Public Release Summary
on

Evaluation of the new active

DICHLORPROP-P

in the product

NUFARM CORASIL PLANT GROWTH REGULATOR

Australian Pesticides and Veterinary Medicines Authority

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FOREWORD

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), Department of Environment and Water Resources (Risk Assessment and Policy Section) and State departments of primary industries and environment.

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 and for all proposed extensions of use for existing products.

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 publication *The Manual of Requirements and Guidelines - MORAG for Agricultural and Veterinary Chemicals [AgMORAG & Vet MORAG]*.

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.

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the APVMA. Alternatively, the reports can be viewed at the APVMA Library, 18 Wormald St, Symonston, ACT 2609.

The APVMA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Program Manager, Pesticides Program, Australian Pesticides and Veterinary Medicines Authority, PO Box E240, Kingston ACT 2604.

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LIST OF ABBREVIATIONS AND ACRONYMS

AC	active constituent
ACR	Acute to chronic ratio
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose (for humans)
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
CRP	Chemistry and Residues Program
d	day
DAT	Days After Treatment
DM	Dry Matter
DT_{50}	Time taken for 50% of the concentration to dissipate
DT_{90}	Time taken for 90% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EC	Emulsifiable Concentrate
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
ESI	Export Slaughter Interval
EUP	End Use Product
FAO	Food and Agriculture Organisation of the United Nations
Fo	original parent generation
FW	Fresh Weight
g	gram
GAP	Good Agricultural Practice
GC/MS	gas chromatography/mass spectroscopy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
HDPE	High-density polyethylene
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HPLC-UV	High Performance Liquid Chromatography with Ultra-Violet Detector
HR	Highest Residue
id	intradermal
im	intramuscular
ip	intraperitoneal

IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
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
LC-MS/MS	liquid chromatography, mass spectroscopy
LOEC	Lowest Observable Effect Concentration
LOEL	Lowest Observable Effect Level
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be dquantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
MSMS	mass spectroscopy/mass spectroscopy
NOAEC	No Observable Adverse Effect Concentration
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration/Level
OC	Organic Carbon
OM	Organic Matter
PHED	Pesticide Handlers Exposure Database
PHI	Pre-harvest interval
po	oral
POEM	Predictive Operator Exposure Model (UK)
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
STMR	Supervised Trials Median Residue
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram

vmd	volume median diameter
WG	Water Dispersible Granule
WHO	World Health Organisation
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of NUFARM CORASIL PLANT GROWTH REGULATOR, which contains the new active constituent Dichlorprop-P. The product is proposed to be used as a growth regulator in oranges and mandarins.

Responses to this Public Release Summary will be considered prior to registration of the product. They 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.

Copies of full technical evaluation reports on Dichlorprop-P, covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request (see order form on last page). They can also be viewed at the APVMA library located at the APVMA offices, 18 Wormald St, Symonston, ACT 2609.

Written comments should be received by the APVMA by 5 September 2007. They should be addressed to:

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Applicant
Nufarm Australia Limited

Product Details
It is proposed to register NUFARM CORASIL PLANT GROWTH REGULATOR, containing Dichlorprop-P at 25 g/L as a emulsifiable concentrate formulation. NUFARM CORASIL PLANT GROWTH REGULATOR will be imported fully formulated and packaged in 5L, 10L or 20L containers.

NUFARM CORASIL PLANT GROWTH REGULATOR is to be used for the improvement of the size of fruits in oranges and mandarins.

Overseas registrations: Dichlorprop-P formulations are currently registered in many overseas countries including Europe and the Americas.

CHEMISTRY AND MANUFACTURE

ACTIVE CONSTITUENT

The active constituent Dichlorprop-P 2-ethylhexyl ester is manufactured in the UK by Nufarm UK Limited, Crabtree Manorway North, Belvedere, Kent DA 17 6BQ, United Kingdom and is approved by the APVMA (Approval Number: 60053).

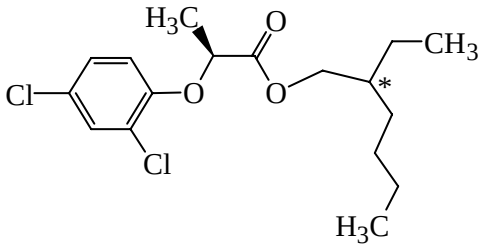
Chemical Characteristics of the Active Constituent

Common name: Dichlorprop-P 2-ethylhexyl ester

Chemical name (IUPAC): (R)-2-(2,4-dichlorophenoxy)propionic acid, 2-ethylhexyl ester

Chemical Abstracts Service (CA): (+)-2-(2,4-dichlorophenoxy)propanoic acid, 2-ethylhexyl ester

(CAS) Registry Number: 865363-39-9
Molecular formula: $C_{17}H_{24}Cl_2O_3$
Molecular weight: 347.28
Chemical structure:



Physical and Chemical Properties of the Active Constituent

Physical state: Liquid
Colour: Amber
Odour: Characteristic phenolic
Boiling point: 350 °C
Density: 1.125 g/cm^3
Vapour pressure: 1.92 mPa (25ºC) (estimated)
Henry's law constant: 5.235×10^{-4} atm-m^3/mol
Water solubility: 0.013 mg/L (estimated)
Octanol-water partition coeff.: Log P_{ow} = 6.69 (estimated)
Flammability: Not flammable
Explosive properties: Not explosive
Oxidising properties: Not an oxidising substance
Corrosion characteristics: Not corrosive
Chemical stability: Hydrolysis is slow in acidic and neutral buffers with 90-91% of parent remaining after 30 days at 25°C. In contrast only

	19 % of ^{14}C-2,4-dichlorprop-P 2 EHE remained intact in pH 9 buffer at the end of 30 days. The major product of hydrolysis was dichlorprop-P acid.
Thermal stability:	Stable as neither the weight loss nor the heat flow trace show signs of decomposition other than a boiling point at 350 °C.

Storage stability: Dichlorprop-P 2-ethylhexyl ester is chemically stable at temperatures of 54 °C for 2 weeks and is expected to be stable for at least 2 years when stored in the presence of metals.

Dangerous Goods:	Not classified as a dangerous good (as per ADG Code)
Solvent solubility:	Soluble in aromatic solvents, the solubility of Dichlorprop-P 2-ethylhexyl ester in acetone, toluene and n-hexane was found to be greater than 1000g/100mL solvent.
UV Spectrum:* (Concentration: 119 mg/L)	Neutral: Water: λ_{max}=284 nm, ε=1830 Lmol^{-1} cm^{-1} Acidic: 1 M HCl, λ_{max}= 283 nm, ε = 1620 Lmol^{-1}cm^{-1} Basic: 0.1 M NaOH, λ_{max} = 284 nm, ε = 1890 Lmol^{-1} cm^{-1}
IR Spectrum:*	2500 – 3500 cm^{-1} O-H stretching 1714 cm^{-1} C=O stretching 1200 - 1600 cm^{-1} C-C (aromatic stretching, CH_3 deformations and C-OH in plane deformation
Mass Spectrum:*	234 M^+, 189 m/z (M^+-COOH), 162 m/z (M^+-COOH-$CHCH_3$)
^{1}H-NMR Spectrum:	Typical resonances: δ 7.35 1H, 6.78 1H, 7.11 1H, 4.74 2H, 1.65 3H
Chemical family:	Aryloxyalkanoic acid (phenoxy propionic acid)

*Please note that these properties were tested for technical Dichlorprop-P acid (900 g/kg)

PRODUCT

Distinguishing name:	*Nufarm corasil plant growth regulator*
Formulation type:	Emulsifiable concentrate
Active constituent concentration:	Dichlorprop-P 2-ethylhexyl ester (25 g/L)

Mode of Action: A selective hormone type herbicide absorbed through leaves with translocation to the roots

Physical and Chemical Properties of the Product

Physical state:	Liquid
Colour:	Light amber
Specific gravity (at 23 °C):	0.887 – 0.943
Acidity, alkalinity or pH value:	6-8
Explosive properties:	Not explosive

Oxidising properties:	Not an oxidising substance
Corrosion characteristics:	Not corrosive
Dangerous goods classification:	Not a dangerous good
Storage stability:	Stability data provided by the applicant supports a storage life of 2 years when stored under normal conditions in fluorinated high density polyethylene containers.
Low temperature stability:	No adverse effects observed

Summary of the APVMA's Evaluation of Nufarm Corasil Plant Growth Regulator

The Chemistry and Residues Program (CRP) has evaluated the chemistry aspects of Nufarm Corasil Plant Growth Regulator (manufacturing process, quality control procedures, batch analysis results, analytical methods, storage stability, and specifications for containers for the product) and found them to be acceptable.

TOXICOLOGICAL ASSESSMENT

Evaluation of Toxicology

The toxicological database for Dichloprop-P, which consists primarily of toxicity tests conducted using animals, is quite extensive. 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 such effects might be generated 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 reactions weigh heavily 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

The absorption, distribution, metabolism and excretion of (^{14}C) dichlorprop-P was investigated following single and repeated oral administration to rats of both sexes (Lappin, 1996a). Radiolabelled dichlorprop-P was absorbed rapidly and extensively at single oral dose levels (5 mg/kg bw and 100 mg/kg bw). Maximum plasma concentrations were achieved in about 3-6 h post dose, and plasma half-life was about 4-7 h. The extent of absorption was >88%. In males, the highest levels of radioactivity were detected in the kidney followed by plasma, thyroid, blood, liver, adrenals, heart and lung. In females, the highest levels were noted in the thyroid followed by kidney, plasma, blood, ovaries, lung, heart, uterus, adrenals, and liver. Of the total excreted, the majority of a single oral dose was not metabolised and excreted unchanged in urine and faeces (~97%). Unidentified minor metabolites accounted for ≤3.0% of the total excreted dose. Rats eliminated the majority (>88%) of a single oral dose in the urine within 24-48 h, and to a much lesser extent in the faeces (4-10%). The majority of the administered dose was excreted rapidly in the urine (<24 h), with 88-96% excreted ≤120 h for the low dose and 88-91% excreted ≤168 h. No radioactivity was detected in expired air. Toxicokinetics following repeat-dosing was similar to that obtained following a single low dose. There was no significant gender difference observed in any of the parameters investigated. The data showed no evidence of tissue accumulation.

The absorption, distribution, metabolism and excretion of (^{14}C) dichlorprop-P 2-ethylhexylester (EHE) was investigated after administration of a single oral dose of 5 mg/kg bw to male rats (Lappin, 1996b). The absorption, plasma pharmacokinetics, metabolism and excretion of dichlorprop-P EHE were similar to that of dichlorprop-P acid (Lappin, 1996a). Dichlorprop-P EHE displayed rapid absorption into the systemic circulation with the peak plasma concentrations being achieved by 3 h, and the plasma half-life was about 4 h. The extent of absorption following administration was estimated to be

85%. Disappearance from the circulation was linked to appearance in the urine. There was no evidence of accumulation in tissues or carcass, with levels of radioactivity in most tissues below the limit of detection by 168 h post-dosing. At 168 h post-dosing, low but detectable residues were found only in the more lipophilic tissues including the skin and fat. The major metabolite detected in urine and faecal samples was dichlorprop-P acid. The parent compound dichlorprop-P EHE was not detected in any of the urine and faecal samples at 0-6, 6-12 and 12-24 h intervals post-dosing. It is therefore assumed that dichlorprop-P EHE is readily hydrolysed to dichlorprop-P *in vivo* by enzymic processes. Of the total radioactivity excreted by 48 h for both test substances, the majority was dichlorprop-P acid (92%) and additional metabolites accounted for the remainder (7.5%). As many as 4 minor metabolites in urinary samples and 8 minor metabolites in faecal samples were detected at 6 h after dosing. The identities of minor metabolites were not established. The majority of administered dose was excreted in the urine and faeces in the first 24 h. Rats eliminated the majority of a single dose in the urine with 84.8% of the administered dose excreted ≤168 h. Faecal excretion did not account for a significant proportion of the administered dose (4.9% excreted ≤168 h). No radioactivity was detected in expired air.

Percutaneous absorption

A rat *in vivo* dermal absorption study for dichlorprop-P 2-ethylhexylester was available for review. When only rat *in vivo* dermal absorption studies are available, the most conservative approach would be to assume that human skin absorption would be equal to rat *in vivo* dermal absorption. The study summary is provided in the following text.

The absorption of dichlorprop-P 2-ethylhexylester *in vivo* was determined following dermal application of the radiolabelled compound on male rats (Cotton & Swalwell, 2004). The amount of the dermal dose absorbed reached a maximum of 9.8% of the administered dose after 10 h of exposure, and 17.8% of the administered dose at the 72 h sampling time point. Urine was the major route of excretion, with as much as 86% of the absorbed dose excreted via this route. Excretion in the faeces was negligible.

Acute Studies

Active

Acute studies have been conducted with the active constituent, dichlorprop-P (the acid form). Four of the acute studies provided in the applicant's dossier were performed prior to GLP/QA and contemporary test guidelines. They included acute oral, acute dermal, skin irritation and eye irritation studies. The older, pre-GLP studies were used in the current assessment as supporting material only. Similar studies have more recently been undertaken by different testing laboratories in accordance with contemporary test guidelines. In these more recent studies, dichlorprop-P displayed low acute oral (LD_{50} of 567 mg/kg bw in rats), dermal (LD_{50} >2000 mg/kg bw in rats) and inhalational toxicity (LC_{50} >2700 mg/m^3, 4-h nose only exposure in rats). It was a non-irritant to the skin and a severe irritant to the eyes of rabbits, but not a skin sensitiser in guinea pigs.

Repeat-dose Studies

A tabulated summary of the repeat-dose studies including toxicological endpoints (NOELs and LOELs) is presented in Table 1. Individual study summaries also appear in the relevant study section types below.

Short-term Studies

No repeat-dose short-term inhalation studies were available.

A comparative pre-GLP study of the toxicity of the dichlorprop racemate and R-isomer during a 4-week period of dietary administration was available for review. In Wistar rats (10/sex/dose), dichlorprop doses of 0, 100 or 500 ppm (equal to 11 or 53 mg/kg bw/d) for either the racemate or the R-isomer were administered via the diet (Kirsch, 1985). Control animals received the same diet without the test substance, under identical conditions. Increases in kidney weights (9-10%) were observed in male rat groups that were fed either the racemate or the R-isomer, and at all doses. The increases in kidney weights in either group were found to be of the same magnitude. In the absence of a dose-relationship and with no corresponding histopathological findings or clinical chemistry alterations, organ weight changes were not considered to be of toxicological significance. Overall, no significant treatment-related effects were observed for the racemate and the R-isomer. For dichlorprop racemate and dichlorprop-P, the NOEL for systemic toxicity in both sexes was 500 ppm (53 mg/kg bw/d), the highest dose tested.

Dichlorprop-P in distilled water was applied dermally to the clipped dorsal region of NZW rabbits (5/sex/dose) under occlusive conditions once daily for a 4 h exposure period, over 21 (males) or 22 (females) consecutive days, at fixed dosages of 0, 10, 100 or 1000 mg/kg bw/d (Allan *et al*., 1993). The concurrent control group received distilled water alone under identical conditions. There were no mortalities or clinical signs. A NOEL for dermal irritation could not be established because of the dermal reactions noted at all doses tested. There was a dose-relationship in the severity of dermal reactions shown following repeated administration. At the highest dose, 7/10 of test animals displayed well-defined erythema at the test site and moderate diffuse acanthosis in the treated skin samples whereas at the lowest dose findings included slight erythema in 2/10 of the test animals and minimal diffuse inflammatory cells in the superficial dermis in 1/10 animals. The repeat-dose dermal irritancy potential appears to be consistent with the low pH of the test substance. Under the conditions of this study, the NOEL for systemic toxicity was the highest test dose of 1000 mg/kg bw/d.

Subchronic Studies

In Beagle dogs (5/sex/dose), dichlorprop-P at doses of 0, 25, 175 or 525 ppm was administered in the diet for 3 months (Hellwig, 1994). The control animals received an untreated diet. The calculated mean daily intake of test compound in the respective groups was calculated as 0, 0.8, 5.4, 16.9 mg/kg bw/d. Diarrhoea was evident (mostly in week 7-10 of study) in the majority of dogs at the high-dose (4 males and 2 females). Repeated occurrence of diarrhoea was evident (>10 times in 7 weeks) in some animals, with others showing only isolated (up to 3 times) occurrences. A statistically significantly decreased plasma triglyceride concentration was detected in the high dose females at mid-study (↓ 41%) and the end of study (↓ 48%).Under the conditions of this study, the NOEL for systemic toxicity in both sexes was 175 ppm (equal to 5.4 mg/kg bw/d) based on clinical signs (diarrhoea) and decreased plasma triglycerides (females) at the higher dose of 525 ppm (equal to 16.9 mg/kg bw/d).

Chronic Studies

In B6C3F1 mice (50/sex/dose), dichlorprop-P at doses of 0, 40, 400 or 2000/3500 (male/female) ppm were administered in the diet for 78 weeks (Mellert, 1996). Control animals received an untreated diet. The top doses of 2000 ppm and 3500 ppm of dichlorprop-P in the feed were considered too high since these concentrations caused severe impairment of body weight in both sexes (up to 20% below controls in males and 36% below controls in females) and high mortality in females (58%). Consequently, the remaining animals in both sexes were sacrificed after 9 months of treatment without further examinations. In order for a carcinogenicity test to be acceptable by OECD guideline No. 451, survival of all groups must be no less than 50% at 18 months in mice. Based on the level of impairment of body weight (~10%), observed at a dose of 400 ppm in males, this dose level fulfilled the OECD criteria of a maximum tolerated dose in males. In order for study authors to meet the OECD requirements for the maximum tolerated dose and a reduced mortality, a supplementary study was subsequently performed in which only female mice received dichlorprop-P in the diet at 0 or a reduced dose of 800 ppm for 78 weeks (50/dose) (Mellert, 1998). Control animals received an untreated diet. The calculated average daily intake values of dichlorprop-P based on food consumption and body weight were 0/0, 6/8, 59/78 and 143 (females) mg/kg bw/d for males/females respectively. Clinical examination, food consumption, body weight, differential blood count, gross-pathology and histopathology analysis were performed. The NOEL was 40 ppm (6 mg/kg bw/d) based on reduced body weight gain in males and an increased incidence of chronic nephropathy and focal calcification in females at higher doses (≥400 ppm). There was no evidence that dichlorprop-P was carcinogenic in mice.

In Beagle dogs (5/sex/dose), dichlorprop-P at doses of 0, 120, 240 and 720 ppm were administered in the diet for approximately 12 months (Bachmann *et al*., 1997). Control animals received an untreated diet. The mean intake of the test substance was 0/0, 3.5/3.9, 7.0/7.7 and 22.2/26.1 mg/kg bw/d for males/females respectively. At 720 ppm, there was a reduction in body weight gain in both sexes accompanied by diarrhoea and a mild anaemia (↓ RBC, ↓ Hb, ↓ Hct). At 720 ppm, mild anaemia was noted in females at test day 95 but not at later times (day 186 or 361) and in males at test day 94 and 185 but not a later times (day 364). A number of dogs at this dose level (4/10) were terminated early due to severe lesions in the oral cavity (histopathology revealed ulcerative and necrotising gingivitis/stomatitis and/or glossitis). Gingivitis ulcerosa and a hyperaemic gingival margin were observed in a male dog at 240 ppm. Oral lesions may have resulted as a consequence of the irritancy potential of dichlorprop-P on mucous membranes. Kidney weights were increased (≥10%) in all treated groups, however the result was only significant at 240 ppm in females. Histopathology of the male kidneys at 720 ppm showed lymphoid cell infiltration (2/5 treated versus 0/5 control) tubular vacuolization (2/5 treated versus 0/5 control) and tubular dilation (1/5 versus 0/5 control). Associated with gross necropsy findings, histopathological findings at 720 ppm revealed focal ulceration of the stomach mucosa (2/5 males, 1/5 females), chronic inflammation of the tonsils, and hyperplasia of the mandibular lymph nodes. Epithelial hyperplasia was observed in the oesophagus of 1/5 female at 720 ppm. In the male epididymides at 720 ppm, hypoplasia/atrophy (2/5), debris in the lumen (2/5), oligospermia (1/5), and epithelial flattening (1/5) were observed. Other lesions occurred at approximately similar frequencies in control or treated animals, or exhibited no dose response relationship, and were therefore considered incidental to treatment. The NOEL was 120 ppm (3.5 mg/kg bw/d) based on gingivitis ulcerosa and a hyperaemic gingival margin in a male dog at 240 ppm. This lesion was considered to be a precursor to more severe oral lesions observed at the high-dose, and

therefore, an appropriate endpoint on which to establish the NOEL. The NOEL for systemic effects was 240 ppm (7 mg/kg bw/d) based on histopathology of the male kidneys lymphoid cell infiltration, tubular vacuolization, and tubular dilation at the higher dose (22.2 mg/kg bw/d).

Reproduction Study

A 1-generation preliminary reproduction study was provided for dichlorprop-P (Milburn, 2001). Groups of rats (12/sex/dose) were fed diet containing 0, 1200, 1500 or 1800 ppm of dichlorprop-P. Control animals received an untreated diet. To avoid the excessive pup toxicity that was ascribed to high dose rates in the previous racemate study, the inclusion of dichlorprop-P in the diet was adjusted to give approximately constant dose rates throughout the current study (0, 101, 128 or 151 mg/kg bw/d respectively). There were no mortalities or clinical signs. Reduced food consumption in males at 1500 ppm and 1800 ppm and in females at 1800 ppm during the pre-mating period appeared to correspond to a decrease in body weight gain (by 15% and 20%, respectively, in males and by 13% in female). Similarly, reduced food consumption during gestation in females at 1500 and 1800 ppm (by 9%) corresponded to a decrease in body weight gain (by 12% and 15% respectively). However, decreased body weight gain was observed in a dose-related manner in all treated female groups during the first 5 days of lactation (by 46%, 52% and 63% respectively) without significant changes in food consumption. Body weight, however, was comparable to control at the end of lactation period, even though total food consumption was reduced in all treated groups during this period (range 12-19%). There was no effect on the length of gestation, the number of litters produced, litter size, live born and survival indices and sex ratio. Pup body weight was slightly reduced at 1800 ppm from day 15 *post partum* onwards compared to controls reaching statistical significance on day 29 (~9% reduction at the high dose). Thus, this study provided information to allow dose selection for a multigenerational reproduction toxicity study, although one was not submitted with the current application.

Developmental Studies

In pregnant Wistar rats (25/dose), dichlorprop-P (suspended in 0.5% aqueous carboxymethyl cellulose) at doses of 0, 20, 80 or 160 mg/kg bw/d was administered via oral gavage from days 6 through 15 of gestation (Hellwig, 1993). Control rats received only vehicle. One dam at 160 mg/kg bw/d died on day 13 of gestation, exhibiting lateral position, labored respiration and poor general state prior to death. Another dam at the same dose also exhibited labored respiration and poor general state after the end of treatment period. Both dams were pregnant and necropsy revealed erosions of the stomach mucosa. Significant reductions in food consumption (~10-20%) and body weight gain (~15-20%) at ≥80 mg/kg bw/d were observed in dams on gestation days 6-15. Corrected body weight gain (minus uterus weight) was also significantly lower (~30%) at 160 mg/kg bw/d. Foetal weight in both sexes at 160 mg/kg bw/d was lower than controls (by 13%; $p<0.01$). Skeletal variations (increased incidence of rudimentary cervical ribs, above the historical control limits) at ≥80 mg/kg bw/d and skeletal retardations (increased incidence of unossified sternebrae, $p<0.05$ and above the historical control limits) at 160 mg/kg bw/d were observed. The marginal increases in foetal incidence rudimentary cervical ribs at 80 mg/kg bw/d was considered to be treatment-related since the value lies outside the historical control range for the strain and supplier stock (0-6.5%). Based on a reduction in body weight gain at ≥80 mg/kg bw/d, the NOEL for maternal toxicity was 20 mg/kg bw/d. Effects on foetal development did not occur in the absence of maternal toxicity. The NOEL for developmental toxicity was also 20 mg/kg bw/d based on skeletal variations (increased incidence of rudimentary cervical ribs)

at ≥80 mg/kg bw/d.

In pregnant Himalayan rabbits (15/dose), dichlorprop-P (suspended in 0.5% aqueous carboxymethyl cellulose) at doses of 0, 20, 50 or 100 mg/kg bw/d was administered via oral gavage from days 7 through 19 of gestation (Hellwig, 1993). Control rabbits received vehicle only. At 100 mg/kg bw/d, 1 dam died on gestation day 22 and another dam was sacrificed prematurely in a moribund state. Clinical signs in these dams included lateral position, no defecation and poor general state. Necropsy revealed ulcerations of the stomach mucosa.
Significantly reduced food consumption was observed throughout the dosing period (15%; $p<0.01$) at 100 mg/kg bw/d. A significant body weight reduction was also observed at 100 mg/kg bw/d between days 7 and 9 of gestation (~25%), a similar level of reduction in net body weight gain (day 7-29) was also apparent but did not attain statistical significance. An significant increase in the incidence of skeletal variations (foetuses with accessory 13^{th} ribs) was observed at 100 mg/kg bw/d and was outside the historic control range. Based on mortality, decreased food consumption and decreased body weight at 100 mg/kg bw/d, the NOEL for maternal toxicity was 50 mg/kg bw/d. Effects on foetal development did not occur in the absence of maternal toxicity. The NOEL for developmental toxicity was also 50 mg/kg bw/d based on skeletal variations (increased incidence of foetuses with accessory 13^{th} ribs) at 100 mg/kg bw/d. This study deviated from the OECD guideline No. 414 which requires at least 20 animals per dose. However, based on the minimal developmental toxicity observed, the study was considered to be acceptable for regulatory purposes.

Neurotoxicity Studies

In Wistar rats (10/sex/dose), a single dose of dichlorprop-P (suspended in 0.5% aqueous carboxymethyl cellulose) was administered by oral gavage at 0, 125, 250, 400 or 500 mg/kg bw (Mellert *et al*., 1995b). Control animals received only vehicle. At 3 days post-dosing, 8 mortalities were recorded at 500 mg/kg bw/d and 1 mortality was recorded at 400 mg/kg bw/d. Clinical signs in these animals included piloerection, hypothermia and half-closed eyes. At 500 mg/kg bw/d, there was a significant reduction in body weight gain (32%) by the end of study (14 days post-dosing). Abnormal clinical signs in the functional observational battery of tests were seen at dose levels of ≥250 mg/kg bw. Typical signs of treatment were piloerection, abnormal posture (abdominal(prone) or lateral position), impaired activity in the open field, impairment of gait, half-closure of eyelids, retarded or missing pupillary reflex, slight hypothermia, impaired coordination of movements, decreased number of rearings, reduced grip strength of forelimbs and hindlimbs, and increased values in the landing foot splay test. Motor activity was also impaired in females ≥250 mg/kg bw. Since all clinical signs, except piloerection, were completely reversible by day 7 and examinations of the central and peripheral nervous systems did not reveal any specific effects, it was concluded that dichlorprop-P was not neurotoxic to rats after a single oral dose. The NOEL was 125 mg/kg bw based on clinical signs at higher doses.
In Wistar rats (15/sex/dose), dichlorprop-P doses of 0, 100, 500, 2000 (males) or 3000 (females) ppm were administered in the diet for 3 months (Mellert, 1995a). Control animals received an untreated diet. The calculated mean daily intake of test compound in the respective groups was calculated as 0, 8, 39, 144(males) and 245(females) mg/kg bw/d. This study was a subchronic oral toxicity and neurotoxicity study. A portion of the test animals (5/sex/dose) were fixed by *in situ* perfusion and

subjected to neurological examinations. A neurological examination was performed and consisted of a functional observational battery (FOB) of tests and measurements of motor activity (10/sex/dose) prior to, and 3 times (4, 8, 13 weeks) during the administration period. Decreased food consumption, food efficiency, water consumption and body weight gain were all observed at the highest dose in both sexes. The majority of high dose animals displayed a moderate or severe grade of cytoplasmic eosinophilia and granular cytoplasm of the hepatocytes. These findings correlated well with the further histopathological finding of central lobular hypertrophy (minimal to moderate severity) and increased relative liver weights in the same animals. Toxicity at the high dose was further characterised by a reduction in RBCs (both sexes). Findings of increased excretion of diluted urine with increased urinary detection of RBCs in addition to changes in creatinine (↑), calcium (↓), potassium (↓) and globulins (↓) and water consumption (↑) in high-dose animals of both sexes were suggestive of a slight functional alteration in kidney function. Blood urea nitrogen level, another indicator of kidney function, was not determined in this study. Plasma lipids (triglycerides and cholesterol) were also lowered in both sexes. There was no evidence of neurotoxicity in this study. Under the conditions of this study, the NOEL for systemic toxicity was 500 ppm (35 mg/kg bw/d in males and 42 mg/kg bw/d in females) based on decreased food consumption, decreased body weight gain, increased water consumption, anaemia, decreased serum cholesterol and triglycerides, increased liver weights, microscopic changes in the liver (cytoplasmic eosinophilia, granular cytoplasm, central lobular hypertrophy and absence of lipid retention (fat storage)), increased serum ALT and AP, increased kidney weights and changes in urinalyses parameters (increased urinary volume, decreased urinary specific gravity and mild haematuria) at the higher dose (144 mg/kg bw/d in males and 245 mg/kg bw/d in females). Despite clear signs of systemic toxicity (reduced body weight gain, haematology and liver changes), neither clinical signs nor histopathological evidence for a neurotoxic potential was observed at dose levels up to 144 mg/kg bw in males and 245 mg/kg bw in females.

Other Studies

Acute Studies - Formulated Product

Acute studies on the formulated product, Corasil Plant Growth Regulator, which contains the active constituent in the ester form, namely dichlorprop-P 2-ethylhexylester (25 g/L), were not available in the applicant's registration dossier.

Acute studies on a similar product formulation (Corasil E) that contained a racemic mixture of dichlorprop isomers in the butoxyethylester form and similar concentrations of non-active constituents were provided by the applicant. The concentration of the acid form of dichlorprop-P (R-isomer) in Corasil E (25 g/L) was identical to that contained within Corasil Plant Growth Regulator. For this reason, Corasil E was considered in the extrapolation of acute product toxicity for Corasil Plant Growth Regulator. Corasil E displayed low acute oral (LD_{50} of 3775 mg/kg bw in rats), dermal (LD_{50} >2000 mg/kg bw in rabbits) and inhalational toxicity (LC_{50} >5120 mg/m^3; 4-h nose only exposure to aerosol in rats). It was a moderate irritant to the skin and a severe irritant to the eyes of rabbits, but was not considered likely to be a skin sensitiser in guinea pigs.

DISCUSSION OF TOXICITY DATA

Dichlorprop-P belongs to a larger class of chemicals known as the phenoxy herbicides, a subclass known as the chlorophenoxy herbicides. According to the Compendium of Common Pesticide Names (http://www.hclrss.demon.co.uk/class_pesticides.html), dichlorprop-P is classified as a phenoxypropionic herbicide on the basis of chemical structure and pesticidal activity. The name *dichlorprop-P* should be distinguished from *dichlorprop*, because it refers to the (R)-(+) optical isomer (or enantiomer) of dichlorprop whereas the latter refers to the racemate (a 50:50 ratio of R:S isomers). Dichlorprop-P is the only isomer to contain herbicidal activity.

Adequacy of submitted toxicology studies

A toxicology database was submitted by Nufarm Australia Limited in support of the new active constituent approval for dichlorprop-P. There were 32 studies submitted for dichlorprop-P, 2 of which had been previously evaluated by the OCS. The submitted studies consisted of the following: 1x metabolism & toxicokinetic, 12x acute toxicity, 2x short-term, 2x sub-chronic, 2x chronic (including 1 carcinogenicity study), 1x preliminary reproduction, 2x developmental, 8x genotoxicity, 1x acute neurotoxicity, 1x sub-chronic neurotoxicity. The majority of the studies submitted complied with GLP, and were undertaken according to the contemporary test guidelines. Six of the acute studies were pre-GLP. Contemporary GLP compliant study counterparts were available for the same study types. The age of the database for dichlorprop-P spanned from the early to mid 1980s through to the mid to late 1990s, with the exception of the preliminary reproduction study which was conducted in 2001. The following 4 studies (1979-1992) for dichlorprop racemate were also submitted in support of dichlorprop-P registration and have been previously evaluated by the OCS: 1x chronic study, 1x full multigeneration reproduction study, 2x developmental studies.

Data deficiencies for dichlorprop-P included the absence of a full multigeneration reproduction study and at least 2 carcinogenicity studies for dichlorprop-P conducted in different species. Instead of the data requirement for a multigenerational reproduction study, an initial dose-range finding reproduction study was submitted for dichlorprop-P (Milburn, 2001). The applicant has intended that the OCS use the dichlorprop racemate full multigenerational study as the main supporting evidence for the determination of reproductive toxicity hazards. In order to validate this approach, the OCS determined whether the R-isomer and the racemate displayed similar toxicological profiles. A detailed discussion of the comparative toxicity profile is provided in the relevant section below. On the basis of similar toxicological profiles (when the same species, route of administration and duration of dosing were compared in acute, short-term and sub-chronic toxicity studies), the dichlorprop racemate reproduction study was considered to be valid supporting evidence for the toxicological evaluation of dichlorprop-P (Hellwig *et al*., 1992).

Toxicological information from a mouse carcinogenicity study was used to establish the ADI limit for dichlorprop-P. In establishing the ADI, an additional safety factor of 2 was applied to account for an incomplete dichlorprop-P database, due to the absence of at least 2 carcinogenicity studies conducted in different species.

Acute toxicity

Active constituent

As a result of animal testing, dichlorprop-P was found to be of low acute toxicity concern via the oral, dermal and inhalation routes in rats. It caused severe eye irritation in rabbits, which appeared to be consistent with its low pH. In a non-OECD guideline skin irritation study (Hildebrand & Kirsch, 1983c), dichlorprop-P was found to be a moderate skin irritant in rabbits. The results of this study were considered to be inconclusive since the exposure was prolonged compared to that in the OECD guideline (24 h compared to 4 h), more intensive (occlusive rather than semi-occlusive) and was performed on abraded skin. In a subsequent OECD guideline skin irritation study (Smith, 1990a), dichlorprop-P did not cause skin-irritation in rabbits. It was concluded that dichlorprop-P was not a skin-irritant in rabbits. There is no evidence of skin sensitising potential for dichlorprop-P, as the substance did not cause skin sensitisation in guinea pigs.

No acute toxicity studies were available for the emulsifiable concentrate (EC) product formulation, Corasil Plant Growth Regulator, which contains dichlorprop-P in the 2-ethylhexylester form. Acute toxicity studies on a similar EC formulation called Corasil E were provided by the applicant. Corasil E contains a racemic mixture of dichlorprop isomers in the butoxyethylester form. The concentration of the R-isomer acids (25 g/L) is identical in both products. Corasil E also contains similar concentrations of non-active constituents. For these reasons, the toxicity studies provided for Corasil E were considered adequate to establish the acute product toxicity of Corasil Plant Growth Regulator. Corasil E was found to be of low acute toxicity via the oral, dermal and inhalation routes in rats. It was a severe eye irritant and a moderate skin irritant in rabbits, but was not considered to be a skin-sensitiser in guinea pigs.

Once absorbed, the acute toxicity of different forms of dichlorprop-P (i.e. acid, ester, salts) were predicted to be very similar since hydrolysis of esters and dissociation of salts takes place very rapidly *in vivo*, although potential differences in the skin/eye irritancy and skin sensitisation potential of the different forms may occur. The toxicity profiles of the ethylhexylester and butoxyethylester forms of dichlorprop were considered to be similar. Differences in non-active constituent concentrations were considered negligible with respect to the overall toxicity profile. From this, it was concluded that both products are likely to display similar acute toxicological profiles. Therefore, Corasil Plant Growth Regulator is likely to be of low acute toxicity (via the oral, dermal and inhalation routes), to cause severe eye irritation and moderate skin irritation, but is not likely to be a skin-sensitiser in guinea pigs. Hazard-based safety directions are thus driven by the moderate skin irritancy and severe eye irritancy potential of the product.

The high content of solvent naphtha (80%) in the undiluted product were also considered in hazard-based safety directions. According to NOHSC *Approved Criteria for Classifying Hazardous Substances*, Nufarm Corasil Plant Growth Regulator is assigned the hazardous risk statement “R67: vapours may cause drowsiness and dizziness” (Section 8). Accordingly, a search of the published literature advises that in humans, petroleum naphtha vapour is a CNS depressant as well as an irritant of the mucous membranes and respiratory tract. Exposure to high concentrations of the vapour can produce headache, dizziness, nausea, and shortness of breath. Dermal contact to vapour or liquid can

produce dermatitis (Sullivan & Krieger, 1992). In a human trial, 880 ppm (4.1 mg/L) of solvent naphtha produced eye and throat irritation and temporary olfactory fatigue (Bingham *et al*., 2001). Please refer to the risk assessment section of this report (Section 7.2.1) for personal and protective equipment (PPE) recommendations.

Mode of action

Similar to other phenoxy growth regulator herbicides, dichlorprop-P is a synthetic structural analogue of the auxin plant hormones. Growth regulator herbicides upset the normal hormonal balance in plants that regulates processes such as cell division, cell enlargement, protein synthesis, and respiration. A precise mode of action for dichlorprop-P in plants is not available.

Dichlorprop-P's precise mode(s) of action in mammals is not known. No mechanistic studies were provided in the applicant's registration dossier. A Californian EPA draft hazard assessment report for dichlorprop-P did provide some useful information regarding one potential mode of action (California EPA, 2001). In animals, phenoxy herbicides are rough structural analogues of fatty acids. They are known to be peroxisome proliferators and influence cholesterol and triglyceride levels in repeat-dose animal studies. Dichlorprop shares structural and functional similarities with clofibrate, a hypolipidemic agent that is known to cause peroxisomal proliferation. Clofibrate acts therapeutically via the peroxisome proliferator activated receptors (PPARs) to lower cholesterol. Many of the steps of cholesterol biosynthesis occur in peroxisomes (Krisans, 1996). Dichlorprop was found to significantly reduce serum cholesterol in rats at higher doses (Ohta *et al*., 1987). In their study, Ohta *et al*. (1987) determined that interference with cholesterol synthesis, rather than absorption or distribution, was responsible for the reduction in cholesterol by dichlorprop.

There is some supporting evidence from the *in vivo* animal data in this dossier to implicate the R-isomer of dichlorprop (dichlorprop-P) as a contributor towards the hypolipidemic properties of racemic dichlorprop. Direct reductions in serum lipids were measured in rats (Mellert, 1995a) and dogs (Hellwig, 1994; Bachmann *et al*., 1997), but not in mice following 3-months of dietary dichlorprop-P. Induction of peroxisomal enzymes is known to cause alterations in lipid metabolism. The light microscopically visible eosinophilia of hepatocytes (Mellert, 1995a) associated with repeated dietary administration of dichlorprop-P is known as a possible correlate of peroxisome proliferation. The decrease of lipid storage in hepatocytes associated with dichlorprop-P administration (Mellert, 1995a) was interpreted as a result of increased lipid metabolism seen in connection with peroxisome proliferation. Indicators of peroxisomal proliferation including increased cyanide-insensitive palmitoyl-CoA-oxidation, light microscopically visible eosinophilia of hepatocytes and single tubular epithelial cells of the kidneys, decreased of lipid storage in hepatocytes were also observed during a 3-month dietary study in mice (Mellert, 1993).

Repeat-dose studies

Dichlorprop-P was administered via the diet in most of the repeat-dose studies submitted, except for a 12-month dog study (gavage) and 2 developmental studies (gavage). The liver was the target organ in shorter term studies (90 days or less) of mice and rats, and to a lesser extent the kidneys of rats. Other effects of dichlorprop-P in shorter term studies included perturbations of circulating lipids (cholesterol and triglycerides) in all species tested (mice, rats and dogs) and anaemia in rats. Rats were considered to be the most sensitive species for liver effects because of the extent of the findings observed and the lower observed effect levels. In a 3-month rat feeding study, increased liver weights, histopathological findings in hepatocytes (cytoplasmic eosinophilia, granular cytoplasm, central lobular hypertrophy and absence of lipid retention (fat storage)) and alterations in associated clinical chemistry parameters (increased serum ALT and AP) were observed in dose groups receiving ≥144 mg/kg bw/d. Decreased food consumption, body weight gain, decreased serum cholesterol and triglycerides, anaemia and kidney effects (decreased water consumption, increased kidney weights, increased urinary volume and decreased urinary specific gravity and mild urinary haematuria) were also apparent in rats at the same dose. Dogs were considered to be the least sensitive species for liver effects in shorter term studies demonstrating only clinical signs (diarrhoea) and a decrease in serum triglycerides and at a dose of 17 mg/kg bw/d. There was no evidence of significant gender sensitivity in the shorter term dietary studies. There was no evidence of systemic toxicity following 21 days of repeated dermal dosing in rabbits up to and including 1000 mg/kg bw/d. The local effects of repeated dermal dosing in rabbits consisted of dermal irritation at all doses tested (10 -1000 mg/kg bw/d).

The critical effect of dichlorprop-P identified in longer term studies (more than 90 days), was observed in the kidneys of both animal species tested: mice and dogs. Mice appeared to be the most sensitive species as an increased incidence of chronic nephropathy was observed in mice fed dichlorprop-P in the diet for 18 months at doses of ≥400 ppm (≥59 mg/kg bw/d). The corresponding NOEL was 6 mg/kg bw/d. Chronic nephropathy was characterised by the presence of proteinaceous casts within the tubules, areas of tubular atrophy, regeneration and dilation, and/or interstitial fibrosis. The incidence of chronic nephropathy was substantially increased (78% of the 400 ppm group, 90% of the 800 ppm group) compared to the control background (14% of the controls) in female mice exposed to doses of ≥400 ppm (≥78 mg/kg bw/d). These data suggested that there may be some degree of gender sensitivity for the renal effects of dichlorprop-P in mice. Mild chronic nephropathy is known as a common lesion of aging mice and there is evidence to show that the rate of progression of chronic renal disease is greater in males than in females in the literature (Hard & Khan, 2004; Silbiger & Neugarten, 2003). Indeed, the untreated male control group (86% of animals) were more susceptible than the untreated female control group (14% of animals) to developing chronic nephropathy. Under the conditions of the 18-month mice study, it would appear that dichlorprop-P treatment in female mice has negated the gender protective effects on the progression to chronic nephropathy. Dichlorprop-P treatment also caused kidney effects in a 12-month feeding study in dogs. Histopathological findings were evident in male kidneys at a dose of 720 ppm (22.1 mg/kg bw/d) and included lymphoid cell infiltration (2/5 dogs), tubular vacuolization (2/5 dogs) and tubular dilation (1/5 dogs), but not in control dogs. The corresponding NOEL for kidney effects was 240 ppm (7 mg/kg bw/d).

Comparative toxicity of the dichlorprop racemate and the R-isomer

The comparative toxicity of dichlorprop-P relative to dichlorprop racemate can be established for acute, short-term and sub-chronic effects because studies which employ the same species, the same route of administration, the same duration of doses and similar dose levels are available for review.

The acute toxicity of the racemate and R-isomer can be compared from data in an oral toxicity (Hildebrand & Kirsch, 1983a), a dermal toxicity (Hildebrand & Kirsch, 1983b), a skin irritancy (Hildebrand & Kirsch, 1983c) and an eye irritancy study (Hildebrand & Kirsch, 1983d). In these pre-GLP studies, the racemate and the R-isomer were tested side-by side at identical dose levels and in identical animal strains. All studies were considered acceptable for regulatory purposes. Information on the racemate is available in Appendix VII and in a previous OCS report. Oral and dermal LD_{50}s were all identical and both forms of dichlorprop were found to be severe eye irritants. The skin irritancy potential of the R-isomer (Draize irritation index 3.0) was found to be slightly higher than for the racemate (Draize irritation index of 2.6). Taken together, study data suggests that the racemate and the R-form exhibit similar acute toxicological profiles.

No significant toxicological differences in rats were observed for the racemate and the R-isomer in a comparative 4-week dietary study for dichlorprop racemate and the R-isomer (Kirsch, 1985). Equivalent dose levels of the respective dichlorprop form were consumed over the duration of study. Increases in kidney weights (9-10%) were observed in male rat groups that were fed either the racemate or the R-isomer, and at all doses (11 and 53 mg/kg bw/d). The increases in kidney weights in either group were found to be of the same magnitude. In the absence of a dose-relationship and with no corresponding histopathological findings or clinical chemistry alterations, organ weight changes were not considered to be of toxicological significance.

Additional comparative information on the toxicity of the R-isomer and the racemate was obtained from 2 separate 3-month rat dietary studies (Mellert *et al*., 1995a; Til *et al*., 1977). Both studies used the same type of rats (Wistar strain), the same route of administration via the diet and comparable dose levels. Dose levels in the study of Til *et al*. (1977) previously evaluated by the OCS were 0, 100, 500, 2500 ppm and were equal to actual doses of 0, 5, 25, 125 mg/kg bw/d. Dose levels in the study of Mellert *et al*. (1995) were 0, 100, 500, 2000 (M) or 3000(F) ppm and were equal to actual doses of 0, 7/8, 35/42, 144 (M) or 245 (F) mg/kg bw/d in males/females respectively. The toxicological profile of the racemate and the R-isomer is similar when comparing the 2 studies. The same effects and test parameters were affected in comparative doses. Decreased food consumption and body weight gain were observed at the highest doses (both sexes) in both studies. The target organ was the liver in both studies. High dose animals (both sexes) displayed statistically significantly increased liver weights which were supported by histopathological findings in the hepatocytes. A much higher degree of detail for these microscopic findings was provided in the more recent of the 2 studies. Observations of increased serum glutamyl oxaloacetic transaminase (racemate), glutamyl pyruvic transaminase (racemate), bilirubin (R-isomer) and alkaline phosphatase (racemate and R-isomer) at the high dose (both sexes) may also be additional indicators of liver damage; although the tissue origin(s) of these serum elevations was not identified in either study. Alterations in blood parameters were noted in both studies at the highest dose (↓ RBCs both sexes for the R-isomer compared to ↓Hb both sexes, ↓ PCV

in males, ↓ RBCs females for the racmate). There was an indication of effects on the kidney with increased kidney weights noted in both studies. Findings of increased excretion of diluted urine with increased urinary detection of RBCs in addition to changes in creatinine (↑), calcium (↓), potassium (↓) and globulins (↓) and water consumption (↑) in high-dose animals of both sexes were suggestive of a slight functional alteration in kidney function in the R-isomer study. Decreased circulating total protein and albumin levels at highest dose of racemate (both sexes) may be suggestive of kidney (and/or liver) effects. In the absence of a clear dose-response relationship for kidney weights and the lack of histopathological correlates, no toxicological significance for these effects could be ascribed in either study. A notable difference between the 2 studies was the lack of effect of the racemate on circulating lipids compared to the significant decrease in serum triglycerides and cholesterol at the highest dose (both sexes) for the R-isomer. Although, the racemate has been demonstrated to reduce serum cholesterol in rats at equivalent dose levels and dosing durations (94 mg/kg bw/d) elsewhere in the literature (Ohta *et al*., 1987).

No studies for the S-isomer of dichlorprop were provided in the applicant's registration dossier. Overall, comparison of the data suggested that the R-isomer contributes to the toxicity profile of the racemate, but that the toxicity is not significantly higher than the technical form. It was concluded that the S-isomer must also possess some biological activity, albeit different. It would be of general interest, but not of regulatory importance for the current assessment, to know whether the kinetics of the R-isomer is fundamentally different from the S- isomer (e.g. stereo specific metabolism).

In conclusion, acute toxicity studies and the short-term comparative dietary study in rats (4 weeks) have shown that the racemate and the R-isomer exhibit similar acute, short-term and sub-chronic toxicological profiles with no significant differences in observed effects. The 2 separate 90-day oral rat studies with the racemate and the R-isomer performed in the same animal strain, and at comparative doses, are in further support this. On this basis of these findings, the use of dichlorprop racemate studies to as supporting evidence for the registration of R-isomer form may be valid in certain circumstances. Closely related phenoxyproprionic herbicides including mecoprop and its R-isomeric (mecoprop-P) are also known to share similar toxicological profiles (when the same species, route of administration and duration of dosing are compared).

Genotoxicity/Carcinogenicity potential

The battery of *in vitro* and *in vivo* genotoxicity tests for dichlorprop-P (point mutation, chromosomal damage, and DNA damage and repair) yielded negative results and did not indicate any predisposition for neoplastic lesion(s) or tumour development *in vivo*. Under the conditions of a life-time dietary exposure study in mice, there was no indication of an increased cancer risk associated with dichlorprop-P (Mellert, 1996; Mellert, 1998). As stated in the APVMA's Manual of Requirements and Guidelines (MORAG), one of the minimum data requirements for the approval of a new agricultural active constituent is the provision of carcinogenicity studies in at least 2 separate animal species. The database for dichlorprop-P was considered incomplete due to the lack of a second carcinogenicity study in a second animal species. As partial supporting evidence, there was no indication of an increased cancer risk associated with racemic dichlorprop in life-time dietary exposure studies in mice and rats (Field, 1979; Mitsumori, 1984). However, a caveat in using these studies as supporting

evidence is that nothing is known with respect to the chronic toxicity of the racemic dichlorprop relative to the dichlorprop-P. Comparative chronic studies that compare the same species, route of administration, doses and duration of doses are lacking.

Dichlorprop is one of the phenoxy herbicides, of which most members (particularly 2,4,5-T and 2,4-D) have been under close scrutiny for some years because of concerns about possible carcinogenicity. In Australia, the NHMRC Scientific Committee on Toxicology (NHMRC 1993), acknowledged that it is almost impossible to obtain a population, which has only been exposed to one type of phenoxy herbicide and resolved to consider phenoxy herbicides as a group in its consideration of the human health effects of these agents. The Committee (which was disbanded in 1994) concluded at its 23rd meeting in March 1993, that:

- reservations about the interpretation (in epidemiological studies) of a positive relationship between exposure to phenoxy herbicides and certain types of cancer such as non-Hodgkin's lymphoma and soft tissue sarcoma were justified;
- that molecular epidemiologic studies and broader studies, which attempt to quantify the impact of phenoxy herbicides on health as a whole, are needed to further an understanding of these pesticides on human health; and such studies might include a meta-analysis of selected epidemiologic studies.

A number of human studies have been published since the Scientific Committee on Toxicology (SCOT) report in 1993, which considered associations between phenoxy herbicide exposure and carcinogenicity. There has been no specific surveillance of personnel working in the plant dedicated to the production of dichlorprop-P in other countries. In general, production facilities are relatively small and most of the studies in the public domain are cohort investigations, often with conflicting conclusions. The most definitive study available is a meta-analysis study (Kogevinas *et al*., 1997), which combined the results of 36 cohorts, involving a total of over 20 000 workers. The study examined cancer mortality in 21 863 male and female workers exposed to phenoxy herbicides, chlorophenols and dioxins in 12 countries during the period 1939 - 1992. The findings of the study indicated that exposure to phenoxy herbicides contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and higher chlorinated dioxins may be associated with a small increase in overall cancer risk and in risk for specific cancers including soft tissue sarcoma, non-Hodgkin's lymphoma and lung cancer. Workers exposed to phenoxy herbicides not contaminated with dioxins showed a cancer incidence similar to that expected in the general population. The overall epidemiological evidence for a carcinogenic potential for phenoxy herbicides is considered to be suggestive, but not conclusive. There is no specific human data available concerning the carcinogenic potential of dichlorprop-P.

Exposures to TCDD and higher chlorinated dioxins occurred historically at locations where process conditions allowed dioxins to occur as by-products of synthesis reactions. Current production methods for dichlorprop-P in particular preclude the formation of dioxins. It should be noted that part of the specification for dichlorprop-P is that the production is dioxin-free.

Taken together, the evidence from animal carcinogenicity studies, in addition to human epidemiological studies on the use of phenoxy herbicides internationally suggest that dichlorprop racemate is unlikely to display carcinogenic potential in humans. However, the evidence against a dichlorprop-P carcinogenicity potential in humans is not considered to be conclusive. The major shortcoming of the database is the absence of a carcinogenicity study in a second animal species for dichlorprop-P. The lack of comparative chronic toxicity studies for dichlorprop-P and dichlorprop

racemate means that dichlorprop racemate carcinogenicity studies cannot be used as strong supporting evidence.

Reproductive and developmental toxicity potential

Developmental toxicity was noted in rat and rabbit developmental studies for dichlorprop-P, and was only observed in the presence of maternal toxicity (Hellwig, 1993a; Hellwig 1993b). Signs of maternal toxicity included decreased food consumption (160 mg/kg bw/d in rats, 100 mg/kg bw/d in rabbits) and decreased body weight gain (≥80 mg/kg bw/d in rats and 100 mg/kg bw/d in rabbits). In addition, there were 2 treatment-related mortalities out of 15 dams (>10% mortality) at the highest dose of 100 mg/kg bw/d in rabbits. Teratogenic effects were associated with an increased incidence of skeletal variations in both species (rudimentary cervical ribs and accessory 13^{th} ribs above the historic control range) at maternally toxic doses only. Signs of growth retardation were also evident at a higher dose (160 mg/kg bw/d) in rat foetuses (decreased mean foetal weight and an increased incidence of unossified sternebrae). The developmental effects observed (skeletal variations and growth retardation) were considered to represent developmental toxicity and could not be discounted as being secondary to maternal toxicity. The current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity. The effective doses that caused developmental effects will need to be compared with likely human exposures to assess the risk to humans.

The adequacy of the database provided in support of reproductive toxicity characterisation for dichlorprop-P was considered carefully. The 2 studies provided included a preliminary dose-range finding reproduction study for the R-isomer (Milburn, 2001) and a full multigeneration reproduction study (2 generations and 2 litters) for dichlorprop racemate (Hellwig *et al*., 1992). Signs of toxicity in parental animals in the dose range-finding study included decreased food consumption and decreased body weight gain at doses of ≥1500 ppm (≥128 mg/kg bw/d) during pre-mating, gestation and lactation. Parental toxicity was consistent with other repeat-dose dichlorprop-P studies including rat and rabbit developmental studies (pregnant dams (≥80 mg/kg bw/d) and a rat 3-month feeding study (≥144 mg/kg bw/d). The small number of test parameters in the dose-range finding reproduction study prevented a further comparison of dichlorprop-P effects. The dose-range finding study for dichlorprop-P delivered constant dietary dose rates to rats throughout the pre-mating, gestation and lactation phase. No effects on the length of gestation, the number of litters produced, litter size, live born and survival indices and sex ratio were observed. At a dose of 151 mg/kg bw/d, foetal toxicity of dichlorprop-P was characterised by a reduction in mean pup body weight (9%) by day 29 post-partum.

The full multigenerational study for the dichlorprop racemate incorporated a broader array of test parameters. Signs of toxicity in parental animals were representative of racemic effects observed in other repeat-dose studies. In accordance, parental animals exhibited increased kidney weights at 400 ppm (~42 mg/kg bw/d) and decreased circulating triglycerides and cholesterol, increased serum AP and alterations in blood parameters (↓ Hct) at 2000 ppm (~226 mg/kg bw/d during pre-mating, gestation and lactation). Significant developmental toxicity was observed at maternotoxic dose of 2000 ppm. There was an early effect of high pup mortality in both generations, surviving offspring in all

litters demonstrated growth retardation (↓ body weight and ↓ body weight gain) and specific effects indicative of developmental delay (absence of pinna unfolding, auditory canal opening and eye opening) were evident. Excessive pup toxicity was ascribed to fluctuating high dietary dose rates of dichlorprop racemate throughout the study (2000 ppm equivalent to 161- 226 mg/kg bw/d during pre-mating, gestation and lactation). The strategy of adjusting the levels of dichlorprop-P to maintain a constant dietary dose rate throughout the whole study significantly reduced the impact on pup survival and avoided the effects of growth retardation and developmental delay.

On the basis of a similar toxicological profile for the dichlorprop racemate and the R-isomer in short-term and sub-chronic studies (refer to "Comparative toxicity of the dichlorprop racemate and the R-isomer" in the Discussion section), the OCS considered the multigenerational reproduction study for the racemate to be a suitable surrogate for the determination of reproductive endpoints in the current evaluation (i.e. maternal toxicity and developmental toxicity). Therefore, the relevant NOEL for maternal toxicity is 8.3 mg/kg bw/d based on increased kidney weights at 42 mg/kg bw/d (dichlorprop racemate). Likewise, the relevant NOEL for foetal toxicity is 42 mg/kg bw/d based on increased pup mortality, growth retardation and developmental delay at 226 mg/kg bw/d (dichlorprop racemate).

Neurotoxicity potential

In an acute toxicity study, dichlorprop-P induced clinical signs of toxicity at or near lethal dose levels (400 mg/kg bw) with no evidence of specific neurological effects (Mellert, 1995b). Clinical signs were apparent within the first few hours of treatment, but were completely reversible on day 7. In a 3-month dietary study (Mellert *et al*., 1995a), despite clear signs of toxicity such as decreased body weight gain, anaemia, and liver effects, no evidence for a neurotoxic potential was observed up to the highest doses tested (144 mg/kg bw in males, 245 mg/kg bw in females). Histopathology of selected organs and tissues and specific locations of the central and peripheral nervous system revealed no treatment-related effects following both single (Mellert, 1995b) and repeated doses (Mellert *et al*., 1995a) of dichlorprop-P. There was no indication of delayed neurotoxicity following both single and repeated doses. The NOEL for systemic toxicity following an acute dose was 125 mg/kg bw and following 3-months of dietary administration was 39 mg/kg bw/d in both sexes. On the basis of these findings, dichlorprop-P was not considered to have neurotoxic potential.

ADI & ArfD CONSIDERATIONS AND PUBLIC HEALTH STANDARDS

ADI

The ADI for humans is the level of intake of a chemical that can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL for the most sensitive toxicological endpoint from a suitable study (typically an animal 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, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The critical effect of dichlorprop-P identified based on chronic toxicity studies is the kidneys and was observed in mice and dogs. Mice appeared to be the most sensitive species for dichlorprop-P with an increased incidence of chronic nephropathy observed at dietary doses ≥59 mg/kg bw/d in an 18 month

study; the corresponding NOEL was 6 mg/kg bw/d. Chronic nephropathy was characterised by the presence of proteinaceous casts within the tubules, areas of tubular atrophy, regeneration and dilation, and/or interstitial fibrosis.
No correction for oral absorption of dichlorprop-P is necessary, since the value is greater than 80% (Lappin, 1996a).
A 100-fold safety factor, consisting of factors of 10 for intra and interspecies variation, was considered appropriate. The toxicological database for dichlorprop-P was considered incomplete due to the absence of an additional carcinogenicity study in a second species. As a consequence of this, an additional safety factor of 2 is considered appropriate. Since no sensitive population groups were identified during the course of this evaluation no additional safety factor is required at this time. A safety factor of 200-fold safety factor was therefore applied to the most sensitive NOEL for the determination of an ADI level. Considering the kidney effects of dichlorprop-P as the most sensitive end-point, an ADI limit of 0.03 mg/kg bw/d is recommended, based on a NOEL of 6 mg/kg bw/d in an 18-month dietary study in male mice, using a 200-fold safety factor.

ARfD

The 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 in 1 meal or during 1 day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.
An acute reference dose (ARfD) was established since dichlorprop-P was considered likely to present an acute hazard to humans. Adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. The following criteria were used for the determination of an ARfD (Solecki *et al*., 2005):

a) Significant treatment-related findings in the acute, short-term, 2-generation reproduction or developmental toxicity studies or in the acute or subchronic neurotoxicity studies to indicate a concern for acute dietary risk at doses up to 500 mg/kg bw/d.
b) Treatment-related mortalities observed at doses up to 1000 mg/kg bw in single dose oral studies.

A summary of the relevant studies appears below:

All rats in the 635 and 800 mg/kg bw dose groups prior to scheduled sacrifice in the single dose oral study of Cummins (1990a). Clinical signs prior to unscheduled death comprised lethargy, unconsciousness, decreased motor activity, prone posture, ataxia, muscle flaccidity, and tremor, bradypnoea, hyperpnoea, pigmented orbital secretion and hunched posture. There were no treatment-related findings observed at necropsy. In the pre-GLP study of Hildebrand & Kirsch (1983a), there was a single mortality at a dose of 825 mg/kg bw in rats. Macroscopic findings at necropsy revealed extensive loam coloured lobular periphery in the liver, but was no further characterisation of this effect was made.
Significant treatment-related findings were observed in a 2-generation reproduction study for dichlorprop racemate and in 2 developmental toxicity studies for the dichlorprop-P. In the racemic dichlorprop reproduction study, a dose level of 2000 ppm (~226 mg/kg bw/d during the study) caused significant toxicity to the offspring but only minor effects on the parental animals. In addition to an

early effect of high pup mortality in both generations at the high dose of 2000 ppm, surviving offspring in all litters demonstrated growth retardation and developmental delay.
In an acute neurotoxicity study (Mellert, 1995b), mortalities were observed at dose levels of ≥400 mg/kg bw (10% at 400 mg/kg bw/d and 80% at 500 mg/kg bw/d). Clinical signs were observed at near lethal doses ≥400 mg/kg bw. There was no evidence of specific neurological effects.
Because effects in developmental effects can occur after a single dose developmental study data was also considered. Teratogenic effects were associated with an increased incidence of skeletal variations in rat and rabbit developmental studies (Hellwig, 1993a; Hellwig 1993b). The effects were only observed in the presence of maternotoxicity (decreased food consumption and decreased body weight gain) and at higher doses only. The LOEL for skeletal variations was 80 mg/kg bw/d in rats (rudimentary cervical ribs) and 100 mg/kg bw/d in rabbits (accessory 13^{th} ribs), respectively. The lowest NOEL was 20 mg/kg bw/d in rats. The developmental effects observed (skeletal variations and growth retardation) were considered to represent developmental toxicity and could not be discounted as being secondary to maternal toxicity.
Considered together, the most sensitive NOEL of 20 mg/kg bw/d for developmental toxicity was considered the most appropriate and used in the derivation of an ARfD. A 100-fold safety factor, consisting of factors of 10 for intra and interspecies variation, was considered appropriate. A safety factor of 100 was applied to this NOEL for the determination of an ARfD level. An ARfD of 0.20 mg/kg bw for dichlorprop-P was established.

Selection of a NOEL for OHS Risk Assessment

Since occupational exposure to pesticides is predominantly via the skin the most appropriate NOELs for an OHS repeat-dose risk assessment are derived from repeat-dose dermal toxicity studies. If the dermal toxicity study indicates that the NOEL is 1000 mg/kg bw/d or greater and there are no reproductive or neurotoxicity toxicity concerns the OCS does not require a quantitative risk assessment to be undertaken.

The most appropriate study for risk assessment purposes was considered to be the 4-week dermal toxicity in rabbits, in which a NOEL value was determined as 1000 mg/kg bw/d, based on the absence of systemic toxicity at the highest dose tested (Allan *et al*., 1993). The OCS concluded that an OHS risk assessment for short-term and chronic dermal and inhalation exposures to dichlorprop-P was not required because no adverse systemic effects were observed at the highest dose tested of 1000 mg/kg/d in the 21-day rabbit dermal exposure study (Allan *et al*., 1993) and there were no reproductive or neurotoxicity concerns. In the same study, local skin irritancy effects were however apparent at all doses tested ≥ 10 mg/kg bw/d.

In performing an OHS risk assessment for dichlorprop-P, personal and protective equipment recommendations will thus only need to be considered for local irritancy risks (e.g. eye irritation, skin irritation).

Poisons Schedule considerations

- Nufarm Australia Limited is seeking registration of the R-(+) stereoisomer of dichlorprop (called dichlorprop-P), a phenoxy herbicide which is to be used in the form of dichlorprop-P 2-ethylhexyl ester in an EC formulation. The product is to be used to improve the size of citrus fruits. The

product is intended only for agricultural/professional use and the most likely route of public exposure would be via the diet. Bystander exposure from spray drift and contamination of farm drinking water supplies are also possible.

- Dichlorprop-P has low acute oral (LD_{50} of 567 mg/kg bw in rats), dermal (LD_{50} >2000 mg/kg bw in rats) and inhalation toxicity (LC_{50} >2700 mg/m^3, 4-h nose only exposure) in rats. It was a not an irritant to the skin and a severe irritant to the eyes of rabbits, but not a skin sensitiser in guinea pigs.

- The critical effects in repeat-dose studies were observed in the kidneys. Mice and dogs appeared to be the most sensitive species to the toxicological effects of dichlorprop-P, with an increased incidence of chronic nephropathy observed at doses ≥59 mg/kg bw/d in the diet for 18 months. Effects in shorter term studies included liver effects (≥144 mg/kg bw/d), altered lipid metabolism (≥17 mg/kg bw/d) and anaemia (≥144 mg/kg bw/d).

- A lifetime study in mice with dichlorprop-P showed no evidence of carcinogenicity. A battery of 3 *in vitro* and 2 *in vivo* genotoxicity studies for dichlorprop-P consisting of all the required end-points including point mutation, chromosomal damage, and DNA damage and repair, did not reveal any genotoxic and/or carcinogenic potential. Although a second carcinogenicity study in another rodent species was not available, the results of the mouse study are comparable to 2 lifetime studies in mice and rats with dichlorprop racemate (a 50:50 ratio of R:S isomers), which failed to identify an increased tumour incidence.

- Phenoxy herbicides have been under close scrutiny because of concerns about their carcinogenicity potential, but the overall epidemiological evidence to date is not considered to be conclusive. A recent meta-analysis study which examined cancer mortality in workers from 36 cohorts in 12 countries over a 50 year period indicated that exposure to phenoxy herbicides contaminated with dioxins may be associated with a small increase in overall cancer risk and in risk for specific cancers (soft tissue sarcoma, non-Hodgkin's lymphoma and lung cancer). However, the current production methods for dichlorprop-P are dioxin-free.

- There was no evidence of neurotoxicity in rats either dosed acutely by gavage or by repeated dietary administration over 3-months duration.

- In a 2-generation reproduction study for dichlorprop racemate, significant toxicity to the offspring was noted but only in the presence of parental toxicity at a dose of 226 mg/kg bw/d. There was an early effect of high pup mortality in both generations and surviving offspring in all litters demonstrated growth retardation and effects indicative of developmental delay. The NOEL for parental toxicity was 8.3 mg/kg bw/d. The NOEL for foetal toxicity was 42 mg/kg bw/d. Under the conditions of a preliminary single generation study, dichlorprop-P was not a reproductive toxicant.

- Developmental toxicity effects as reflected by an increased incidence of skeletal variations were observed in rat and rabbit developmental studies. The effects were only observed in the presence of maternal toxicity and at higher doses only. The LOEL for maternal toxicity (including increased

mortality and decreased food consumption, decreased body weight) and foetal skeletal variations was 80 mg/kg bw/d in rats (rudimentary cervical ribs) and 100 mg/kg bw/d in rabbits (accessory 13th ribs), respectively. Signs of growth retardation were also evident at the highest dose (160 mg/kg bw/d) in rat foetuses (decreased mean foetal weight and an increased incidence of unossified sternebrae). The NOELs for maternal and developmental toxicity were the same: 20 mg/kg bw/d (rats) and 50 mg/kg bw/d (rabbits).

- The NDPSC previously included dichlorprop racemate in Schedule 6 of the SUSDP based on the worst acute oral toxicity observed in rats (LD_{50} 344 mg/kg bw) and severe eye irritation in rabbits (the SUSDP entry 2,4 DICHLORPROP refers to dichlorprop racemate).

- Dichlorprop-P was found to share a similar toxicological profile to that of dichlorprop racemate when acute, short-term and subchronic studies were compared. At its 48th meeting, on 10-12 October 2006, the NDPSC agreed that given the potential for severe eye irritancy, 2,4 Dichlorprop (includes the R and S enantiomers) be included in Schedule 6 of the SUSDP. No cut-off to a lower schedule was recommended for the product due to its severe eye irritancy potential. Other excipients present are likely to have contributed towards the product's acute toxicological profile.

- The existing entry in the SUSDP for "2,4 DICHLORPROP" will be amended to read as follows: "2,4 DICHLORPROP (includes the R and S enantiomers)."

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RESIDUES ASSESSMENT

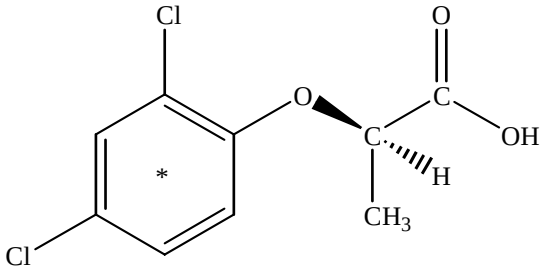
The following sections relate to the metabolism and residue aspects of dichlorprop-P.

Metabolism

Plant metabolism data was not available for dichlorprop-P. In lieu of this, JMPR data for 2,4-D isopropyl ester, which is chemically similar to dichlorprop-P esters and hence a good model, administered to lemons post-harvest was considered.

Post-harvest lemons were treated with sufficient quantities of an aqueous emulsion of ^{14}C-labelled 2,4-D isopropyl to give an average initial residue level of 2.4 mg/kg 2,4-D. The fruit was stored under refrigeration and was sampled regularly for up to 24 weeks post treatment. Within 2 days of treatment, 95% of the residue was found on the peel, with peel residues remaining at 93-97% of the whole fruit total radioactive residue (TRR) throughout the rest of the trial. Correspondingly, juice and pulp TRRs did not exceed 2.5% or 3.8% respectively of the whole fruit TRR. 68% of the peel TRR was identified as free or bound 2,4-D acid, with minor metabolites at levels of up to 1% of TRR being identified. These included 2,4-D esters, hydroxylated 2,4-D and 2,4-dichlorophenol. 83% and 50% respectively of the TRRs in the pulp and juice were identified as free or conjugated 2,4-D acid.

The metabolism of dichlorprop-P was investigated in lactating goats and rats using ^{14}C phenyl labelled dichlorprop-P, as shown in the following diagram.



Lactating goats were dosed for 7 days with ^{14}C phenyl labelled dichlorprop-P at 0.159 or 1.428 mg/kg bw/day, equivalent to 5 or 50 ppm in the diet. The feed consumption was ~1.6-2 kg/day. The majority of the administered dose (~93%) was recovered from excreta and cage wash. Residues in the milk samples (AM and PM milkings) during the study period ranged from 0.003 to 0.007 mg/L equivalents.

The highest concentration of radioactive residues in tissues was found in the kidneys, at 0.488 mg/kg equivalents. The concentration of TRR in other tissues were (mg/kg equivalents): liver (0.047); muscle (0.008); and fat (0.009-0.011).

Parent dichlorprop-P was the major component identified in liver and kidney. It comprised 54% and 89% of the TRR in liver, and 86% of the TRR in kidney samples. Minor, unidentified metabolites were found in kidney (1.0% and 2.1%) of the TRR and liver (7.9% of the TRR). The results of the goat study indicate that dichlorprop-P is readily absorbed and eliminated from the goat.

Rats received ^{14}C dichlorprop-P in both the acid form and as the 2-ethylhexyl ester, in both single-dose and repeat-dose studies. The ester form was rapidly and essentially completely hydrolysed to the acid form, with the acid form being mostly rapidly excreted unchanged in the urine (~85%) and faeces (~4-10%). Due to its rapid elimination, dichlorprop-P appears to have little potential for accumulation upon repeated administration. For further details see the toxicology section of this document.

Poultry metabolism studies were not available for dichlorprop-P. In lieu of metabolism data for poultry, JMPR data from studies in laying hens dosed with the chemically similar compound 2,4-D was considered.

Three groups of five laying hens were dosed orally for 7 days with ^{14}C phenyl-labelled 2,4-D at approximately 1.4 mg/kg bw/day, equivalent to 18 ppm in the diet.

The majority of the administered dose was excreted (89-86%). Only low levels were detected in muscle and eggs (less than the LOQ of 0.02 mg/kg for the animal commodities analytical method). The highest tissue residue, 0.8 mg/kg, was found in the kidney. Gizzard residues were up to 0.142 mg/kg, while other offal residues were all below 0.05 mg/kg. Levels of radioactivity in tissue and egg samples were below 0.l% of the administered dose in all cases.

Analytical methods

Determination of dichlorprop-P residues in plant tissues

Several GC/MS methods were presented for analysis of dichlorprop-P residues in citrus fruits. These involved extraction of fruit samples with a polar solvent such as acidified aqueous methanol or sodium hydroxide solution. Various cleanup steps were incorporated such as extraction into methyl *tert*-butyl ether and solid phase extraction, ion exchange resin, and partitioning with organic solvents such as toluene or dichloromethane. Dichlorprop-P acid was derivatised to the methyl ester before analysis by GC/MS in all cases.

Each method was validated with LOQs of between 0.01-0.05 mg/kg. Recoveries were conducted with fortification at concentrations of 0.01 to 0.5 mg/kg and ranged from 84% to 112%.

Determination of dichlorprop-P residues in animal tissues

Meat, liver, kidney and egg samples were analysed using a reverse phase isocratic HPLC method with UV detection. Milk and fat samples were analysed using a slightly modified method incorporating gradient elution. Quantification was achieved using calibration plots generated by the external standard method.

Samples were extracted by maceration in trifluoroacetic acid in acetonitrile, the extracts were filtered, and combined, before evaporation and re-dissolution. All sample extracts were cleaned up using a C18 cartridge, and the eluates evaporated. Egg, milk and fat extracts were dissolved up in a known volume of trifluoroacetic acid/methanol ready for analysis. Beef, liver, kidney and chicken meat extracts were further cleaned up using a diol cartridge, then dissolved in trifluoroacetic acid/methanol. The method was validated (see below).

Tissue	Limit of quantitation (mg/kg)	Recovery (n = 5)
Milk	0.01	76-96%
Cattle meat	0.02	76-99%
Cattle fat	0.02	99-127%
Cattle liver	0.05	69-74%
Cattle kidney	0.05	80-97%
Eggs	0.02	84-92%
Poultry meat	0.02	77-90%

A couple of recoveries are slightly outside the normally accepted range (70-110%). However, these recoveries were for cattle fat, and given that dichlorprop does not partition preferentially into fat, this is not a concern as fat will not be analysed separately from meat or offal. Overall, the method appears to be suitable for the proposed purpose and is acceptable.

Residue definition

Residues of dichlorprop-P are likely to be detected in treated citrus fruit. Dichlorprop-P is applied as the 2-ethylhexyl ester, however this is rapidly metabolised, with the majority of the residue being found as dichlorprop-P acid. Available data shows that quantifiable residues of dichlorprop-P are unlikely to be found in the tissues, milk or eggs of stock given feed commodities derived from treated citrus fruit. Analytical methods are available for the determination of dichlorprop-P in plant and animal commodities with LOQs of 0.01-0.05 mg/kg. These methods hydrolyse any remaining esters of dichlorprop-P to the acid form, prior to analysis. Therefore, the following residue definition is recommended for dichlorprop-P for the purposes of dietary exposure assessment and for compliance and monitoring:

Compound	Residue
Dichlorprop-P	Sum of dichlorprop acid, its esters and conjugates, hydrolysed to dichlorprop acid, and expressed as dichlorprop acid

Storage stability

In the residue trials submitted, all samples were maintained under freezer conditions, (i.e. –18 °C) prior to analysis and tested within 4 months of collection. Some residues storage stability results were available from the trials conducted in Spain, where the same sample was extracted on several different dates after varying storage times (up to four months between extraction dates). The protocol required re-analysis if significant change (>20%) from the original result was noted. No such changes were reporting, indicating that residue samples are stable for the actual storage periods and conditions used.

Residue trials

The proposed use of *Nufarm Corasil Plant Growth Regulator* in Australia is application to oranges and mandarins during the period of physiological fruit drop, corresponding to 12-30 mm diameter fruit in oranges and 8-20 mm in mandarins (BBCH 73-74) at rates of 5 g a.i./100 L (oranges) or 2.5-5 g a.i./100 L (mandarins) and a withholding period of “Not Required When Used As Directed”.

Citrus fruit

Australian trials were conducted on oranges, mandarins and tangelos, with a single application of dichlorprop-P at rates ranging from 3.75-7.5 g a.i./100 L (0.75-1.5X rate) at crop stage BBCH 73 to 74 (period of physiological fruit drop) giving residues at harvest (169-204 days after treatment) which ranged from 0.01 to 0.11 mg/kg (median residue of 0.048 mg/kg). Trials conducted with a single application at 10 g a.i./100 L (2X rate) at the same stage gave residues at harvest (142-207 days after treatment) ranging from 0.02 to 0.22 mg/kg (median result of 0.066 mg/kg).

The following MRL is recommended for citrus fruit in conjunction with the proposed WHP of "NOT REQUIRED WHEN USED AS DIRECTED".

Table 1

Compound	Food		MRL (mg/kg)
Dichlorprop-P	FC 0001	Citrus fruits	0.2

Animal feeds

Dried citrus pulp

Dried citrus pulp can comprise up to 20% of the diet of dairy and beef cattle (Appendix IX, FAO Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed, second edition, 2002, Food and Agriculture Organisation of the United Nations). The APVMA Stockfeed Guideline Document 1 indicates that fruit by-products can form up to 20% of the diets of cattle, sheep, pigs and poultry.

Given that residues of dichlorprop-P mainly concentrate in the peel, and some of the flesh (pulp) of the fruit will be lost to the juice, a good safe estimate of the processing factor for the transformation from whole fruit to wet citrus pulp is the concentration factor from whole fruit to peel. This information is available from the Spanish residues trials and the Australian processing study. Concentration factors from whole fruit to peel range from 1.08 to 3.57, with a mean value of 2.35. Wet citrus pulp has a mean dry matter content of 19.7%. The maximum concentration factor for drying citrus pulp is therefore 5.08, giving a range of overall processing factors from 5.49 to 18.1, with a mean value of 11.9.

Multiplying the maximum processing factor by the highest residue (HR), 0.11 mg/kg would give a residue level of 1.99 mg/kg. Therefore, 2 mg/kg is a suitable stockfeed MRL for dichlorprop in dried citrus pulp. The following entry is recommended for inclusion in Table 4 of the MRL Standard:

Table 4

Compound	Animal feed commodity	MRL (mg/kg)
Dichlorprop-P	AB 0001 Citrus pulp, dry	2

Crop rotation

Given that citrus trees can be productive for in excess of 30 years, they are regarded as a permanent crop, not a rotational crop. Therefore, rotational crop metabolism and residues studies are not required.

Processing studies

Processing data was supplied as part of residues trials conducted in Australia and Spain. These showed that residues of dichlorprop-P preferentially concentrate in the peel, with processing factors for whole citrus fruit to citrus peel ranging from 1.08 to 3.57, with a mean value of 2.35. Correspondingly, processing factors for whole fruit to peel range from 0.07 to 0.8, with a mean value of 0.44. Little residue is found in the juice, with processing factors of 0.08 and 0.33 (mean = 0.21) for the transformation from whole fruit to juice.

Animal commodity MRLs

Animal feeding studies have not been conducted on dichlorprop-P. The metabolism studies show that dichlorprop-P is rapidly and extensively metabolised in goats. JMPR metabolism data for 2,4-D (a phenoxycarboxylic acid herbicide with a very similar chemical structure and mode of action to dichlorprop-P) in laying hens showed similar results. Residues in animal tissues, milk and eggs are likely to be below their respective LOQs following exposure to treated crops and crop portions. Based upon these data and the residues data and processing information for citrus fruits, the following animal commodity MRLs are recommended:

Edible offal (mammalian)	*0.05 mg/kg
Eggs	*0.02 mg/kg
Meat (mammalian)	*0.02 mg/kg
Milks	*0.01 mg/kg
Poultry meat	*0.02 mg/kg
Poultry, edible offal of	*0.05 mg/kg

Estimated dietary intake

The chronic dietary intake risk for dichlorprop-P has been assessed. The ADI for dichlorprop-P is 0.03 mg/kg bw/day, based upon a NOEL of 6 mg/kg bw/day and a 200 fold safety factor. The NEDI of dichlorprop-P is equivalent to <1% of the ADI. The acute reference dose (ARfD) for dichlorprop-P is 0.2 mg/kg bw, based on a NOEL of 20 mg/kg bw and a 100 fold safety factor. The highest NESTI for dichlorprop-P was calculated at 5.9% (for oranges in 2-6 year olds). It is concluded that the acute and chronic dietary exposure to dichlorprop-P is low and the risk from residues in food is acceptable when *Nufarm Corasil Plant Growth Regulator* is used according to label directions.

Bioaccumulation potential

The octanol-water partition coefficient (log K_{OW}) of dichlorprop-P acid is 1.91 (pH 4), -0.67 (pH 7) and –0.83 (pH 9). Dichlorprop-P-2-ethylhexyl is significantly more lipophilic than the acid form, with

an estimated log K_{OW} of 6.69. However, the animal metabolism studies have shown that the ester is readily and essentially completely hydrolysed to the acid form, so any ester ingested by an animal will be quickly converted to dichlorprop-P acid, which has a very low potential for bioaccumulation based on the values of the octanol-water partition coefficient. Further evidence of the low fat solubility/bioaccumulation potential is given by the low solubility of the acid in aliphatic hydrocarbons (e.g. 0.898 g/L in hexane).

Recommendations

The following amendments to the *MRL Standard* are recommended in relation to the proposed use of *Nufarm Corasil Plant Growth Regulator*:

Table 1

Compound	Food		MRL (mg/kg)
ADD:			
Dichlorprop-P	FC 0001	Citrus fruits	0.2
	MO 0105	Edible offal (mammalian)	*0.05
	PE 0112	Eggs	*0.02
	MM 0095	Meat (mammalian)	*0.02
	ML 0106	Milks	*0.01
	PO 0111	Poultry, edible offal of	*0.05
	PM 0110	Poultry meat	*0.02
DELETE:			
Dichlorprop	FC 0001	Citrus fruits	T0.1

*MRL set at the limit of quantitation.

Table 3

Compound	Residue
ADD:	
Dichlorprop-P	Sum of dichlorprop acid, its esters and conjugates, hydrolysed to dichlorprop acid, and expressed as dichlorprop acid

Table 4

Compound	Animal feed commodity	MRL (mg/kg)
ADD:		
Dichlorprop-P	AB 0001 Citrus pulp, dry	2

The following withholding periods are required in conjunction with the above MRLs:

HARVEST WITHHOLDING PERIOD

ORANGES AND MANDARINS: Not required when used as directed.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Overseas registration status and MRLs

Codex MRLs have not been determined for dichlorprop-P. The applicant has indicated that dichlorprop-P (as the 2-ethylhexyl ester) is registered in France and Spain as a citrus fruit plant growth regulator, while racemic dichlorprop (as the butoxyethyl ester) is registered as a citrus fruit plant growth regulator in Uruguay, Jordan, South Africa and Cyprus. The following relevant overseas MRLs are established for dichlorprop-P:

Country	Commodity Group	MRL Value (mg/kg)
EU	Oranges	0.05
EU	Mandarins	0.05

Potential risk to Australian export trade

Detectable residues of dichlorprop-P may occur in citrus fruit, and therefore, may prejudice trade in citrus fruit. A general trade statement has been recommended for the label:

'Treated citrus fruit destined for export may require extra time being allowed between application and harvest, to be accepted in some export markets. Before you use this product, you are advised to contact Nufarm Australia Ltd and/or your industry body about any potential trade issues and their management.'

Dried citrus pulp, derived from oranges or mandarins treated with dichlorprop-P, may be used as a livestock feed. The feeding of this commodity to livestock is not expected to result in detectable residues in animal commodities, and thus prejudice trade in animal commodities.

The overall risk to export trade in animal commodities from the registration of *Nufarm Corasil Plant Growth Regulator* is considered to be negligible. There is a potential risk to export trade in citrus fruit, which should be mitigated by the label statement proposed above.

The APVMA welcomes comment with regard to whether the proposed use of Dichlorprop-P on oranges and mandarins, or livestock fed on commodities treated with Dichlorprop-P poses an undue prejudice to Australia's trade in these commodities.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Introduction

Nufarm Australia Limited is seeking approval of the synthetic phenoxy herbicide dichlorprop-P and registration of the product Nufarm Corasil Plant Growth Regulator, containing the single R-(+) stereoisomer of dichlorprop (termed dichlorprop-P). Dichlorprop-P is present in the product as the 2-ethylhexylester form at 40.5 g/L (equivalent to 25 g/L of the acid form). The product is proposed for use once per annum in sub-tropical and temperate regions of Australia to improve the size of citrus fruits. The product is intended only for professional agricultural use.

Assessment of Occupational Health and Safety

There were 32 studies submitted in the dichlorprop-P database, two of which had been previously evaluated by the OCS. The majority of the studies submitted complied with GLP, and were undertaken according to the contemporary test guidelines. Six of the acute studies were pre-GLP. Contemporary GLP compliant study counterparts were available for the same study types. The age of the database for dichlorprop-P spanned from the early to mid 1980s through to the mid to late 1990s, with the exception of a preliminary dose-range finding reproduction study which was conducted in 2001. Four studies (1979-1992) for dichlorprop racemate (R:S isomers at ratio of 50:50) were also submitted in support of dichlorprop-P registration and have all been previously evaluated by the OCS. Those studies included a full multigeneration reproduction study for dichlorprop racemate. Data deficiencies for dichlorprop-P included the absence of a full multigeneration reproduction study and a second carcinogenicity study in a different species. The R-isomer and the racemate were found to display similar toxicological profiles in acute, short-term and sub-chronic studies when comparing similar routes of administration, administered doses, study durations and animal strains. The data provided in the 32 toxicology studies for dichlorprop-P formed the basis for the establishing public health standards.

After an oral dose, dichlorprop-P was rapidly and extensively absorbed in rats. There was no evidence of accumulation in tissues and very limited metabolism of the parent compound occurred. The majority of dichlorprop-P was excreted in the urine unchanged within 24-48 h of administration. Metabolism and toxicokinetic data were similar for the dichlorprop-P acid and 2-ethylhexylester forms. After an oral dose, the ester form was hydrolysed rapidly *in vivo*.

Dichlorprop-P has low acute oral (LD_{50} of 567 mg/kg bw in rats), dermal (LD_{50} >2000 mg/kg bw in rats) and inhalation toxicity (LC_{50} >2700 mg/m^3) in rats. It was a not a skin irritant, but was a severe eye irritant in rabbits. It was not a skin sensitiser in guinea pigs. The main target organ for the effects of dichlorprop-P in repeat-dose studies was the kidneys. Mice and dogs appeared to be the most sensitive species to the toxicological effects of dichlorprop-P.

There was no evidence of carcinogenicity for dichlorprop-P in a lifetime study of mice. A battery of three *in vitro* and two *in vivo* genotoxicity studies for dichlorprop-P did not reveal any genotoxic potential. Although a second carcinogenicity study in another rodent species was not available, the results of the dichlorprop-P mouse study were similar to two dichlorprop racemate lifetime studies in mice and rats, which failed to identify an increased tumour incidence.

There was no evidence of delayed neurotoxicity in rats. Dichlorprop-P was not considered to be a reproductive toxicant or developmental toxicant.

Conclusion

Based on the findings of toxicological studies evaluated, the product was considered to have low acute oral, dermal and inhalation toxicity. It is likely to be a moderate skin irritant, a severe eye irritant, but not a skin sensitiser. Based on the toxicological profile and the intended use pattern of the product, the appropriate public health standards, Safety Directions and personal protective equipment (PPE) are recommended within the report. Furthermore, the proposed use of "Nufarm Corasil Plant Growth Regulator" will not be an undue health hazard to humans according to the criteria stipulated in Section 14 (5)(e) criteria of the Ag/Vet Code Act of 1994.

Additional information is available in the MSDS provided for Nufarm Corasil Plant Growth Regulator.

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL EXPOSURE

Environmental exposure to dichlorprop-P 2-ethylhexyl ester is expected to be low as Corasil Plant Growth Regulator will be used at low rates as a citrus sizing agent, with a single application in late spring or early summer, rather than the much higher rates needed for weed control.

The applicant has provided a full data package for dichlorprop-P and some bridging studies for the 2-ethylhexyl ester. The phenoxy herbicides are known to have very low solubilities (ppb range) in their ester forms, which complicates the conduct of certain studies, such as aqueous hydrolysis. As was determined in the APVMA review of 2,4-D, available data tend to demonstrate that phenoxy esters are short-lived compounds (<1 week) in normal agricultural soil and natural water conditions. Under these conditions, the environmental exposure from dichlorprop-P 2-ethylhexyl ester is expected to be limited in both terrestrial and aquatic environments.

Standard abiotic hydrolysis studies for the ester and its acid metabolite were supplemented by a more realistic but non-standard hydrolysis study for the ester in aqueous soil slurries. The studies indicate that the ester resists hydrolysis in sterile media under neutral to acidic conditions, but hydrolyses rapidly to the acid in the presence of soil.

ENVIRONMENTAL CHEMISTRY AND FATE

No studies were provided on the photolysis of dichlorprop-P 2-ethylhexyl ester. The photolysis of dichlorprop-P was studied in solution and on the surface of soil. The acid was found to photodegrade in aqueous solution and on the surface of soil with half-lives of a few days to a week.

No studies were provided on the metabolism of dichlorprop-P 2-ethylhexyl ester in laboratory soils because of the rapid hydrolysis to the acid, as demonstrated in field studies with the ester. Metabolism of dichlorprop-P in laboratory soils and aquatic systems was studied in the usual way. Dichlorprop-P was found to be nonpersistent in laboratory soils, slightly persistent under aerobic aquatic conditions, and moderately persistent under anaerobic aquatic conditions.

Dichlorprop-P 2-ethylhexyl ester is expected to sorb strongly to soils, but the sorption of the ester is of limited relevance to its environmental fate as it is expected to be rapidly hydrolysed to the acid in the moist soils typical of citrus production areas. Testing therefore used the acid. Standard batch equilibrium and column leaching studies found dichlorprop-P to be highly to very highly mobile in laboratory soils, as outlined below.

No volatility studies were presented. Although dichlorprop-P 2-ethylhexyl ester is likely to have some volatility from foliage, this will be limited by its uptake into the plant, by the low application rate, and by the size of the alkyl group. The primary metabolite, dichlorprop-P, is expected to show low volatility as it is a carboxylic acid with a relatively high molecular weight.

Field dissipation studies with dichlorprop-P 2-ethylhexyl ester used the high rate (6.7 kg/ha acid equivalents) for weed control in rights of way or the turf rate (1.3 kg/ha acid equivalents) rather than

the much lower rate (0.12 kg/ha acid equivalents) proposed for fruit sizing in Australian citrus. The studies were conducted under worst case conditions, including application to bare ground, with supplementary irrigation to ensure that the treated plots received 110% of the average monthly rainfall for the two wettest months in the year.

Dichlorprop-P, as ester and acid, was the main residue detected in soil in these studies. Both forms were nonpersistent (half-lives less than 2 weeks) under field conditions. The two secondary metabolites, 2,4-dichloroanisole and 2,4-dichlorophenol, were only detected in low concentrations. Residues were mostly confined to the surface 15 cm, although the acid form of dichlorprop-P was detected to 120 cm following high rate application to a sandy soil in Washington State, with the leaching attributed to a combination of high soil porosity and substantial irrigation.

Dichlorprop-P 2-ethylhexyl ester is likely to be lipophilic based on its estimated partition coefficient, but is unlikely to bioaccumulate in fish because of the ease of hydrolysis, and the hydrophilicity of its primary metabolite, dichlorprop-P.

As neither dichlorprop-P 2-ethylhexyl ester nor its acid metabolite are persistent in field soils, and the proposed use will require a single application per season as a foliar spray to citrus at a low rate, no accumulation of residues in soils is to be expected.

The studies submitted confirm that dichlorprop-P 2-ethylhexyl ester is a typical phenoxy ester herbicide. Both the ester and its acid metabolite degrade rapidly in agricultural soils and aerobic aquatic systems, with environmental exposure expected to be limited in both terrestrial and aquatic environments.

ENVIRONMENTAL EFFECTS

The toxicity of dichlorprop-P 2-ethylhexyl ester has been studied in birds, aquatic organisms, terrestrial invertebrates and grapevines. The results of this testing, and of supplementary testing with acid and salt forms, indicate that the general toxicity of dichlorprop-P is no more than slight. Moderate toxicity was seen in fish and daphnids exposed to the ester, but the applicant contends that results should not be relied on for risk assessment because they exceed the water solubility of the ester, which degrades rapidly in the water column. Dichlorprop-P is an herbicide and therefore toxic to plants, but will be applied at sublethal rates and is not expected to harm nontarget plants exposed to spray drift, as indicated by testing in grapevines.

Avian toxicity studies were submitted for the 2-ethylhexyl ester and the dimethylamine salt of dichlorprop-P. In acute oral studies, the ester was slightly toxic to bobwhite quail, and the amine salt moderately toxic. Ester and amine salts were practically nontoxic to bobwhite and mallards when administered in the diet.

The applicant has submitted aquatic toxicity studies with the acid and the ester, but contends that results for the ester are unreliable and should not be used for risk assessment, except for the common findings that dichlorprop-P 2-ethylhexyl ester is unlikely to be toxic to aquatic organisms at

concentrations below the solubility limit, and that harmful effects from the ester are most unlikely given its low solubility and instability.

Dichlorprop-P 2-ethylhexyl ester was nontoxic to aquatic organisms at concentrations below its solubility limit (0.17 mg/L) with effects only seen when solvents or emulsifiers were used at levels above guideline recommendations to achieve test concentrations in excess of that limit. The most sensitive organism tested was probably *Daphnia magna*, with a conservative lower limit of 1.5 mg/L (mean measured concentration) for the acute EC50 determined under flow-through conditions. Although this result should be treated with caution as full dissolution was not achieved, it can be used as the basis for a conservative, screening level risk assessment. Acid and amine salt forms were practically nontoxic to fish and daphnids, as is usual for these water-soluble forms. The potassium salt was slightly toxic to duckweed, and the acid slightly toxic to green algae and blue green algae.

Testing has been conducted with the ester in honey bees, predatory mites and parasistic wasps. Supplementary testing has been conducted with the acid and amine salt. No significant toxic effects were seen.

Harmful effects on nontarget plants from the proposed use of Corasil are not expected because of its limited use pattern as a citrus sizing agent rather than an herbicide. Testing in grapevines supports this prediction.

ENVIRONMENTAL RISK ASSESSMENT

Testing of the ester in honey bees, predatory mites and parasitic wasps indicates that invertebrates in citrus are unlikely to be harmed by dichlorprop-P 2-ethylhexyl ester at the rates proposed for fruit sizing in citrus.

Application of the ester at 202.5 g/ha acid equivalents would leave very low residues on citrus foliage, estimated to be about 23 mg/kg. These residues are very unlikely to be harmful to birds as they are two orders of magnitude below dietary no effect concentrations.

Residues in soil would similarly be very low, and very unlikely to harm resident organisms. Data indicate that earthworms and soil microbial function are unlikely to be sensitive, while residues of the ester and its acid metabolite are nonpersistent in soils.

Although dichlorprop-P 2-ethylhexyl ester is likely to have some volatility from foliage, the risk to nontarget plants is low as Corasil will be applied at sublethal rates to citrus foliage, with very low off-target contamination expected. Grapevines, which are sensitive to such synthetic auxins, were unaffected when treated at 4% of the maximum rate of 5 L/ha Corasil. Drift would fall below this threshold within 10 m.

Application of the ester at 202.5 g/ha direct to water would leave residues of 135 µg/L, which would be unlikely to harm fish, aquatic invertebrates or aquatic flora based on the available test results for these organisms. For example, the predicted concentration is just 9% of the lower limit of 1.5 mg/L (mean measured concentration of the ester) for the EC50 in *Daphnia magna*. Note that such direct

overspray of water would be very unlikely to arise when Corasil is applied to citrus foliage, and that any aquatic contamination that may occur would be at very low levels (low ppb range) and transient. Even with high volume application (10000 L/ha) to large citrus trees, as may occur with oscillating booms, the concentration from overspray would be less than 40% of the lower limit for the EC50 in *Daphnia magna*, reducing to less than 4% if spray drift of 10% is assumed. Drift would fall below this threshold within 10 m.

CONCLUSIONS

Corasil will be applied to citrus foliage at a low rate for fruit sizing. Most of the applied active is expected to be intercepted by the plant. Any residues that enter soil or water will be at low levels, and unlikely to persist.

Dichlorprop-P 2-ethylhexyl ester has low toxicity to nontarget terrestrial animals and is nontoxic to aquatic organisms at concentrations below its solubility limit, but is toxic to plants because it is an herbicide. Corasil will be applied at low rates for fruit sizing rather than vegetation control, and is not expected to harm nontarget plants when used in this way.

The Department of the Environment and Water Resources recommends that the APVMA be satisfied that use of Corasil Plant Growth Regulator as proposed and according to good agricultural practice would not be likely to have an unintended effect that is harmful to animals, plants or things, or to the environment.

EFFICACY AND SAFETY ASSESSMENT

PURPOSE OF THE APPLICATION AND JUSTIFICATION OF USE

The proposed product is to increase the size of citrus fruits at harvest by treating early in fruit development without having adverse effects on other fruit characteristics, such as yield or juice levels. The product proposes to provide a more effective and economic alternative to hand-thinning. There is evidence to suggest that treatment not only results in larger fruit but that those fruit could be off better quality, with higher juice levels and thinner skins. The reviewer accepted that with relatively minor amendment to the claim for use in 'citrus fruits' and the calibration of spray rates, the proposed label for Corasil Plant Growth regulator is justified.

DATA ASSESSED

The applicant submitted some 20 trials to support efficacy of the proposed product. Of these, 8 were overseas data and except for one trial, all yielded statistical data. The remaining 12 trials were conducted in Australia. All of these studies yielded statistically significant data. The 14 statistical trials examined existing knowledge of 2,4-DP (Corasil) and examined aspects of dosage and timing of sprays and resultant effects on fruit size and total yield vital to this application.

The overseas trials were conducted in Spain, South Africa and France and used acceptable methodology and were well designed and statistically analysed. In these trials historical data was reviewed and formulation timings and dosage examined. The statistically-sound trials conducted in Australia served to expand upon and supplement the overseas data. The data demonstrated the positive effect of Corasil in increasing fruit size at harvest, without consistent thinning of fruit or other undesirable effects. Most of the evidence, presented in the trials that were considered to be statistically valid, showed that Corasil and related analogues could increase fruit size. The evidence presented applied to Oranges and Mandarins but not other citrus fruit.

PROPOSED USE PATTERN

The overseas data established that rates of 50 to 200mg/100L Corasil was effective in increasing fruit size in Oranges and Mandarins. This work was confirmed by most of the Australian work. Although a higher level of 300mg/100L was included in one trial, it was no more effective. The rates are consistent with those on the label.

The timing of the spray was also established in the early work overseas as being at physiological, natural fruit drop. This was confirmed for Oranges and Mandarins in Australia. This data was properly addressed in further trials and the range of fruitlet sizes at application complies with the label.

A trial specifically shows how levels of effective tree cover can significantly affect performance. Matching spray concentrations, spray application volumes and spray application techniques is an increasing need in determining how to compute dosage in devising a label recommendation. The

modification of the label prompted by this trial data has given an example of how this problem can be approached. Some modern droplet adjusted sprayers spray effectively at very low volumes and the label should accommodate these techniques in addition to the high volume cases, which has been done.

Fruit thinning

There was no consistent evidence that Corasil achieved better fruit size by thinning and crop reduction. The data shows that Corasil increases size and fruit juice by increasing cell activity at a very early stage in fruit growth rather than by causing more fruit abscission.

As the likely time of effective application would be at the period of natural fruit drop, comparison of untreated controls with treated trees the true thinning effect is clear. This situation is adequately proven and explained in the data provided.

ASSESSMENT OF INFORMATION

Corasil is proposed for use to increase the size of Oranges or Mandarins where the market requires larger fruit. No consistent thinning effects have been found and as such Corasil should not be used as a fruit thinner or be expected to produce a thinning effect when used as directed. The mechanism is of the auxin in Corasil increasing the size of locules and vesicles in the fruit, which in turn increase the capacity to accumulate juice and consequently increase the size of the fruit. Fourteen of the trials had significant data and showed that Corasil is effective at increasing fruit size when used at 100 to 200mg/100L on a range of timings at natural fruit shedding.

As stated above the overseas work gave a good background on Corasil's mode of action on Oranges and Mandarins. The timing and concentration data was excellent and it gave the breadth of different climatic conditions. The trials in Australia were also in many locations using various cultivars. In all cases the trials focussed on the methodology of improving fruit size without causing deleterious effects. None of the trials showed any damage to the crop or trees. One trial that focussed on a susceptible non-target crop in grapevines and found no damage to crop or vines.

The overseas trials, while not specifically designed to fit the label formulation, they provided a good basis for understanding the effects of these auxins on fruit size in Oranges and Mandarins. The seven Australian trials, with proper statistical analysis, were well designed and generally focussed on addressing the claims of the label under various conditions and locations.

The trial design was appropriate in the 14 satisfactory trials, previously mentioned, with proper planning and statistics.

The trials focus on 2 aspects of validation. The overseas trials represent the original work that showed that the Corasil could increase the size and juice content of Oranges and Mandarins by increasing cell size. It was also established that this happens without significant reduction in total yield. That work

established the basis of the best auxin to use, the timing and dosage of spray to use for optimum results.

The Australian trails have confirmed the overseas work for Australia and shown that similar results are obtained in a range of conditions in the fruit growing areas and that the label, as proposed for the use of increasing fruit size, is validated. It was also established that, when used as per label, no crop damage would occur to fruit or other parts of the tree. It was also established that no damage would occur to susceptible crops, such as setting grapes when sprayed at label rates of Corasil. Validation is only for Oranges and Mandarins.

CONCLUSIONS

Corasil can increase fruit weight in Oranges and Mandarins when used as described on the label. Besides fruit weight increases in juice content can accompany weight increases.

Corasil should not be relied on as a fruit thinner. If it is applied at a time when natural fruit drop is occurring any effect is confounded. Most data shows that the increase in fruit weight is not associated with a corresponding reduction in crop load. Corasil is safe to use on Oranges and Mandarins and at the proposed rates of use it is not expected to affect other susceptible crops if spray drifts on to those crops such as grapevines.

Conclusion

Sufficient statistically analysed data from suitably designed and scientifically conducted trials has been presented to substantiate the claims for use shown on the draft label. The proposed product should be suitable for the proposed purposes when used according to label instructions and Good Agricultural Practice.

LABELLING REQUIREMENTS

POISON
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

NUFARM

CORASIL®

Plant Growth Regulator

ACTIVE CONSTITUENT: 25 g/L DICHLORPROP-P PRESENT
AS THE 2 ETHYL HEXYL ESTER
SOLVENT: 773 g/L LIQUID HYDROCARBON

A Plant Growth Regulator for the improvement of
the size of Orange and Mandarin fruits.

Contents: 5L, 10L and 20L

Nufarm Australia Limited
ACN 004 377 780
103-105 Pipe Road
Laverton North, Victoria 3026
Tel: (03) 9282 1000
Fax: (03) 9282 1001

Barcode
APVMA Approval No. 59999/*L/0907
Batch No. Date of Manufacture.

DIRECTIONS FOR USE:

Situation	Purpose	Rate per 100L of Water	Critical Comments
Mandarins	Plant growth regulator to increase fruit size	100 ml to 200 ml	Apply to fruit of the following sizes: Mandarins: 8 to 20 mm Oranges: 12 to 30 mm These size ranges approximate the period of physiological fruit drop. Only use the lower rate in mandarins at early timings. Application to small fruit may increase fruit drop. Apply in a spray volume of 2500 to 3000 L/ha for trees of 4 meters height with a MEDIUM to COARSE spray quality, ensuring thorough coverage of the foliage. If spraying at higher volumes (eg. 5000 to 6000 L/ha) then the rate of Corasil should be reduced in direct proportion to the spray volume increase. If spraying at a lower volume, the rate of Corasil should be increased in direct proportion to the spray volume decrease. See **Application** section.
Oranges		200 ml	

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

WITHHOLDING PERIOD
HARVEST: NOT REQUIRED WHEN USED AS DIRECTED.

GENERAL INSTRUCTIONS:
Before opening, carefully read Directions for Use, Pre-cautionary Statements, Safety Directions and First Aid Instructions.
Apply on trees in good health and nutrition, which have not undergone any significant modification in their vegetation.

RESIDUE MANAGEMENT IN EXPORT PRODUCE
Treated citrus fruit destined for export may require extra time being allowed between application and harvest, to be accepted in some export markets. Before you use Corasil you are advised to contact Nufarm Australia Ltd and/or your industry body about any potential trade issues and their management.

MIXING INSTRUCTIONS:
Nufarm Corasil is readily miscible with both hard and soft water. Add the required amount of this product to water in the spray tank and stir thoroughly.
Add Activator Surfactant at the rate of 50 to 125 ml per 100 L of water or Spraymate LI-700 at 100 ml per 100 L water. DO NOT add copper products to the mix if using Spraymate LI-700.

APPLICATION
Corasil should be applied in a spray volume of 2500 to 3000 L/ha for citrus trees of 4 meters height. The spray volume should be adjusted to suit larger or smaller trees but if a different volume is selected for trees of 4 meters height, the rate of Corasil must be changed in direct proportion to the change in spray volume eg. If a volume of 5000 to 6000 L/ha was applied to 4 meter trees the rate of Corasil would be halved. Spray volumes below 2500 to 3000 L/ha would require a rate increase to maintain the same amount of Corasil per hectare.

COMPATIBILITY
DO NOT tank mix other crop protection products or fertilizers with Corasil.

EQUIPMENT MAINTENANCE AND USAGE:
Equipment that has been used for this chemical should not be used for the application of other materials to sensitive plants unless it has been washed out with Nufarm Tank and Equipment Cleaner or a 1% solution of ammonia, followed by several clear water rinses.

PRECAUTION
Re-entry period
DO NOT allow entry into treated area until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each days use.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS:
DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto nearby susceptible plants/crops, cropping lands or pastures.

PROTECTION OF WILDLIFE, FISH, CRUSTACEA AND ENVIRONMENT:
DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

STORAGE AND DISPOSAL:
Store in the closed, original container in a cool, well-ventilated area. DO NOT store for prolonged periods in direct sunlight. Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point.
If not recycling, break, crush, or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should NOT be burnt.

SAFETY DIRECTIONS:
Will damage eyes. Will irritate the skin. Avoid contact with eyes and skin. Avoid inhaling vapour when opening the container and preparing spray. If product in eyes, wash it out immediately with water. If product on skin, immediately wash area with soap and water. Ensure adequate ventilation during use. When opening the container and preparing spray, wear elbow-length PVC gloves, goggles and half face piece respirator. After each day's use, wash gloves, goggles and respirator (if rubber, wash with detergent and warm water). Wash hands after use.

FIRST AID:
If poisoning occurs, contact a Doctor or Poisons Information Centre (Phone Australia 13 11 26). If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

MATERIAL SAFETY DATA SHEET
For further information refer to the Material Safety Data Sheet (MSDS), which can be obtained from your supplier, or from the Nufarm website – www.nufarm.com.au.

CONDITIONS OF SALE:
Nufarm Australia Limited ('Nufarm') shall not be liable for any loss, injury, damage or death whether consequential or otherwise whatsoever or howsoever arising, whether through negligence or otherwise in connection with the sale, supply, use or application of this product. The supply of this product is on the express condition that the purchaser does not rely on Nufarm's skill or judgement in purchasing or using the same, and every person dealing with this product does so at his own risk absolutely. No representative of Nufarm has any authority to add to or alter these conditions.

In case of emergency: Phone 1800 033498
Ask for shift supervisor. Toll free 24 hours.

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APVMA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of Dichlorprop-P in the product *NUFARM CORASIL PLANT GROWTH REGULATOR*, please fill in this form and send it, along with payment of $30 to:

David Hutchison
Pesticides Program
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to: David Hutchison, Pesticides Program at (02) 6210 4766.

Name (Mr, Mrs, Ms, Dr)_____

Position _____

Company/organisation _____

Address _____

Contact phone number (___) _____

I enclose payment by cheque, money order or credit card for $_____

Make cheques payable to 'Australian Pesticides and Veterinary Medicines Authority'.

___ Bankcard ___ Visa ___ Mastercard

Card number _____/_____/_____/_____ Expiry date ...../...../.....

Signature_____ Date _____