC
PPO concentration	Not less than 0.5 kg/m3 and not greater than 0.7 kg/m3
Chamber vacuum after injection of inert gas	–17 to –20 kPa vacuum
Duration of pasteurisation	4 hours
Aeration cycles	Not <4 and not >14
Post ventilation	38-43°C for 2 days or above 15°C for 5 days.

This procedure is only applicable for pasteurisation of bulk-packed almonds on double or single stacked pallets.
Individual treatment facilities must be validated and equipment calibrated to demonstrate they are operating within the established parameters.

Operating Precautions:
Plant:
Progas should only be used in fumigation chambers fitted with scrubbers and mist eliminators to ensure environmental release of the exhaust gas is negligible. All equipment including feed drums is to be earthed as a precaution against build up of static electricity (ignition source). Feed lines/pipes are to be regularly cleaned/maintained.
Personal Protective Equipment (PPE):
In case of emergency sufficient PPE (full-body suit, face shields and respirators) for each operator must be strategically placed throughout the plant.
Placarding:
All entrances to the fumigated area must be placarded with the statement “DANGER, area under fumigation. DO NOT ENTER, unless wearing appropriate personal protective equipment.” The placard should also carry the skull and crossbones pictogram.
Monitoring:
The control system must be continuously monitored to ensure that the process is maintained under negative pressure (between –17 and –20 kPa as per standard operating procedure).
The plant is to be equipped with a suitable system for monitoring air levels of propylene oxide in ‘high risk’ work areas (e.g. gas chromatograph with a remote automatic air sampler). Operators must check detector readings before entering ‘high risk’ areas. On-line detectors (sensors) are to have an alarm response preset to 5 mg/kg (12 mg/m^3) propylene oxide. Alarms should be located around chamber doors, in the off-gassing room, in the storage room and in the control room. Should alarms be triggered, the working area should be evacuated until airborne levels of propylene oxide are below 2 mg/kg (4.8 mg/m^3). Workers may re-enter the area provided they are equipped with the PPE specified above until airborne levels are below 2 mg/kg (4.8 mg/m^3).

Ventilation:
Mechanical ventilation to an external exhaust system is to be installed in all potential leak areas with a scavenger air extractor system set up at floor level under the chamber doors. Backup extraction systems must also be installed. The chamber must have an automated door locking system to prevent manual opening of the chamber at levels of propylene oxide higher than 5 mg/kg (12 mg/m3). Alternatively, the PPE described above must be worn when the chamber is opened.
Following purging, the chamber door should be opened (only where chamber concentration of propylene oxide is below 5 mg/kg) with the vacuum pump turned on (to draw air through the chamber before unloading into the aeration (off-gassing) room.
Aeration:
Following treatment the chamber should be evacuated through an acid scrubber and mist eliminator. To ensure effective off-gassing, a minimum of two (2) carbon dioxide purges, followed by a minimum of four (4) air purges must be completed. The purge cycle is: Vacuum (–96 kPa); CO_2 purge back to –10 kPa (x2), followed by Vacuum (–96 kPa); air to atmospheric pressure (x4). Each air-wash should be held under vacuum for 15 – 20 minutes to facilitate desorption of gases.
Off-Gassing:
Fumigated goods must be stored in a well-ventilated area at a temperature above 25ºC for a sufficient period of time to ensure that propylene oxide residues/emissions are below 2 mg/kg (4.8 mg/m^3) before being released for off-site transportation. This area should be maintained under negative pressure (using an extraction system) and sealed off from other areas of the plant. The seal must be sufficiently robust to prevent leaks during power/fan failures.
Handling Precautions:
This product is an extreme fire hazard. Keep away from heat, sparks, open flame and heated surfaces. Drums may be under pressure when opened. Relieve pressure by slowly opening the small bung in a safe, well-ventilated area, standing upwind if outdoors and with the drum between the operator and the nearest point of air exhaust if indoors. If a hissing sound is heard do not further open the small bung until the hissing sound stops. Only when the small bung is completely opened is the pressure to be considered as relieved. When emptying drums, first electrically ground the drum. The best procedure is to displace the contents with an inert gas. Care must be taken to ensure that no appreciable pressure is exerted on the drum. A pressure relief device set to several inches of water should be installed on the inert gas line.
Do not allow foreign material to get into the drum especially acidic or alkaline materials as hazardous polymerisation may occur.

PRECAUTIONS

DO NOT enter the chamber, where full fumigation concentrations are present.
In cases of extreme emergency, self-contained breathing apparatus (SCBA) or ambient air breathing apparatus must be employed.
DO NOT open chamber door until measured levels of propylene oxide are below 5 mg/kg (12 mg/m3).

RE- HANDLING PERIOD

DO NOT allow handling of the fumigated goods for off-site transportation until propylene oxide residues /emissions are below 2 mg/kg / 4.8 mg/m^3 (2 ppm)

PROTECTION OF LIVESTOCK, WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT:

DO NOT contaminate dams, streams or waterways with chemical or the used container. Do not allow chemical to enter drains or sewers. May cause explosions.

STORAGE AND DISPOSAL

Store in a well-ventilated, cool, secure area away from heat, flame, sparks, electrical equipment, or other ignition sources.

Empty drums may contain explosive vapour. Immediately after emptying, fill drum with water and drain completely. Triple or (preferably) pressure rinse empty drums before recycling. Do not dispose of undiluted chemicals on site. Replace cap and return clean drums to recycler or designated collection point.

In case of spillage, evacuate immediate area of spill or leak. Use self-contained breathing apparatus or a combination of air-supplied respirator / self- contained breathing apparatus for entry into affected area to correct the problem. Move leaking or damaged containers outdoors or to an isolated location away from sources of ignition, observing strict safety precautions. Work upwind if possible. Wash fumigant into soil or cover with soil or other absorbent material. Do not permit entry into spill area by unprotected persons until concentration of propylene oxide is determined to be less than 20 ppm.

SAFETY DIRECTIONS

Can kill if inhaled or swallowed. Harmful if absorbed by skin contact. Will irritate the skin. Will damage the eyes. Repeated exposure may cause allergic disorders.
Avoid contact with eyes and skin. Do not inhale vapour.
When handling propylene oxide drums/cylinders, and when entering areas where exposure to propylene oxide vapour above 1 ppm is likely, wear chemical resistant clothing buttoned to the neck and wrist and washable hat, elbow-length butyl rubber gloves, impervious footwear (not steel capped) and full-face respirator with organic vapour cartridge.
Wash hands after use. After each day's use wash gloves, goggles, respirator and if rubber wash with detergent and warm water and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26; New Zealand 0800 764 766. If skin contact occurs, remove contaminated clothing and wash skin thoroughly. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet (MSDS).

NOTICE TO BUYER

R.A.Dibbs & Sons Pty Ltd will not accept any responsibility whatsoever and howsoever arising and whether for consequential loss or otherwise in connection with the supply or use of these goods other than responsibility for the merchantable quality of the goods and such responsibilities mandatory imposed by Statutes applicable the sale or supply of these goods. To the extent allowed by such statutes the liability of R.A.Dibbs & Sons Pty Ltd is limited to the replacement of the goods or (at the option of R.A.Dibbs & Sons Pty Ltd)

the refund of the price paid and is conditional upon a claim being made in writing and where possible sufficient part of the goods to enable proper examination being returned to R.A.Dibbs & Sons Pty Ltd within thirty days of delivery.

BATCH NO:

DATE OF MANUFACTURE:

APVMA Number:

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AgMORAG	Agricultural products - Manual of Requirements and Guidelines
ARfD	Acute reference dose
BCF	Bio-Concentration Factor
bw	bodyweight
°C	Degrees Celsius
CHO	Chinese Hamster Ovary
Codex	Codex Alimentarius Commission
Codex CXL's	Codex Maximum Residue Limits
CT product	Concentration multiplied by Time
d	day
DAT	Days After Treatment
DNA	Deoxyribonucleic acid
DSEWPaC	Department of Sustainability, Environment, Water, Populations and Communities
F_0	original parent generation
F_1	First generation offspring
F_2	Second generation offspring
g	gram
GAP	Good Agricultural Practice
GC-FID	Gas Chromatograph – Flame Ionisation Detector
h	hour
JMPR	Joint Meetings on Pesticide Residues
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
K_{ow}	Octanol-Water partition coefficient

kPa	kiloPascal
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
m	metre
MeBr	Methyl Bromide
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NA-AAF	N-acetoxy-2-actelaminoflourine
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Dietary Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOAEL	No Observable Adverse Effect Concentration Level
NOEC/NOEL	No Observable Effect Concentration/ Level
nm	nanometres
OCS	Office of Chemical Safety [Department of Health and Ageing]
OECD	Organisation for Economic Co-operation and Development
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
PPO	Propylene Oxide

s	second
SCBA	Self-Contained Breathing apparatus
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
t	tonne
UDS	Unscheduled DNA Synthesis
µg	microgram
US EPA	United States Environment Protection Agency
WHO	World Health Organisation
WHP	Withholding Period
y	Year

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of an absorbed material from a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	Water repelling
Leaching	Removal of a compound by use of a solvent
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

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