Public Release Summary
on

Evaluation of the new active

Indoxacarb (S-Isomer)

in the product

DUPONT STEWARD EC INSECTICIDE

Australian Pesticides and Veterinary Medicines Authority

FEBRUARY 2007

Canberra
Australia

ISSN1443-1335

This document is published by the Australian Pesticides and Veterinary Medicines Authority. In referencing, the APVMA should be cited as both the author and publisher of this document. For further information, please contact:

Laura Leis
Australian Pesticides and Veterinary Medicines Authority
PO Box E 240
KINGSTON ACT 2604

Ph: (02) 6210 4763
Fax: (02) 6210 4776

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 the Environment Water and Resources, and State departments of agriculture 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 publications *Ag Manual: The Requirements Manual for Agricultural Chemicals* and *Ag Requirements Series.*

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.

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

[blank page here]

CONTENTS

[blank page here]

LIST OF ABBREVIATIONS AND ACRONYMS

[This list should be modified to include all the acronyms and abbreviations that actually appear in the publication.]

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% 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
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
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
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
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
NDPSC	National Drugs and Poisons Schedule Committee
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter

PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
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
WHP	Withholding Period

[blank page here]

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *DUPONT STEWARD EC INSECTICIDE,* which contains the new active ingredient, indoxacarb (S- isomer). The product is proposed to be used for the control of *Helicoverpa armigera* (cotton bollworm) and *Helicoverpa punctigera* (native budworm) in adzuki beans, cotton, chickpeas, faba beans, mungbeans and soybeans; *Creontiades dilutus* (green mirid) in cotton; *Creontiades spp.* (mirids) and *Thysanoplusia orichalcea* (soybean looper) in adzuki beans, mungbeans and soybeans.

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 indoxacarb (s- isomer), 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 2nd April 2007. They should be addressed to:

Laura Leis
Pesticides Program
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
KINGSTON ACT 2604

Phone: (02) 6210 4763
Fax: (02) 6210 4776
Email: laura.leis@apvma.gov.au

Applicant
DuPont Australia Pty Ltd

Product Details
It is proposed to register DUPONT STEWARD EC INSECTICIDE, containing indoxacarb (S- isomer) at 150 g/L as an emulsifiable concentrate formulation. DUPONT STEWARD EC INSECTICIDE will be packaged in 10L, 110L, 200L and 1000L HDPE containers.

Currently indoxacarb is approved and used in the registered product DuPont Steward Insecticide. The indoxacarb currently approved contains a mixture of both the S and R isomers (Indoxacarb 75 S:25 R), whereas the proposed indoxacarb to be used in the product DuPont Steward EC Insecticide contains only the S isomer. The S isomer is the active component.

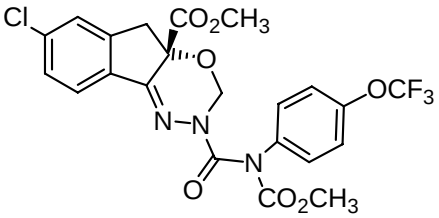
DUPONT STEWARD EC INSECTICIDE is for the control of cotton bollworm, native budworm and green mirid in cotton, chickpeas and faba beans, control of cotton bollworm, native budworm, mirids and soybean looper is adzuki beans, mung beans and soy beans, and cotton bollworm and native budworm in chickpeas and faba beans. Application is via ground or aerial application.

CHEMISTRY AND MANUFACTURE

ACTIVE CONSTITUENT

Indoxacarb is an insecticide, which acts by contact and ingestion. Affected insects cease feeding, with poor co-ordination, paralysis and ultimately death.

The active constituent indoxacarb has the following properties:

IUPAC name:	methyl (*S*)-*N*-[7-chloro-2,3,4a,5-tetrahydro-4a-(methoxycarbonyl)indeno[1,2-*e*][1,3,4]oxadiazin-2-ylcarbonyl]-4'-(trifluoromethoxy)carbanilate
CAS name:	methyl (*S*)-7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]-indeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylate
CAS No.:	173584-44-6
Molecular Formula:	$C_{22}H_{17}ClF_3N_3O_7$
Molecular Weight:	527.8
Structure:	
Appearance:	fine white powder
Relative density:	1.498
Melting point:	88.1 ^oC
Optical rotation: $[\alpha]20_{589}$	37.04 (mean n=5)
Solubility	
Water:	0.20 mg/L
n-octanol:	11.3 g/L
n-hexane:	1.3 g/L
methanol:	110.9 g/L
Dissociation constant:	None observed
n-octanol/water partition coefficient:	Log K_{ow}=4.65
Vapour pressure:	$9.8x10^{-9}$ Pa @ 20^oC $2.5x10^{-8}$ Pa @ 25^oC
Henry's law constant:	k= $6x10^{-5}$ Pa-m^3/mol
Hydrolysis (aqueous)	
pH=5	DT_{50} > 1 year
pH=7	DT_{50} = 22 days
pH=9	DT_{50} = 0.3 days
Photodegradation:	DT_{50} = 3 days (pH=5)
pH @ 1%	5.62
Safety Properties	Non-flammable, not sensitive to thermal, impact or friction stimuli
Oxidising properties:	Non-oxidising

The Chemistry and Residues Program (CRP) of the APVMA has evaluated the chemistry aspects of indoxacarb (manufacturing process, quality control procedures, batch analysis results and analytical methods).

Indoxacarb (S-isomer) is a new active constituent on the basis of the data provided, it is proposed to establish the following active constituent Standard for indoxacarb:

Constituent	**Specification**	**Level**
Indoxacarb	*S*-isomer *R*-isomer	900 g/kg minimum 10 g/kg maximum

Other characteristics of indoxabarb (toxicology, environmental fate etc) are covered in subsequent sections of this Public Release Summary.

FORMULATED PRODUCT

The CRP has assessed the chemistry and manufacturing data submitted for the formulated product.

Distinguishing name:	***DuPont Steward EC Insecticide***
Formulation type:	Emulsifiable Concentrate
Active constituent concentration:	150 g/L

PHYSICAL AND CHEMICAL PROPERTIES OF THE PRODUCT

Appearance:	Light amber liquid
Relative density	0.947 g/mL
pH:	6.6
Volatility	Non-volatile
Explosive properties	Not explosive, thermally stable
Flashpoint	69^{o}C
Storage stability:	Stable for at least two years when stored under normal conditions

SUMMARY OF THE CHEMISTRY EVALUATION OF DUPONT STEWARD EC INSECTICIDE

DUPONT STEWARD EC INSECTICIDE will be formulated in the USA, France and India.

The manufacturing and quality control procedures, including compliance with the release specifications, are acceptable.

The applicant provided the results of real time stability testing conducted using samples stored in HDPE containers (the proposed commercial container). The results indicate that the formulated product is expected to be stable for at least two years when stored under normal conditions in the proposed commercial packaging.

Based on a review of the data provided by the applicant to the APVMA, the APVMA is satisfied that the chemistry and manufacturing details of DUPONT STEWARD EC INSECTICIDE are acceptable.

TOXICOLOGICAL ASSESSMENT

EVALUATION OF TOXICOLOGY

The toxicological database for indoxacarb, 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 (Acceptable Daily Intake - ADI and Acute Reference Dose - ARfD) at which no adverse health effects in humans would be expected.

The current submission of supplementary toxicological data completes a comprehensive database that commenced in 1999 when Du Pont submitted data to support the approval of indoxacarb (75 (S-isomer):25 (R-Isomer). The proposed new product contains indoxacarb (S-isomer).

Chemically the indoxacarb molecule has a single chiral centre and was originally commercially available as a racemic mixture which was denoted with the code DPX-JW062. The indoxacarb racemate contains two enantiomers (S:R), designated DPX-KN128 and DPX-KN127 but only the S-isomer has insecticidal activity. The indoxacarb racemate DPX-JW062 has been used in several toxicological studies. Subsequent refinements in the chemical synthesis process has enabled commercial production of a mixture enriched approximately 3:1 with

the insecticidally active isomer. The database contains a series of "bridging" studies on DPX-MP062 to demonstrate its toxicological equivalence with DPX-JW062.

Considering the similar toxicity profiles of DPX-KN128, DPX-MP062 and DPX-JW062, the OCS considered the toxicology database provided for DPX-KN128 is adequate for the current risk assessment.

Toxicokinetics and Metabolism

Existing studies on Steward 200SC (75S:25R) were considered adequate to explain the toxicokinetics and metabolism for Steward EC.

Acute Studies

Indoxacarb (S-isomer) has low to moderate acute oral toxicity (Rat LD_{50} = 843 mg/kg bw in males and 179 mg/kg bw in females; 10/20 deaths in males and 13/20 deaths in females) and, low acute dermal toxicity (LD_{50} >5000 mg/kg bw in rats) and inhalation toxicity (extrapolated LC_{50} >2000 mg/m^3 in rats). It is not an eye or skin irritant in rabbits, but is a skin sensitiser in guinea pigs (Magnusson-Kligman maximisation test).

Steward EC has low acute oral toxicity (LD_{50} = 976.8 mg/kg bw in females rats, 5 deaths), dermal toxicity (LD_{50} > 5000 mg/kg bw in rats, no deaths) and inhalation toxicity (LC_{50} >5200 mg/m^3 in rats, 4-h exposure, no deaths). It is a slight eye and skin irritant in rabbits, but not a skin sensitiser in guinea pigs.

Short-term studies

In a 28-day dermal toxicity study, rats received indoxacarb (75:25) technical at 50, 500, 1000 or 2000 mg/kg bw/d. Exposure to the highest dose produced statistically significant decrease in survival and in the incidence of a few non-specific clinical signs of toxicity. All haematology and pathology changes were minimal and were not considered to be toxicologically significant at doses tested in this study. The NOEL was 1000 mg/kg bw/d in male rats and 50 mg/kg bw/d in female rats based on reduced body weight gain and food consumption.

Subchronic Studies

Existing information on Steward 200SC (75S:25R) was considered adequate address subchronic effects potentially caused by use of the product.

Chronic and Carcinogenecity Studies

Existing information on Steward 200SC (75S:25R) was considered adequate address chronic and carcinogenistic effects potentially caused by use of Steward EC.

Reproduction Studies

Existing information on Steward 200SC (75S:25R) was considered adequate address the potential effects on reproduction caused by use of Steward EC.

Developmental Studies

Indoxacarb (S-isomer) technical was administered by gavage to groups of 20 mated rats from days 6 to 20 of gestation at daily dose levels of 0, 0.5, 1, 2 or 3.5 mg/kg bw in polyethylene glycol 400 (PEG technical grade). There were no mortalities or test substance-related clinical signs of toxicity. There were no fetal variations, except for the incidence of supernumerary rib at 3.5 mg/kg bw/d (23 fetuses in 13 litters vs. 10 fetuses in 7 litters in the control group), which was considered incidental since the percent of affected fetuses per litter was not statistically significant compared to the control group. Furthermore, the supernumerary rib observation consisted of extra ossification sites of pinpoint size, which are not permanent and are generally not considered indicative of developmental toxicity. The maternal and developmental NOEL for rats was 2 mg/kg/d, based on reduction of maternal and foetal body weight gain at 3.5 mg/kg bw/d.

Genotoxicity Studies

Four genotoxicity studies have been submitted on indoxacarb (S-isomer) technical, including bacterial reverse mutation test (Ames) with and without metabolic activation, *in vitro* mammalian chromosome aberration test, CHO/HGPRT mutation assay and *in vivo* micronucleus assay. All these test results were negative.

Neurotoxicity Studies

Existing information on Steward 200SC (75S:25R) was considered adequate address subchronic effects potentially caused by use of the product.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

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

Indoxacarb is currently in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). The new toxicity data considered in this assessment indicate that this schedule is appropriate for indoxacarb (S-isomer). There are provisions for appropriate first-aid instructions and safety directions on the product label.

No-observed-Effect-Level (NOEL) and Acceptable Daily Intake (ADI)

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

The dog seems to be the most sensitive species to the effects of indoxacarb. However since there are now data to show that erythrocytes in dogs are more susceptible to lysis than those in humans the threshold haemolytic effect observed in the 12-month dog study may be considered to be a NOEL. This NOEL of 1.1 mg/kg bw/d in the dog study is supported by a NOEL of similar magnitude (1.04 mg/kg bw/d) in a rat 2-year dietary feeding study and the two-generation rat dietary study (1.25 mg/kg bw/d). Since there is an adequate database available for indoxacarb, a safety factor of 100 is considered suitable. A revised ADI of 0.01 mg/kg bw/d was established from the NOELs observed in the three studies (two rat and one dog) and a 100-fold safety factor.

Acute Reference Dose (ARfD)

The acute reference dose is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event.

An ARfD of 0.1 mg/kg bw/d was set for indoxacarb by applying a 100-fold safety factor to a NOEL of 12.5 mg/kg bw/d established in an acute neurotoxicity study conducted in rats.

RESIDUES ASSESSMENT

As part of the residue assessment for indoxacarb, metabolism, supervised residue trials, processing studies, trade aspects, environmental fate and chemistry were considered and details are provided below. This application involves approval of indoxacarb containing only the optically active s-isomer. Currently, indoxacarb manufacturing concentrate consists of isomeric mixtures of s-isomer (active) and r-isomer (inactive form) with a nominal 75 % of the active form.

Metabolism of indoxacarb

The metabolism of indoxacarb was previously reported in a separate public release summary published in October 2000, which is available on the APVMA web site. In the metabolism studies, the various isomeric forms of indoxacarb were considered. The applicant provided no additional metabolism data for target plant or animals.

The metabolism studies previously reviewed, showed that in plant commodities (cotton and lettuce) the parent compound comprised the largest proportion of the total radioactive residues (TRR), i.e. greater than 80%. There was no significant biotransformation found. In animals (rats, hens, lactating cows), indoxacarb was extensively eliminated in the urine and faeces (>73% in lactating cows). The highest TRR found in rat tissues was in fat, at up to 8.8% of the total administered dose.

In the lactating cow study, with dosing equivalent to 10 ppm in the feed for 5 days, significant residues of parent compound were found in milk (25-49.1% of TRR, up to 0.028 ppm from composite samples), muscle (28.7-37.0% of TRR, up to 0.02 ppm), liver (7.1-11.4% of TRR, up to 0.079 ppm), kidney (42.0-61.3% of TRR, up to 0.177 ppm) and peri-renal fat (66.7-80.5% of TRR, up to 0.89 ppm). The demethoxy carbonyl metabolite (code IN-JT333), which was stated to have insecticidal activity, was only detected in peri-renal fat (5.2-7.7% of TRR, up to 0.08 ppm). Indoxacarb residues in cream concentrated 10× compared to residue levels in whole milk.

Analytical Methods

Details of validated methods used to determine indoxacarb and its r-isomer in animal and plant commodities were provided.

In summary, plant samples were homogenised and extracted into ethyl acetate. An aliquot of the organic extract was cleaned-up using solid phase extraction with silica and carbon cartridges. Analysis was performed either by gas chromatography/mass spectroscopic detection with selective ion monitoring (GC/MS) or by gas chromatography with electron capture detection (GC/ECD). The reported LOQs were 0.05 mg/kg and 0.02 mg/kg, respectively for plant matrices.

For animal tissues (muscle, fat, liver, kidney), samples were extracted with acetonitrile and hexane, and the organic phase cleaned up by gel permeation chromatography followed by solid phase extraction using a silica cartridge. The recovered extracts are analysed by gas chromatography with electron capture detection (GC/ECD). The reported LOQ was 0.01 mg/kg for all animal matrices

In the methods used to determine indoxacarb residues, both the s-and r-isomers elute as a single chromatographic peak. This is not of concern, as isomeric determination is not required with respect to significant toxicological differences between the isomers or the current residue definition for indoxacarb.

Residue definition

The current residue definition for indoxacarb is parent compound, which refers to both the active s-isomer and inactive r-isomers[1]. Residue analysis does not distinguish between s- and r-isomers, and both are included in the current MRLs for indoxacarb. Now that the Australian standard for the active constituent for indoxacarb will refer to the active s-isomer only, the residue definition for indoxacarb requires amendment so that it refers to both indoxacarb and the r-isomer.

Since the initial evaluation of indoxacarb in Australia, the JMPR has reviewed the toxicological data for indoxacarb and have nominated the demethoxy carbonyl metabolite (IN-JT333), methyl 7-chloro-2,5-dihydro-2-[[[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxidiazine-4a(3H)-carboxylate) for inclusion in the residue definition for animal commodities due to its toxicity. However, data from feeding studies show that the metabolite was only found at ~5% of the parent compound in fat and it was not detected in other tissues (kidney, liver, muscle) or in milk. In the cow metabolism study, it was present at <8% TRR in perirenal fat. As its relative contribution to the total residues in animal tissues and milk is low (ie <10%), it will not be included in the Australian residue definition.

[1] Standard for indoxacarb manufacturing concentrate active constituent, http://www.apvma.gov.au/actives/standard_indoxacarb.shtml

Thus, in agreement with the APVMA active constituent specification for indoxacarb, the following residue definition is supported for indoxacarb for monitoring purposes:

Indoxacarb: ***Sum of indoxacarb and its r-isomer***.

The amended residue definition does not lead to corresponding amendments to Table 1 or Table 4 of the MRL Standard.

Residue trials

1) Cotton

The maximum proposed rate of indoxacarb on cotton is 127.5 g ai/ha (S-isomer), which is the same rate approved for Steward Insecticide (product number 52111), which is a suspension concentrate (SC) formulation. When used as directed, a withholding period of 28 days applies for cotton for both products. When indoxacarb was applied as the EC formulation, residues in harvested cottonseed were not detectable (LOQ =0.01 mg/kg, n=4). These results are below the current cottonseed MRL of 1 mg/kg for indoxacarb. Based upon good agricultural practice for cotton and waste by-products, the feeding of cotton forage and trash to livestock is not permitted, and a feeding restraint to this effect appears on the product label, similar to the statement on the label of Steward Insecticide. In conclusion, the proposed use of indoxacarb on cotton is supported and the current MRL of 1 mg/kg for cottonseed remains appropriate.

2) Pulses

The maximum rate of application of indoxacarb on chickpeas and faba beans is 45 g ai/ha and 60 g ai/ha for adzuki beans, mung beans and soybeans. The use is proposed with a 21-day withholding period to harvest. Steward 200SC (52111) is registered for use on chickpeas, mung beans and soybeans at similar rates of active (S-isomer) proposed for Steward EC. A withholding period of 28 days is approved for the SC product.

In the current submission, the applicant provided comparative residues data conducted on chickpeas (n=4), mung beans (n=4) and adzuki beans using both formulation types. These are in addition to trial data previously submitted for evaluation of the SC product for use on soy beans (n=23, includes 20 USA trials), chickpeas (n=4) and mungbeans (n=3).

When indoxacarb was applied to pulse crops according to the proposed GAP with a 21-day harvest withholding period, residues on harvested pulses ranged between <0.02 and 0.13 mg/kg. The highest residue of 0.13 mg/kg was reported in a chickpea trial conducted in NSW in 1999, with an application rate of 60 g ai/ha (1.3×) and using the SC formulation. The pulse data obtained for chickpeas, soybeans, mung beans and adzuki beans may be extrapolated to faba beans and adzuki beans and together support establishment of a group pulse MRL of 0.2 mg/kg, when indoxacarb is used as directed. The pulse MRL of 0.2 mg/kg will replace the current MRLs of 0.2 mg/kg for chickpea, mung bean and soybean, and the temporary MRL of T0.2 mg/kg for adzuki beans.

With respect to livestock feeds resulting from harvested crops, residue data were generated for forages (ie whole plants), trash and stubble when indoxacarb was used on soya bean, chickpea and mung beans according to GAP. Indoxacarb residues in treated forage/fodder ranged from 0.13 to 9.6 mg/kg (DM). The highest residue of 9.6 mg/kg was in mung bean stubble collected in a trial in NSW in 2003, following a single application of indoxacarb SC at 1× and sampled at 21 days after application. At 28 days after application, the residue level was reported as 3.2 mg/kg. Collectively, these data support establishment of a legume animal feed MRL of 10 mg/kg. This MRL will replace the current soya bean, chickpea and adzuki forage, fodder and hay MRLs (various, ranging 3-10 mg/kg) for indoxacarb.

Animal commodity MRLs

Grazing Livestock and Animal Commodity MRLs

In the previous submission for Steward Insecticide (product number 52111), a lactating cow feeding study was evaluated. In that study, animals were fed up to 94 ppm (10×) in the diet of indoxacarb and its r-isomer (75:25) for 28 days. This is equivalent to ~3.4 mg/kg bw/day based upon animals ranging 500 to 680 kg in bodyweight and consuming 16 to 25 kg dry feed/day). The maximum feed level of 10 ppm based upon pulse fodder falls between the 1× and 3× dose levels in the feeding study. The highest residues in milk, cream and skim milk following dosing at 3× were 0.09 mg/kg in whole milk, 0.89 mg/kg in cream and 0.038 mg/kg in skim milk. Following dosing at 1×, highest residues were 0.026, 0.25 and <0.01 mg/kg in whole milk, cream and skim milk, respectively. On the basis of these data, an MRL of 0.1 mg/kg is recommended for whole milk and 1 mg/kg for milk fat.

In the current submission, the applicant provided a new beef cattle feeding study following intake of indoxacarb and its r-isomer (75:25 isomeric mixture) at dose levels ranging 77 – 98 ppm in the diet for 14 days. Animals were slaughtered at 0, 7, 14, 21, 28, 35 days after completion of the dosing period. At 0 days depuration (ie after 14 days dosing), maximum residues in fat, kidney, liver and muscle were 6.6 mg/kg (subcutaneous or back fat), ~0.78 mg/kg, ~0.03 mg/kg and ~0.05 mg/kg, respectively. When these data are compared to the maximum feed

level of 10 ppm from pulse fodder, expected residues are ~0.7 mg/kg in mammalian fat, 0.08 mg/kg in kidney, and ~<0.01 mg/kg in liver and muscle. The following MRLs are therefore recommended: 1 mg/kg for meat [in the fat]; 0.2 mg/kg for mammalian kidney and *0.01 mg/kg for edible offal (mammalian), except kidney.

In both feeding studies, fat is the primary tissue for indoxacarb residues, which is not unexpected as indoxacarb is fat soluble (log K_{OW} of 4.65). When residues in fat from both studies are plotted against administered dose on a mg/kg bw basis, there is a noticeable difference in the magnitude of the residues in the beef animals compared to the dairy animals.

In dairy animals, milk is an important elimination pathway which is not available in beef cattle, and this may be part of the reason for higher residue concentrations being found in the fat of beef animals compared to dairy animals. In addition, the fat samples in the dairy study were composited and not analysed individually, whereas in the beef animal study samples from perirenal, omental and subcutaneous fat were analysed separately. Differences in feed intake and bodyweights of the animals may also make an impact on the resulting residue. During the depuration phase, it is observed that residues in the fat decline quicker in dairy cows than beef animals. The depuration half-life is discussed further in the trade considerations.

Poultry exposure to indoxacarb is limited to pulses and cotton seed/meal, which comprise their feed ration. Based upon a feed intake of cottonseed (30%) and chickpea (70%), the expected indoxacarb intake is equivalent to ~0.09 ppm in the feed ration.

Although no residue transfer studies have been provided on poultry, poultry metabolism data are considered acceptable for assessing the likelihood of residues occurring in poultry tissues and eggs. As reviewed in the previous submission, laying hens were dosed daily for 5 consecutive days with ^{14}C-indoxacarb at a dose level equivalent to 10 ppm in the diet. Animals were sacrificed at the completion of dosing, and the total radioactive residues (TRR) were measured in tissues and eggs. The TRR in parent compound equivalents, were a maximum of 0.51 mg/kg in fat, 0.10 mg/kg in egg white, 0.33 mg/kg in egg yolk, 0.15 mg/kg in liver and 0.04 mg/kg in muscle. Metabolic profiling indicated that parent compound residues were 0.03 mg/kg in fat, 0.01 mg/kg in egg yolk, 0.01 mg/kg in liver and <0.01 mg/kg in muscle. As the metabolic dose rate was ~ 100× (ie 10/0.09) the anticipated dietary exposure level, detectable residues are not expected to occur in any poultry tissues or eggs above the analytical method LOQ of 0.01 mg/kg (ie parent indoxacarb in fat, 0.03/100=<<0.01 mg/kg). It is concluded that the current MRLs of *0.01 mg/kg for poultry commodities remain appropriate for use of indoxacarb in Steward EC on pulses.

Processing studies
In previous submissions of Steward 200SC, processing data for cotton and soy bean were evaluated. Assessment of these data led to the establishment of the soya bean oil, MRL of 0.2 mg/kg for indoxacarb. In the current submission, no additional processing studies were provided. As the pulse MRL of 0.2 mg/kg adequately accommodates residues in the refined soy bean oil (ie MRLs of the same value), the separate processed oil MRL is not required. Therefore, the soya bean oil, refined MRL of 0.2 mg/kg will be deleted from the MRL Standard.

SPRAYDRIFT
With respect to livestock feeding on pasture contaminated by spray drift, necessary no spray zones were calculated to achieve using the maximum feeding level of 6.75mg/kg (4.5ppm x 1500g dry matter/ha). European meat MRL's for indoxacarb. The Agdrift spray model program was used to determine appropriate no spray zones.

The potential for spray drift using indoxacarb is Steward EC is likely to be no higher compared to the use of currently registered Steward 200SC (52111). For aerial application, both products are used in a minimum of 30L/ha water and the application is via nozzles which produce a medium spray quality. The resulting output from the Agdrift model shows that a no spray zone of 50m for aerial application is below the threshold of 6.75mg/kg. The model shows a steep drop in the amount of active/ha for ground application, and is below the threshold at 20m downwind. Once the level of active constituent is below the threshold the APVMA can be satisfied that the potential residues in stock would not exceed the current MRL's for trade internationally and in addition would not exceed Australian MRL's. The following no spray zone restraint statement will be included on the label:

DO NOT apply within 50 m (aerial application) or 20 m (ground application) when there are livestock, pasture or any land that is producing feed for livestock downwind from the application area.

OUTCOMES OF RESIDUE ASSESSMENT

Dietary risk assessment

The chronic and acute dietary intake estimates of indoxacarb have been assessed. The National Estimated Daily Intake (NEDI) of indoxacarb is equivalent to <13% of the ADI of 0.01 mg/kg bw/day. With respect to acute dietary intake, the highest acute dietary intake was estimated at <50% of the ARfD of 0.1 mg/kg bw/day. It is concluded that the chronic and acute dietary exposure to indoxacarb is within health standards, and that residues in food are unlikely to pose an undue hazard to the safety of consumers.

Changes recommended to MRL Standards

The following changes are recommended to Tables 1, 3, and 4 of the MRL Standard upon registration of Steward EC Insecticide:

Table 1

Compound	Food		MRL (mg/kg)
Indoxacarb			
DELETE:	VD 0560	Adzuki bean (dry)	T0.2
	VD 0524	Chick-pea (dry)	0.2
	MO 0105	Edible offal (mammalian)	*0.01
	MM 0095	Meat (mammalian) [in the fat]	0.5
	VD 0536	Mung bean (dry)	0.2
	VD 0541	Soya bean (dry)	0.2
	OR 0541	Soya bean oil, refined	0.2
ADD:	MO 0105	Edible offal (mammalian) [except kidney]	*0.01
		Kidney (mammalian)	0.2
	MM 0095	Meat (mammalian) [in the fat]	1
	ML 0106	Milks	0.1
		Milk fats	1
	VD 0070	Pulses	0.2

Table 3

Compound	Residue
Indoxacarb	
DELETE:	Indoxacarb
ADD:	Sum of indoxacarb and its r-isomer.

Table 4

Compound	Animal feed commodity		MRL (mg/kg)
Indoxacarb			
DELETE:		Adzuki bean forage, fodder and hay	T10
		Chickpea forage, fodder and hay	3
		Soya bean and mungbean forage, fodder and hay	10
ADD:	AL 0157	Legume animal feeds	10

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported

Cotton seed oil and pulse grains are considered major trade commodities. Also, as a result of livestock feeding on treated pulse crops, meat and milk products are also considered for residues in trade risks.

Destination and Value of Exports

Production of cottonseed in 2004-05 was 912.3 kt, of which 214 kt was exported (23%)[6]. Total value of oilseed exports was $1261m, with cotton making up 17% of exports (by volume). In addition to oilseed, exports of cottonseed oil was 2.19 kt and cottonseed meal of 6.42 kt. The major markets for cottonseed are China, Japan, Korea, Saudi Arabia and USA.

The production and export of pulse crops for 2004-05 is shown in the following table[2]:

Pulse	Production, kt	Exports, kt	Exports, %	Exports, $m
Lupins	891	342	38%	71.4
Field peas	320.8	116.1	36%	33.4
Chickpeas	115.6	151.2	131%	65.3
Total pulses †	1586.1	833.7	53%	291

† Includes lupin, field peas, chickpeas, faba beans, mung beans, navy beans, vetch and lentils

The Indian Subcontinent countries of India, Pakistan and Bangladesh are all major export markets for Australian field peas, desi and Kabuli chickpeas, and for lentils.

Proposed Australian use-pattern

Steward 200SC (52111), containing 75% indoxacarb is registered for use on cotton, chickpeas, mung beans and soybeans. In addition to these crops, the proposed use of Steward EC Insecticide includes new use-patterns for faba beans and adzuki beans. The proposed application rates are similar to those approved for Steward Insecticide 52111. The proposed Australian use-pattern is given below.

DuPont Steward EC Insecticide (150 g/L indoxacarb)

CROP	PEST	STATE	RATE	CRITICAL COMMENTS
Cotton	Cotton bollworm *(Helicoverpa armigera)* Native budworm *(H. punctigera)*	NSW, NT, Qld and WA only	650 mL/ha or 850 mL/ha	**Use the lower rate of Steward® EC when:** *H. armigera* specific field levels are less than or equal to 60 % prior to treatment application AND egg and larvae pressure ARE AT 5 –10 brown eggs and 2 very small (first instar) or small larvae (second instar) per 10 cotton terminals AND where preservation of beneficial insects is desirable.
				Use the higher rate of Steward® EC when: *H. armigera* specific field levels are greater than 60 % prior to treatment application AND egg and larvae pressure ARE AT 5 – 15 brown eggs and 2 very small (first instar) or small larvae (second instar) per 10 cotton terminals AND where preservation of beneficial insects is desirable.
	Green mirid (*Creontiades dilutus*)			Target nymphs and/or adults when they reach the economic spray threshold. **Under high populations suppression only may be observed.**
	Cotton bollworm *(Helicoverpa armigera)* Native budworm *(H. punctigera)*		650 mL/ha + 2 L/ha Ovasyn® insecticide (or 200 g/L Amitraz EC formulation)	Use Steward® EC+ Ovasyn® or 200 g/L Amitraz EC when: egg and larvae pressure ARE AT 15 – 20 brown eggs and 2 very small (first instar) or small larvae (second instar) per 10 cotton terminals AND where limited preservation of beneficial insects is required.
Chickpeas, Faba beans	Cotton bollworm *(H. armigera)* Native budworm *(H. punctigera)*	All States and territories	300 mL/ha	Target brown eggs and hatchling (neonates or first instar) to small larvae (second instar) when they reach the economic spray threshold and before they become entrenched in flowers (particularly relevant to faba beans) or pods.

[2] Australian Commodity Statistics, 2005

Adzuki beans, Mungbeans, Soybeans	Cotton bollworm *(H. armigera)* Native budworm *(H. punctigera)*		400 mL/ha	Target brown eggs and hatchling (neonates or first instar) to small larvae (second instar) when they reach the economic spray threshold and before they become entrenched in flowers and pods.
	Mirid complex: Green mirid (*C. dilutus*); Brown mirid (*C. pacificus*); Crop mirid (*Sidnia kingbergii*) Yellow mirid (*Campylomma liebknechti)*			Target nymphs and/or adults when they reach the economic spray threshold. **Under high populations suppression only may be observed.** Please note: Steward® EC has limited residual activity in controlling new infestations of mirids (either new hatchlings of nymphs or influx of adults) post spray.
	Soybean looper (*Thysanoplusia orichalcea)*		200 mL/ha	Target hatchling (neonates or first instar) to small larvae (second instar) when they reach the economic spray threshold.

Withholding periods:
Harvest
Cotton: DO NOT harvest for 28 days after application.
Adzuki beans, chickpeas, faba beans, mung beans, soybeans: DO NOT harvest for 21 days after application.

Grazing
Cotton: DO NOT allow livestock to graze crops, cotton stubble or gin trash treated with steward® EC Insecticide.
Adzuki beans, chickpeas, faba beans, mung beans, soy beans: DO NOT graze or cut for stock food for 21 days after application.

Comparison of Australian MRLs with Codex and overseas MRLs.
The Codex Alimentarius Commission (Codex) through the Codex Committee on Pesticide Residues (CCPR) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries and some countries may accept Codex CXLs when importing foods.

Codex MRLs are currently under consideration for indoxacarb (at step 5/8 as of June 2006). Overseas MRLs/ tolerances for indoxacarb have also been established in USA and Japan. The relevant MRLs are shown in the table below:

Comparison of Australian MRLs with overseas MRLs for indoxacarb.

Commodity	Australia	Codex (4)	Japan (1)	USA	Korea (2)	EU (3)
Animal commodities						
Mammalian meat		-	0.05	0.05	-	*0.01
Mammalian meat, in the fat	1	1	1	1.5	-	0.3
Milk	0.1	0.1	0.1	0.15	-	0.02
Milk, fat	1	2	-	4.0	-	0.3
Mammalian offal	*0.01 (except kidney)	0.05 (except pigs)	0.02 (liver and kidney)		-	*0.01
Kidney	0.2	-	-	-	-	*0.01
Pulse/cotton commodities						
Soybean (dry)		0.5	0.5		-	-
Beans (dry)		-	0.2		-	-
Other legumes/pulses		-	0.2		-	-
Soybean seed		-		0.8	-	-
Chickpea (dry)		0.2			-	-
Cotton seed		1			-	-
Mung bean		0.2			-	-

1) Positive list system for Agricultural Chemical Residues in Foods, MHLW Notification No. 499
2) No animal commodity MRLs are established in the Korean standard.
3) No EU MRLs are currently established for indoxacarb.
4) Codex MRLs currently at Step 5/8, which require final ratification.

On the basis of the information tabulated above, the target market with respect to meat is the EU with an MRL of 0.3 mg/kg in meat fat, which is the target tissue. This level will be regarded as the target concentration for the ESI determination.

Potential risk to trade

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

Export trade risks for use of indoxacarb on cotton and pulse grains were previously considered as part of the registration of Steward 200 SC. These considerations are accessible in a Public Release Summary dated October 2000 (for use on cotton) and in a Trade Advice Notice dated December 2002 (for use on pulse crops).

1) Cotton

The proposed use of Steward EC on cotton is similar to that approved for the Steward 200SC, and indoxacarb residues are expected to remain within the current cottonseed MRL of 1 mg/kg. Therefore, the proposed use of Steward EC Insecticide on cotton is unlikely to raise any additional risks to trade.

2) Pulses (chickpeas, mung beans, soybeans, adzuki and faba beans)

When Steward EC Insecticide is used on pulses as proposed, detectable residues of indoxacarb may occur in grains from treated crops. However, residue levels found in mung beans, soybeans and chickpeas will comply with the existing Australian MRLs of 0.2 mg/kg for these commodities when using the product as proposed above. Accordingly, there are unlikely to be any additional trade risks for pulse grains when using the new formulation.

The extension of use of Steward EC Insecticide to include faba beans and adzuki beans may pose potential risks to trade, as Australian use-patterns have not previously been established for these commodities. However, the proposed Australian MRL of 0.2 mg/kg for pulse grains is comparable to other pulse MRLs established for indoxacarb in overseas countries. It is expected that the potential risk from trading faba and adzuki beans is considered negligible, as they are not major pulse commodities. However, APVMA requests comment on the potential trade risks posed by Steward EC when used on pulses (ie chickpea, mung bean, soybeans, faba and adzuki beans) from Pulse Australia and relevant industry bodies.

3) Dairy products

In the previous trade considerations for Steward 200SC, it was argued that dairy cattle exposure to feeds (particularly fodder) containing indoxacarb residues was expected to be very low, and that the likelihood of finding detectable residues in milk and milk products was also very low. When animals are exposed to pulse fodder from treated crops, residues in milk are expected to comply with the milk MRL of 0.1 mg/kg. Animal transfer data from dairy cows show that indoxacarb residues concentrate in the fat portion of milk or the cream and following exposure at the maximum feed level of 10 ppm, the data support establishment of a milk fat MRL of 1 mg/kg.

The use of cottonseed and/or pulse grains from treated crops as part of the dairy ration is not likely to result in detectable residues in milk commodities or processed milk products. The Australian milk MRL of 0.1 mg/kg is comparable to MRLs established in Japan, the USA and that proposed by Codex. The milk fat MRL of 1 mg/kg is lower than the MRL of 2 mg/kg proposed by Codex and 4 mg/kg established in the USA. However, no equivalent milk fat MRLs are established in other major overseas markets, such as Japan, Korea, and the EU, and this may pose a potential trade risk for milk exports.

In the current submission, the APVMA is seeking comment from the dairy industry on the potential risks posed by the registration of Steward EC following exposure to pulse fodder from treated crops.

4) Beef/meat industry

In beef cattle, when animals are exposed to the highest residue of 10 ppm of indoxacarb in the diet, as a result of feeding on fodder of pulse crops, detectable residues are expected to occur in fat of ~0.7 mg/kg and in kidney of ~0.08 mg/kg. No detectable residues are expected to occur in liver or other offal commodities.

Depuration data obtained from a beef cattle study show that indoxacarb residues in fat decline with a half-life ranging 4.8-6.2 days in various fat depots. When applying a conservative half-life of 7 days, residues in fat of ~0.71 mg/kg are expected to decline to below a target level of 0.3 mg/kg (EU MRL) in approximately 3 half-lives or 21 days when animals are maintained on feed containing no indoxacarb residues. These data confirm the current ESI of 28 days clean feed (4 weeks) when animals are destined for overseas markets.

The ESI will need to be observed when animals are fed pulse fodder from treated crops. As with the Steward 200SC, a grazing/feeding restraint will apply to cotton forage and trash. Indoxacarb residues that may be found in pulse grain and cottonseed from treated crops are not significant enough to result in detectable residues in animal tissues when used as animal feeds. The following ESI is recommended for Steward EC:

LIVESTOCK DESTINED FOR EXPORT MARKETS
The grazing withholding period only applies to stock slaughtered for the domestic market. Some export markets apply different standards. To meet these standards, ensure that in addition to complying with the grazing withholding period, that the Export Slaughter Interval is observed before stock are sold or slaughtered.

EXPORT SLAUGHTER INTERVAL (ESI) – 28 days:
After observing the grazing withholding period, livestock that has been grazed on or fed pulse fodder from treated crops should be placed on clean feed for 28 days (4 weeks) prior to slaughter.

When Steward EC Insecticide is used as directed and the above withholding periods and/or export intervals are observed, treated grain and livestock commodities are considered acceptable for export. However, export requirements are subject to change. Consult your exporter for updated information about specific market requirements.

Conclusions on the assessment of overseas trade aspects

1) Cotton

The available residue data show that the current cottonseed MRL of 1 mg/kg remains appropriate for the proposed use of indoxacarb in Steward EC. There are unlikely to be additional trade risks posed by the registration of the EC formulation on cotton.

2) Pulses

The proposed use of Steward EC on chickpeas, soybeans and mung beans is unlikely to pose additional trade risks, as residues will be within the current Australian MRLs of 0.2 mg/kg for these commodities. Extension of Steward EC to include faba beans and adzuki beans may pose potential risks to trade, as Australian use-patterns have not previously been established for these commodities.

The proposed Australian MRL of 0.2 mg/kg for pulse grains may potentially impact upon the export of Australian pulses to overseas markets. The APVMA welcomes comment in relation to whether indoxacarb residues will unduly prejudice Australian trade in pulse grains.

3) Dairy industry

When milk-producing animals are exposed to pulse fodder from treated crops, the milk MRL of 0.1 mg/kg is recommended for the proposed use of indoxacarb in Steward EC, and the data support establishment of a milk fat MRL of 1 mg/kg. The milk MRL is comparable to MRLs in the USA, Japan, and the proposed Codex MRL. No detectable residues are expected in milk commodities when animals are fed pulse grains and /or cottonseed from treated crops. In the previous assessment of indoxacarb in the product Steward 200SC (52111), the feeding of pulse fodder to dairy animals was not considered to be common practice, and accordingly, residues in milk were expected to be very low.

The proposed Australian MRL of 1 mg/kg for milk fat may potentially impact upon the export of Australian milk products to overseas markets, although the milk MRL to comparable to MRLs established in some export markets and Codex. The APVMA welcomes comment in relation to whether indoxacarb residues will unduly prejudice Australian trade in milk.

4) Beef/meat industry

The APVMA has considered the trade impact for livestock that have been exposed to indoxacarb through grazing and/or feeding on pulse fodder from treated crops. The feeding of cotton forage, fodder and trash crops is not considered to be good agricultural practice and is therefore not considered further. When Steward EC Insecticide is used as proposed on pulse crops, the feeding of fodder may result in detectable residues in mammalian meat [in the fat] and in mammalian kidney. This has resulted in an amendment of the current mammalian meat [in the fat] MRL from 0.5 to 1 mg/kg, and establishing a separate kidney MRL of 0.2 mg/kg. In a new depuration study in beef cattle, a depuration half-life of approximately 6 days was observed. On the basis of requiring 4 half-lives to reach a target concentration in fat in EU markets, an ESI of 28 days should be observed to ensure residues are below target concentrations before animals are slaughtered for overseas markets. Thus, the following trade advice statement is recommended on the product label:

LIVESTOCK DESTINED FOR EXPORT MARKETS

The grazing withholding period only applies to stock slaughtered for the domestic market. Some export markets apply different standards. To meet these standards, ensure that in addition to complying with the grazing withholding period, that the Export Slaughter Interval is observed before stock are sold or slaughtered.

EXPORT SLAUGHTER INTERVAL (ESI) – 28 days:
After observing the grazing withholding period, livestock that has been grazed on or fed pulse fodder from treated crops should be placed on clean feed for 28 days (4 weeks) prior to slaughter.

When Steward EC is used as directed and the above withholding periods and/or export intervals are observed, treated grain and livestock commodities are considered acceptable for export. However, export requirements are subject to change. Consult your exporter for updated information about specific market requirements.

The APVMA welcomes comment on the proposed Australian export slaughter interval of 28 days for use of indoxacarb in Steward EC, and whether it is appropriate to mitigate potential residues in trade issues for the export of meat and meat products.

Health hazards

Indoxacarb (S-isomer) has low to moderate acute oral toxicity and, low acute dermal and inhalation toxicity. It is not an eye or skin irritant in rabbits, but is a skin sensitiser in guinea pigs. Based on low to moderate acute oral toxicity (LD_{50} = 179 mg/kg bw in female rats and 843 mg/kg bw in male rats) and skin sensitisation potential, the following risk phrases apply for indoxacarb DPX-KN128 (100% S-isomer):

R25	Toxic if swallowed
R43	May cause sensitisation by skin contact

Steward EC has low acute oral, dermal and inhalation toxicity. It is a slight eye and skin irritant in rabbits, but not a skin sensitiser in guinea pigs. Based on its toxicity, Steward EC is classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004), with the following risk phrases:

R22	Harmful if swallowed
R38	Irritating to skin

Formulation, packaging, transport, storage and retailing

Steward EC will be formulated overseas and imported into Australia in 10 L high-density polyethylene (HDPE) containers, 110 L small-volume-refillables (SVR) HDPE containers with tamper evident fitting, 200 L high molecular weight HDPE drums (such as Mauser drums) and 1000 L blow moulded HDPE (with a galvanized and welded steel grid mesh) intermediate bulk containers. Transport workers and store persons will handle the packaged product and could only become contaminated if packaging were breached.

Use pattern

Steward EC will be used for the control of cotton bollworm and native budworm in adzuki beans, cotton, chickpeas, faba beans, mungbeans and soybeans; green mirid in cotton and mirid complexes and soybean looper in adzuki beans, mungbeans and soybeans.

The product will be applied using ground boom or aerial application equipment, using an application rate of 650 - 850 mL product/ha in cotton, 300 mL product/ha in chickpeas and faba beans and 200 - 400 mL product/ha in adzuki beans, mungbeans and soybeans, with a minimum spray volume of 100 L/ha for ground application and 30 L/ha for aerial application. A maximum of 3 applications per season for cotton and one application per season for other field crops will be used.

A withholding period of 28 days for cotton harvesting and 21 days for harvesting of adzuki beans, chickpeas, faba beans, mungbeans and soybeans are recommended. A withholding period of 21 days is recommended for crops for grazing or cut for stock feed.

Exposure during use

Farmers and contract spray workers will be the main users of the product. Contract workers will be exposed to the product repeatedly. Workers may become contaminated with the product/spray during mixing/loading, spraying, cleaning up spills and maintaining equipment. The main routes of exposure to the product will be dermal and inhalation.

There are no worker exposure studies on indoxacarb or Steward EC available for assessment. In the absence of worker exposure data, the OCS used the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) to estimate worst-case worker exposure based on maximum product use according to the Australian use pattern (6.375 kg indoxacarb/day for ground application and 25.5 kg indoxacarb/day for aerial application).

These estimations in conjunction with toxicology data demonstrated that the use of cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves are required to protect workers when opening the container and preparing spray.

Exposure during re-entry

Workers entering treated areas can be exposed to product residues during crop management activities. In the absence of worker exposure data for workers undertaking crop management activities after the spray application,

the OCS estimated post application dermal exposure using the US Occupational Post-Application Risk Assessment Calculator (US EPA Policy 003.1).

Considering the likely risks to workers performing low to high exposure activities in cotton and other field crops, a re-entry statement is recommended until the spray has dried.

Recommendations for safe use

Users should follow the instructions and Safety Directions on the product label. Safety Directions include the use of cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves when opening the container and preparing spray.

The PPE recommended should meet the relevant Australian Standards.

Re-entry statement

Do not allow entry into treated areas until the spray has dried unless wearing cotton overalls (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Precautionary statement

Do not use human flaggers/markers unless they are protected by engineering controls such as enclosed cabs.

Conclusion

Steward EC can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product MSDS.

ENVIRONMENTAL ASSESSMENT

INTRODUCTION

Steward EC contains a new active constituent, which exists as 100% of the insecticidally active S isomer of indoxacarb belonging to the novel oxadiazine class of insecticides. The R isomer does not display insecticidal activity. In addition to the current registered use pattern for the reference product Steward 200SC for use in cotton, chickpeas, mungbeans and soya beans, the applicant has also proposed to extend the use pattern of the new product to include adzuki and faba beans for the control of cotton bollworm and native budworm and for the control of mirid complexes and soybean looper in adzuki beans. The proposed maximum application rate is 850 mL/ha corresponding to 127.5 ac/ha on cotton. This proposed maximum rate is identical to the currently maximum registered rate for the reference product (200 g/L), taking into consideration the proportion of S isomer present in the mixture (75:25).

ENVIRONMENTAL FATE

No new data were provided for the active constituent. As the active constituent is an isomer of the previously assessed chemical indoxacarb which contains a mixture of S and R isomer, there is unlikely to be a significant difference in physico-chemical properties except for the optical properties between the active constituent and the mixture. On the basis of the assessed data for the registered reference product, the conclusion reached in fate studies for indoxacarb is also representative of the active constituent.

ENVIRONMENTAL TOXICOLOGY

No new data were provided for the active constituent. Previous ecotoxicity data were derived from studies on a mixture of the S and R isomers (ratio 75:25) of indoxacarb. The available literature data suggest only minor differences between optically active isomers in respect of aquatic toxicity. Therefore, it is reasonable to assume, on the basis of the identical application rate with respect to the S isomer between the reference product and the proposed product, the conclusions reached in the ecotoxicity studies for the reference active constituent are representative of the new active constituent.

ENVIRONMENTAL RISK

Given that the proposed maximum application rate and the use pattern for the active constituent on cotton are identical to the reference product, and the additional environmental exposure from extension of use to adzuki and faba beans is not significant, there is unlikely to be an undue environmental risk under the proposed use pattern.

CONCLUSION

The proposed use of Steward EC is not expected to lead to any unintended effect that is harmful to animals, plants or the environment following good agricultural practice.

EFFICACY AND SAFETY ASSESSMENT

EVALUATION OF EFFICACY OF DUPONT STEWARD EC INSECTICIDE

Chickpeas, Mungbeans, adzuki beans and soybeans
Eight trials for these crops were provided in support of this application. Three on chickpeas, three on mung beans and adzuki beans and two on faba beans. The proposed product was compared against Steward 200SC and some registered carbamate alternatives considered as industry standards. The reviewer advised that the trial designs were suitable, being laid out as randomized blocks in commercial crops with adequate replications. All, but one trial reflected accurately current commercial standard practice with regard to water volume (mostly >125L), nozzle type (flat fan) and pressure (>250kpa). All trials included an untreated control. Trial sites were spread across a wide geographic area and meteorological conditions at spraying were typical of what would be expected for the three crops trialled.

In all trials in all crops, Steward EC gave comparable control to Steward 200SC, giving on average 88% versus 87% control respectively. The trial results showed for control of loopers, *Helicoverpa spp* and mirids (using 400mL/ha) the difference in percentage control for Steward 200SC and Steward EC was no greater than 2% which demonstrated that efficacy for Steward EC was comparable to the registered Steward 200SC as this difference was not significant. Trials on adzuki beans gave greater than 90% control of *Helicoverpa spp.* Adzuki beans have similar architecture to mung beans and therefore the control of *Helicoverpa spp* is expected to be similar to those on mungbeans.

For *Helicoverpa spp*, the majority of trials contained both *Helicoverpa armigera* and *Helicoverpa punctigera*. Larval sizes were an accurate reflection of what is expected at time of spraying. On average, larvae were much larger than the sizes specified on the label, therefore increasing credibility of the data. Trial crops were at the growth stages commonly attacked by *Helicoverpa spp*. And there was adequate pest pressure.

Mirid pressure at 0 days after treatment (DAT) was low in one trial, but at 1.25/m^2 was still in excess of the threshold of 0.5/m^2. In this particular trial mirid populations in the untreated control increased to >3/m^2 by 7 DAT but only reached 36% of this level in both Steward treatments. The proposed Steward EC is only claiming suppression under high pest pressure.

Looper pressure was moderate and was considered acceptable to evaluate the performance of the proposed product in their control. The trials involved both the Steward 200SC and the proposed product being applied at 400mL/ha as opposed to the recommendation on the label of 200mL/ha. Given the similarity of the percentage control given in various crops tested and the similarity of the products (i.e. both are applied at the same rate of the active s isomer) it is concluded that efficacy of the proposed product at 200mL/ha will be achieved as which has been previously proven for the reference product.

Based on the above consideration of trial results and the similarities drawn between the currently registered Steward 200SC, Steward EC was demonstrated to be efficacious as proposed on pulse crops.

Cotton
Four efficacy trials on cotton were provided in support of this application. The trials were conducted in cotton growing districts under high *Helicoverpa spp*. pressure at the proposed label rate of 850mL/ha.

The trial designs and experimental methods used were considered appropriate. Data for four treatments (including a control) are presented for each trial. For each trial, small plot field treatments were arranged in a randomized complete block design of four replications.

The first trial compared the proposed Steward EC, Steward 200SC and Affirm Insecticide (51321) in the control of *Helicoverpa spp*. Larvae. The percentage levels of larval reductions 7 DAT were 84% Steward SC, 79% Steward EC and 58% for Affirm Insecticide. The *Helicoverpa* larval infestations were considered high throughout the trial ranging from 0.32 to 1.27 larvae per terminal in the untreated control plots.

There were no significant differences in the levels of adult *Helicoverpa* suppression for treatments 7 DAT. The results demonstrated 95%, 95% and 79% for Steward 200SC, Steward EC and Affirm insecticide respectively. The reviewer also advised there were no significant statistical differences in the level of fruit damage between the two Steward treatments, (Steward 200SC – 5.1% and Steward EC – 1.6%).

The second trial compared the same formulations as those mentioned above for the control of *Helicoverpa* larval populations. The *Helicoverpa* larval infestations were considered high throughout the trials ranging from 0.60 to 1.15 larvae per terminal in the untreated control plots. The percentage larval reductions 4 DAT

were 80%, 89% and 65% for Steward 200SC, Steward EC and Affirm insecticide respectively. The percentage larval reductions 8DAT were 90%, 73% and 73% for Steward 200SC, Steward EC and Affirm insecticide. However no significant statistically differences were seen between the proposed product and the comparison products.

Again, in the third trial the application of each formulation significantly reduced the *Helicoverpa spp.* larval populations. The *Helicoverpa* larval infestations were considered high throughout the trials ranging from 0.43 to 0.58 larvae per terminal in the untreated control plots. The percentage larval reductions at 6 DAT were 100%, 82% and 77% for Steward 200SC, Steward EC and Affirm insecticide. Again no statistically significant differences were seen between the proposed product and comparison products.

The final trial demonstrated larval reductions of 94%, 90% and 84% for Steward 200SC, Steward EC and Affirm respectively at 7 DAT. The *Helicoverpa* larval infestations were considered high throughout the trials ranging from 3.5 to 5.3 larvae per terminal in the untreated control plots. No statistically significant differences were seen between the proposed product and comparison products.

In conclusion the data presented in all four cotton trials indicate that the proposed product will be equally as effective as the industry standards for control of *Helicoverpa spp.*

The applicant also proposed a lower rate of 650mL to be used in situations of low pest pressure. Given that the proposed use on cotton is identical to that currently registered for Steward 200SC, and the trials provided at the higher rate of 850mL/ha prove equivalency of the two products at high pest pressure, the inclusion of the lower rate is acceptable as the product are considered bioequivalent.

Along with the lower rate for control of *Helicoverpa spp.* in cotton, the applicant requested that the lower rate be mixed with Ovasyn EC insecticide (as per Steward 200SC) for the control of *Helicoverpa spp.* in cotton when limited preservation of beneficial insects is required and when egg and larvae are at 5 – 15 brown eggs per 10 cotton terminals. The applicant provided a trial mixing Steward EC with another product containing the same amount of amitraz (200g/L) as Ovasyn in a tank mix for the control of *Helicoverpa spp*. The pest pressure in the trial exceeded that recommended to be controlled on the product label. Although the trials conducted also included 500mL Rogor (400g/L dimethoate product) in the tank mix, and therefore the actual percentage pest controlled was not applicable, this trial demonstrated that there were no adverse effects caused to the crop. Given that the currently registered Steward 200SC product is considered similar to the proposed product (as a result of trial results for other rates/crops/situations) the tank mixture with Ovasyn EC insecticide is acceptable and is expected to be as efficacious as the reference product. Given the proposed use with Ovasyn is on the currently registered Dupont Steward 200SC label and on the basis that Steward EC is considered bioequivalent to Steward 200SC, the proposed tank mix is acceptable.

CROP SAFETY
In all trials there was no evidence of phytotoxicity to cotton applied at the highest label rate of 850mL/ha. All product applications were completed using medium spray droplet size.

CONCLUSION
The data as presented were adequate to demonstrate the efficacy and crop safety criteria has been met when the product is used according to the proposed label instructions.

GLOSSARY

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

APVMA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of [active constituent] in the product [product name], please fill in this form and send it, along with payment of $30 to:

[name]
[section]
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to:
[name and section] at (06) [number].

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 'National Registration Authority'.

___ Bankcard ___ Visa ___ Mastercard

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

Signature_____ Date _____