

**Public Release Summary  
on**

**Evaluation of the new active**

**INDOXACARB**

**in the product**

*DuPont Steward Insecticide*

**(proposed distinguishing number 52111)**

**National Registration Authority  
for Agricultural and Veterinary Chemicals**

**October 2000**

**Canberra  
Australia**

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## FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) 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 NRA works in close cooperation with advisory agencies, including the Department of Health and Family Services (Chemicals and Non-prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission (Worksafe Australia) and State departments of agriculture and environment.

The NRA 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 NRA 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 NRA'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 NRA 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 NRA. Alternatively, the reports can be viewed at the NRA Library, Ground Floor, 22 Brisbane Avenue, Barton, ACT.

The NRA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Executive Manager—Registration, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston ACT 2604.



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## LIST OF ABBREVIATIONS AND ACRONYMS

<b>ac</b>	active constituent
<b>ADI</b>	Acceptable Daily Intake (for humans)
<b>AHMAC</b>	Australian Health Ministers Advisory Council
<b>ai</b>	active ingredient
<b>d</b>	day
<b>EC<sub>50</sub></b>	concentration at which 50% of the test population are immobilised
<b>EEC</b>	Estimated Environmental Concentration
<b>EUP</b>	end use product
<b>F<sub>0</sub></b>	original parent generation
<b>h</b>	hour
<b>HPLC</b>	high pressure liquid chromatography <i>or</i> high performance liquid chromatography
<b>id</b>	intra dermal
<b>im</b>	intramuscular
<b>ip</b>	intraperitoneal
<b>iv</b>	intravenous
<b>in vitro</b>	outside the living body and in an artificial environment
<b>in vivo</b>	inside the living body of a plant or animal
<b>kg</b>	kilogram
<b>L</b>	litre
<b>LC<sub>50</sub></b>	concentration that kills 50% of the test population of organisms
<b>LD<sub>50</sub></b>	dosage of chemical that kills 50% of the test population of organisms
<b>LOEC</b>	Lowest Observable Effect Limit
<b>mg</b>	milligram
<b>mL</b>	millilitre
<b>MRL</b>	Maximum Residue Limit
<b>MSDS</b>	Material Safety Data Sheet
<b>NDPSC</b>	National Drugs and Poisons Schedule Committee
<b>ng</b>	nanogram
<b>NHMRC</b>	National Health and Medical Research Council
<b>NOEC/NOEL</b>	No Observable Effect Concentration/Level
<b>po</b>	oral
<b>ppb</b>	parts per billion
<b>PPE</b>	Personal Protective Equipment
<b>ppm</b>	parts per million
<b>s</b>	second
<b>sc</b>	subcutaneous
<b>SC</b>	suspension concentrate
<b>SUSDP</b>	Standard for the Uniform Scheduling of Drugs and Poisons
<b>T-Value</b>	a value used to determine the First Aid Instructions for chemical products that contain two or more poisons
<b>TGAC</b>	Technical Grade Active Constituent
<b>WHP</b>	Withholding Period



## EXECUTIVE SUMMARY

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) has considered an application to register a new agricultural chemical product, *DuPont Steward Insecticide*, which contains the new chemical indoxacarb for the control of heliothis (*Helicoverpa* spp.) in cotton (NSW, NT, QLD and WA only), as specified in the Directions For Use table on the product's label (pp. 31 – 39).

This publication outlines the regulatory considerations and summarises the data reviewed by the NRA for the proposed registration of *DuPont Steward Insecticide*. Before deciding whether to register this product and approve labels for use in Australia, the NRA invites public comment. Comments should be submitted by 17 November 2000 to the NRA at the address indicated on page 1.

The NRA has assessed the data submitted by the applicant in support of this use of indoxacarb and provides the following information for public comment.

### Public health aspects

Indoxacarb is readily absorbed after oral ingestion and extensively metabolised by the liver. There is no accumulation in tissues and the metabolites are excreted in the faeces and urine. Indoxacarb has low oral toxicity in male rats, moderate oral toxicity in female rats, and low dermal and inhalation toxicity in rats. It is a moderate eye irritant but is not a skin irritant in rabbits. Indoxacarb is a strong skin sensitising agent in guinea pigs. The product, *DuPont Steward Insecticide*, which contains 200 g/L indoxacarb (150 g/L as the active S-isomer and 50 g/L as the inactive R-isomer), has low acute oral, dermal and inhalational toxicity. The product is a slight eye and skin irritant and is a strong skin sensitiser.

In repeat dose studies in mice, rats and dogs, the main adverse effect of indoxacarb after ingestion or application of a large quantity of indoxacarb to the skin, was a mild reduction in the number of red blood cells (anaemia). At very high doses, there was depletion of blood-forming elements in the bone marrow and lymphoid organs and, in some studies in mice and rats, signs of neurotoxicity, including unsteadiness, head tilt, reduced activity and muscle weakness. It is likely that the reduction in the number of red blood cells is caused by the damaging effects of a metabolite. In long-term studies, there was no evidence of an increase in cancer. This result is further supported by several studies which showed that indoxacarb does not damage genetic material.

Indoxacarb had no effect on the reproductive behaviour or performance of rats. At doses that were not toxic to the mother, there were no effects on the foetal development of rats or rabbits.

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

## Residues in food and trade aspects

Residues in cotton and lettuce following application of radiolabelled test substance were almost exclusively due to the presence of the parent compound. No transformation products of indoxacarb were identified as being present in either crop. In animals indoxacarb was extensively eliminated in urine and faeces. In hens and goats less than 2% of the radiolabelled dose was present in tissues at sacrifice. A residue definition of indoxacarb per se is adequate for monitoring Good Agricultural Practice (GAP).

The applicant provided residue data from 5 Australian trials and 11 US trials that were considered to comply with proposed Australian GAP. Taken as a whole the residue data support the establishment of a MRL of 1 mg/kg for cotton seed.

Evaluation of animal transfer data and predicted dietary burdens indicates that the following animal commodity MRLs are required: meat [in the fat] 0.5 mg/kg, edible offal \*0.01 mg/kg and milk 0.05 mg/kg. An MRL of \*0.05 mg/kg is recommended for cotton seed meal and hulls.

Registration of *DuPont Steward Insecticide* should not pose an undue risk to human health or Australia's export trade.

The following amendments to the MRL Standard are recommended:

<b>Compound</b>	<b>Food</b>	<b>MRL (mg/kg)</b>
<b>DELETE:</b>		
Indoxacarb	SO 0691 Cotton seed	T 3
	MM 0095 Meat (mammalian) [in the fat]	T 0.2
	ML 0106 Milks [in the fat]	T 0.5
	MO 0105 Edible offal (mammalian)	T *0.01
<b>ADD:</b>		
Indoxacarb	SO 0691 Cotton seed	1
	MM 0095 Meat (mammalian) [in the fat]	0.5
	ML 0106 Milks	0.05
	MO 0105 Edible offal (mammalian)	*0.01

T = Temporary

\* = At or about the Limit of Quantitation (LOQ)

**Table 4**

<b>Compound</b>	<b>Animal Feed Commodity</b>	<b>MRL (mg/kg)</b>
ADD: Indoxacarb	Cotton seed meal and hulls	*0.05

\* = At or about the Limit of Quantitation (LOQ)

The following withholding period statements are recommended to support the above MRLs:

Harvest

Cotton: DO NOT harvest for 28 days after application.

Grazing

Cotton: DO NOT allow livestock to graze crops, stubble or gin trash that may have been treated with Steward Insecticide.

**Occupational health and safety aspects**

The National Occupational Health and Safety Commission (NOHSC) has conducted a risk assessment on *DuPont Steward Insecticide* containing indoxacarb at 200 g/L (75:25 R-S isomers) as a suspension concentrate. *DuPont Steward Insecticide* can be safely used by workers when handled in accordance with the control measures indicated in this assessment.

Indoxacarb and *DuPont Steward Insecticide* were classified as hazardous substances in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances. Hazardous substances are subject to workplace controls outlined in NOHSC publications.

*DuPont Steward Insecticide* will be formulated overseas and will be imported as a finished product.

*DuPont Steward Insecticide* will be applied to control *Helicoverpa* spp. in cotton, either by ground rig (blanket or banded spray) or by aerial application.

Workers may become contaminated with *DuPont Steward Insecticide* during mixing, loading, spraying, cleaning up product spills, maintaining equipment, human flagging or at re-entry. The main hazards associated with *DuPont Steward Insecticide* are skin irritation and skin sensitisation. During mixing and loading, as well as spray application, workers should wear cotton overalls buttoned to neck and wrist and a washable hat and elbow length PVC gloves.

NOHSC has recommended to the NRA the following re-entry and precautionary statements on the final product label:

Re-entry: Do not allow entry into treated areas until the spray has dried. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrist and a washable hat and chemical resistant gloves. Clothing must be laundered after each day's use".

Precaution: Human flagging is not supported unless flaggers are protected by engineering controls such as vehicles with cabs.

## **Environmental aspects**

Indoxacarb hydrolyses quickly at pH 9 with a half-life of 1 day, and very slowly at pH 5 (half-life > 400 d) to the main product of IN-KT413. Photolysis is moderate with half-lives of 3.2 – 4.0 d in aqueous solutions but very slow on soil. Aerobic metabolism in soil was generally rapid initially with DT<sub>50</sub> values of 3 – 23 d but was followed by a slow lag phase with a wide range of metabolites; however, the DT<sub>50</sub> was >120 d in one soil which is moderately persistent to persistent. The insecticidally active metabolite IN-JT333 was slightly persistent. In anaerobic soil flooded with water, the half-life in water was 6 d with a DT<sub>50</sub> of 26 – 35 d for the whole water-soil system and metabolites of IN-JT333 and IN-KT413. The DT<sub>50</sub> values in three natural water, sediment and whole systems were 2, 28 – 39 and 10 – 17 d, respectively. In batch studies, parent indoxacarb was slightly mobile to non-mobile in four soils while IN-JT333 showed even lower mobility and the maximum leaching of aged residues was 16% of parent travelling 5 cm through a loam soil column. Field dissipation DT<sub>50</sub> values were variable at 16 – 114 d but generally followed a relatively rapid initial loss followed by a long lag phase (biphasic); both parent and IN-JT333 were detected mostly in the top 15 cm of soil and rarely in lower depths. Calculations show accumulation in soils and water/sediment systems is not expected. The bioconcentration factor (BCF) in whole bluegill sunfish was 1130 – 1560 with a maximum of 22,000 in whole fish lipids. The active S isomer had the lowest BCF of 76 – 104 compared to the inactive R isomer's BCF of 2000 – 2500.

Indoxacarb was moderately toxic to northern bobwhite quail in single oral dose and 5-d dietary exposures, but slightly to practically nontoxic to mallards in the dietary exposures. The metabolite IN-JT333 was slightly toxic to quail in a single dose. Chronic one-generation dietary exposures to bobwhite determined NOEC and LOEC values of 118 and 613 mg a.i./kg food, respectively, while the chronic NOEC to mallards was >613 mg a.i./kg food. Rainbow trout and bluegill sunfish were highly to very highly sensitive to indoxacarb in various formulations and technical IN-JT333. However, the proposed *DuPont Steward Insecticide* caused no mortality or sublethal effects to bluegills at 0.85 mg a.i./L. Only slight toxicity was observed on early life stages of rainbow trout with a maximum acceptable toxicant concentration of 0.15 mg a.i./L and a low acute to chronic ratio of 3.4. The metabolites IN-KT413 and IN-JU874 were at worst moderately toxic to trout with no effect at 1.06 mg/L and a 96-h LC<sub>50</sub> between 13 and 21 mg/L, respectively. Indoxacarb as the TGAC or formulated (including as the proposed *DuPont Steward Insecticide*) was highly toxic to daphnids in 48-h experiments, as was the metabolite IN-JT333. However, the parent compound was only moderately toxic to daphnids in chronic 21-d exposures resulting in an acute to chronic ratio

of about 11. IN-KT413 at 0.967 mg/L caused 15% immobility resulting in a 48-h EC<sub>50</sub> >0.967 mg/L. Indoxacarb was also moderately toxic to mysid shrimp in 28-d tests. A green alga was not affected by indoxacarb (and less sensitive to IN-JT333) at the single concentrations tested in the various Tier I limit studies; 72-h NOEC and LOEC values to the proposed *DuPont Steward Insecticide* formulation were <620 and 620 µg a.i./L, respectively. The TGAC caused no effect to duckweed after 14 d at 63.2 µg a.i./L.

Both the TGAC and IN-JT333 were slightly toxic and IN-KG433 was very slightly toxic to earthworms but the proposed *DuPont Steward Insecticide* was highly toxic to honey bees in 48-h oral and contact exposure experiments in the laboratory. Although only transient adverse effects were observed when actively foraging bees were directly sprayed at 50 g a.i./ha in semifield studies, it is unknown what effect the maximum proposed rate for *DuPont Steward Insecticide* of 127.5 g a.i./ha would have. Mixed results were seen on predatory mites with one study showing adverse effects on juvenile mortality and eggs laid when apple leaves were treated at 61.7 g a.i./ha but not the following year when trees were treated at 50 g a.i./ha. Other field studies on grapes and apples found no adverse effects on mites at 44.5 – 77.4 g a.i./ha with 3 – 6 applications and a laboratory study found no effect at up to 100 g a.i./ha on certain parameters. Up to six sprays of 50.1 g a.i./ha on cabbage plants had no effect on adult and larval hoverflies, but a parasitic wasp suffered ≥93% mortality with treatments as low as 5 g a.i./ha. A different wasp species experienced 35 – 88% mortality after exposure to cabbage plants sprayed one, three and six times at 50 g a.i./ha. In a field study on cotton in NSW, mean differences were significant for ants, pirate bugs, predatory bugs (not identified to species) and unspecified predators at 127.5 g a.i./ha. Only transient effects on beetles and predatory bugs were seen in a similar study in Qld. A concentration of 0.23 mg a.i./kg soil caused no lasting adverse effect on microbial nitrification or respiration processes with a tolerable deviation in the nitrate concentration at 28 DAT. A loamy sand treated at 0.132 and 1.32 mg a.i./kg soil dw (equivalent to 0.78 and 7.8 times the application rate for *DuPont Steward Insecticide*) showed deviations from controls of <10% at 28 DAT indicating negligible effect. The metabolite IN-JT333 at 0.08 mg/kg soil also caused a tolerable effect on nitrification at 42 DAT and negligible effect on respiration by 28 DAT. IN-KG433 at 0.0756 mg/kg soil caused negligible deviations of <16% from controls at 28 DAT.

The environmental hazard of indoxacarb will be highest to organisms living in the vicinity where it will be applied possibly tank mixed with amitraz as an ovacide. Surface water, uncultivated land and nearby non-target areas are likely to be contaminated through spray drift and/or run-off of material sorbed to soil particles. There is no expected hazard to bobwhite quail, mallard ducks, earthworms, terrestrial plants or soil microbial processes from either acute or chronic exposures to indoxacarb residues. However, the hazard to honey bees and parasitic wasps (*Aphidius colemani* and *Diaeretiella rapae*) is unacceptable unless mitigated by restricted use or label warnings of the hazard to users. A similar unacceptable hazard exists for ants, pirate bugs, beetles and other arthropods (unspecified as to species in submitted studies) which were adversely affected by the proposed use of *DuPont Steward Insecticide* in cotton fields in Australia. The hazard of *DuPont Steward Insecticide* to predatory mites and hoverflies could not be assessed as ecotoxicology tests were not performed using the maximum proposed application rate. The direct overspray of a water body with *DuPont Steward Insecticide* represents an unacceptable hazard for a range of organisms, but a worst case spray drift of 10% reduces the hazard from the parent compound to an acceptable level. Terrestrial plants are not expected to be adversely affected by the

proposed use of *DuPont Steward Insecticide* as it is proposed for use on cotton and indoxacarb is proposed for use on other plants in other EUPs.

The hazard of various metabolites could only be assessed for those organisms for which ecotoxicity studies were submitted. IN-JT333 is not expected to be a hazard to birds, earthworms and soil microbial processes. If minimum buffer zones of 100 and 300 m as specified by the cotton best management practices manual are used for ground and aerial applications respectively, the hazard to fish and aquatic invertebrates is expected to be acceptably low. IN-KG433 is not expected to be a hazard to earthworms but presents an unknown hazard to soil microbes. IN-KT413 poses an acceptable hazard to rainbow trout and daphnids (and is similarly expected to aquatic plants) in the worst case of a direct overspray.

### **Efficacy and phytotoxicity aspects**

Indoxacarb is the first member of a new insecticide group the oxadiazines, effective against resistant populations of *H. armigera* and less disruptive to beneficial insect species than traditional broad-spectrum groups. Indoxacarb has a novel mode of action with no known cross-resistance to existing chemical groups in *Helicoverpa* species. This will significantly contribute to our ability to effectively rotate chemical groups, essential for the successful implementation of Insecticide Resistance Management (IRM). Indoxacarb will be an extremely useful management tool in cotton, both in terms of IPM and IRM.

Trials carried out under a range of conditions and soil types typical of those experienced during the Australian cotton season give a thorough indication of the efficacy of the product. Details of the proposed label for *DuPont Steward Insecticide* are explained and supported by data in the submission.

*DuPont Steward Insecticide* alone shows no phytotoxicity to cotton in the submitted trial data. Limited (acceptable) phytotoxicity to cotton was reported in one of the trials with *DuPont Steward Insecticide* in mixture with amitraz. Greater selectivity of this product to a range of beneficial insect species common in cotton growing systems, compared with broad-spectrum alternatives (such as endosulfan and bifenthrin), is consistent with a good potential fit for *DuPont Steward Insecticide* in cotton IPM.

## INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed application of the chemical indoxacarb as an insecticide for the control of *Heliothis* spp. in cotton. It also seeks public comment prior to the chemical product being approved for use in Australia.

Responses to this public consultation will be considered prior to registration of the product detailed in this document. They will be taken into account by the NRA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Copies of full technical reports on toxicology, occupational health and safety, environmental impact, and residues in food are available from the NRA on request.

Written comments should be received by the NRA by 17 November 2000, and be sent to:

Mr Gavin Hall  
Senior Product Evaluator  
Agricultural and Veterinary Chemicals Evaluation  
National Registration Authority  
PO Box E240  
KINGSTON ACT 2604  
Fax: 02 6272 3218

### **Applicant**

Du Pont (Australia) Limited has applied for registration of an insecticide product containing a new active constituent, indoxacarb, for use in cotton.

### **Active Constituent**

Indoxacarb is a racemic mix of R and S isomers (25:75). Only the S-isomer is insecticidally active. For the purposes of labelling, indoxacarb will be declared as the racemic mix accompanied by the level of active isomer. Where this document describes "indoxacarb", it refers to the racemic mix.

### **Product details**

Indoxacarb will be marketed under the trade name *DuPont Steward Insecticide*, a suspension concentrate product containing 200 g/L INDOXACARB (25:75) (equivalent to 150 g/L active S-isomer).

*DuPont Steward Insecticide* will be formulated and packed outside Australia.

Du Pont (Australia) Limited intends to market *DuPont Steward Insecticide* for the control of *Helicoverpa* spp. in cotton (NSW, NT, QLD and WA only).



## CHEMISTRY AND MANUFACTURE

### Active Constituent

The active constituent, indoxacarb, is manufactured in the USA by Du Pont Agricultural Products, Mobile Manufacturing Centre, Highway 43, Azis, Alabama 36505.

### Chemical characteristics of the active constituent

Common name: Indoxacarb

Synonyms and code number: DPX-MP062 (S:R ratio 75:25), DPX-JW062 (S:R ratio 50:50)

Chemical names: (CAS): (R,S)-methyl-7-chloro-2,5-dihydro-2-[[methoxycarbonyl][4-trifluoromethoxyphenyl]amino]carbonyl]-indeno-[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate.

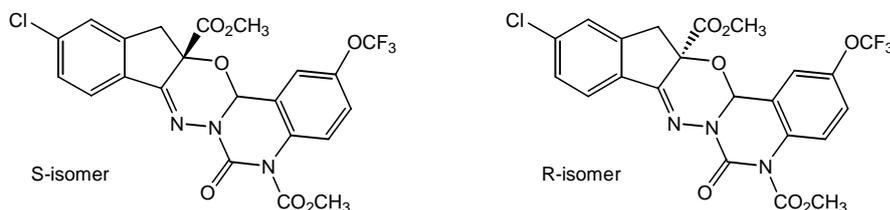
(IUPAC): (R,S)-7-chloro-3-[methoxycarbonyl-(4-trifluoromethoxyphenyl)-carbamoyl]-2,5-dihydro-indeno-[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylic acid methyl ester .

CAS Number: 144171-61-9 (1:1 mixture of R and S-indoxacarb)  
173584-44-6 (3:1 S:R isomer mixture)

Molecular formula:  $C_{22}H_{17}ClF_3N_3O_7$

Molecular weight: 527.84 g/mol

Chemical structure: Indoxacarb has one chiral centre. Two enantiomers are possible. The S isomer (DPX-KN128) is the insecticidally active isomer, while the R isomer (IN-KN127) is insecticidally inactive. Indoxacarb TGAC contains a mixture of S and R isomers in the approximate ratio of 3:1 respectively.



### ***Physical and Chemical properties of the Active Constituent***

Physical state:	solid
Colour:	white
Odour:	mild, innocuous
MP:	87.7 – 88.5°C
Density:	1.44 g/mL at 20°C
Solubility in water:	0.20 mg/L at 25°C
Solubility in n-octanol:	9.49 mg/mL at 25°C.
Vapour pressure:	$9.8 \times 10^{-9}$ Pa (20°C); $2.5 \times 10^{-8}$ Pa (25°C)
Octanol/water partition coefficient:	$\log P_{OW} = 4.60$
Storage stability:	Indoxacarb (technical material) was shown to be stable for 14 days at 54°C; 14 days at 27°C under continuous artificial sunlight; 32 days at 27°C in dark in presence of ferric and ferrous ions.
Pesticide group:	Insecticide
Chemical family:	Oxadiazine derivative

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of the Indoxacarb TGAC (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. On the basis of the data provided, it is proposed that the following minimum compositional standard to be established for indoxacarb manufacturing concentrate:

#### *Active constituent*

Indoxacarb            Not less than 467 g/kg active S-isomer.

## **Product**

Formulation type:	Suspension concentrate
Active constituent:	200 g/L Indoxacarb (equivalent to 150 g/L active S-isomer)
Mode of action:	Indoxacarb inhibits the entry of sodium ions into the target pest nerve cells, resulting in paralysis and death.

### ***Physical and chemical properties of the product***

Physical state:	suspension concentrate
Colour :	ivory
Odour:	cooking oil
pH:	3.7 (1% aqueous solution))
Density:	1.039 g/mL (25°C)
Viscosity:	530 cp (30 rpm), 1440 cp (6 rpm)
Storage stability:	stable for 14 days at 54°C
Corrosive hazard:	not corrosive to packaging materials

The source of the Technical Grade Active Constituent to be used in the products has been approved by the NRA (approval number 51669).

Specifications for the inactive constituents were provided and are acceptable. A review of the product chemistry data supports the registration of *DuPont Steward Insecticide*.

## TOXICOLOGICAL ASSESSMENT

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 at which no adverse health effects in humans would be expected.

### **Toxicokinetics and Metabolism**

After oral administration to rats, indoxacarb was readily absorbed. The compound was equally excreted in the faeces (33 – 47%) and urine (35 – 45%). The elimination half-life was shorter in male rats (35 hours) than in females (52 hours). Elimination in bile accounted for 17 – 23% of the administered dose. Indoxacarb was extensively metabolised; only small amounts of parent compound were detected in the faeces (1 – 5%) and no parent compound was detected in urine or bile. No single metabolite accounted for more than 4% of the dose. There was no evidence of tissue accumulation of indoxacarb.

### **Acute Studies**

Indoxacarb has low oral toxicity in male rats (LD<sub>50</sub> 1730 mg/kg bw) and moderate oral toxicity in female rats (LD<sub>50</sub> 268 mg/kg bw), low dermal toxicity (LD<sub>50</sub> >5000 mg/kg bw), and low inhalation toxicity (LC<sub>50</sub> >5400 mg/m<sup>3</sup> in males and 4200 mg/m<sup>3</sup> in females) in rats. It is a moderate eye irritant but is not a skin irritant in rabbits. Indoxacarb is a strong skin sensitising agent in guinea pigs.

*DuPont Steward Insecticide* (150 g/L S-indoxacarb as a suspension concentrate) has low acute oral toxicity (LD<sub>50</sub> 751 mg/kg in females), low dermal toxicity (LD<sub>50</sub> >5000 mg/kg) and low inhalational toxicity (LC<sub>50</sub> >2700 mg/m<sup>3</sup>/4h) in rats. The product is a slight eye and skin irritant and is a strong skin sensitiser in guinea pigs.

### **Short-Term Studies**

In a 28-day study, indoxacarb was applied to the skin of rats at 0, 50, 500, 1000 or 2000 mg/kg/day. Body weight gain was decreased during the first two weeks of treatment. All animals at 1000 and 2000 mg/kg/day had evidence of mild haemolytic anaemia, but significant decreases in indicators of circulating erythrocyte mass, red blood cells, haemoglobin and haematocrit were found only in females at 2000 mg/kg/day. Increased mean corpuscular volume and polychromatophil numbers indicated that the anaemia had elicited a bone marrow regenerative response.

Mice fed diets containing indoxacarb at concentrations of 0, 12, 59, 118, 235, 400, 1225 and 2450 ppm for 28 days showed excessive toxicity at 2450 and 1225 ppm. Body weight gain, food consumption and food efficiency was decreased in males and females at 235 and 400 ppm and in males at 118 ppm. At 235 and 400 ppm, abnormal gait, head tilt and tremors were suggestive of neurotoxicity. The NOEL in this study was 59 ppm (10.8 mg/kg/day) in males and 118 ppm (21.5 mg/kg/day) in females.

Rats were fed diets containing indoxacarb at concentrations of 0, 12, 29, 59, 118, 235 or 400 ppm for 28 days, resulted in deaths of 3/5 females at 400 ppm and 2/5 females at 235 ppm. Females at 400 ppm showed abnormal gait and dehydration and, at 235 ppm had pallor and ruffled fur. There were no clinical signs of toxicity in the males. Male rats at 400 and 235 ppm and females at 59, 118, 235 and 400 ppm showed significant decreases in body weight gain. In females, food consumption was decreased at 118 ppm and food efficiency was reduced at 235 ppm. The NOEL in this study was 118 ppm (8.85 mg/kg/day) in males and 29 ppm (2.61 mg/kg/day) in females.

In a dose range-finding study, dogs were fed indoxacarb in the diet for 21 days at concentrations of 0, 900 or 1280 ppm, equivalent to 0, 26 and 43 mg/kg/day, respectively, for males and 0, 15 and 29 mg/kg/day, respectively, for females. At both 900 and 1280 ppm, body weights and food consumption were decreased throughout the treatment period. There was evidence of haemolysis (decreased RBC, Hb, Hct and increased MCV, MCH and platelet count, Heinz bodies and reticulocyte counts) and liver weights were increased, but no other gross pathological changes were noted.

Mice fed diets containing 0, 35, 75, 150 or 300 ppm indoxacarb for 90 days showed clinical signs suggestive of neurotoxicity (abnormal posture/gait/mobility) at 150 ppm (females) and 300 ppm (males and females). Males and females at 300 ppm showed reduced body weight gain, food consumption and food efficiency. There was evidence of mild haemolysis at 75 ppm and above (increased reticulocyte counts, leukocytosis and increased incidence of Heinz bodies), mild increased incidence of haemosiderin deposits and erythropoiesis in the spleen and liver, and small spleens with microscopic evidence of lymphoid depletion in the spleen. The NOEL was 35 ppm (5.5 mg/kg/day for males and 7 mg/kg/day for females), based on increased reticulocyte counts and/or microscopic evidence of mild haemolysis at the higher dose levels.

Rats fed indoxacarb at dietary concentrations of 0, 10, 25 (females only), 50, 100 or 200 (males only) ppm for 90 days showed decreased food consumption, food efficiency and body weight loss during the first 2 weeks. Females at 100 ppm had weakness and ataxia during weeks 1 to 3. Male rats at  $\geq 50$  ppm and females at all dose levels showed evidence of mild haemolytic anaemia (decreased RBC, Hb, Hct). Increased MCV, suggestive of a bone marrow regenerative response, was also observed in these groups. Histopathology revealed increased haemosiderin in macrophages in the liver and/or spleen, with evidence of haemopoiesis in the spleen. Female rats at 100 ppm found dead or killed *in extremis* showed atrophy of the spleen, thymus and/or bone marrow, due to loss of lymphoid and haemopoietic cells. Haemoglobin pigment was also observed in the kidneys of early-death rats, suggesting that haemolysis may have been a factor, while surviving rats showed evidence of phagocytosis of erythrocytes by hepatic and splenic macrophages. A NOEL could not be established in this study due to the presence of mild haemolytic anaemia at the lowest dose (10 ppm, equal to 0.76 mg/kg/day) in females.

Rats fed indoxacarb in the diet at 0, 15 (females only), 30, 60, 125 or 250 (males only) ppm for 90 days, gained less body weight than controls, and had decreased food consumption and/or food efficiency throughout the study. Male rats at 250 ppm and females at 125 ppm showed a statistically significant reduction in RBC, Hb and/or Hct, with increases in MCV and reticulocyte counts, indicative of mild haemolytic anaemia. Histopathology revealed increased haemosiderin in the spleen and liver of male and female rats at 30 ppm and above, with increased erythrocytic hyperplasia in the spleen and bone marrow. The NOEL for female rats was 15 ppm (0.99 mg/kg/day). A NOEL for males could not be established in this study, due to microscopic evidence of mild haemolysis at the lowest dose level (30 ppm, equivalent to 1.9 mg/kg/day)

Rats fed diets containing 0, 3 (females only), 8, 20, 50, 100 or 200 (males only) ppm indoxacarb for 90 days showed reduced body weight gain in the higher dose groups (males at 200 ppm and females at 50 and 100 ppm), with decreased food consumption and/or food efficiency throughout the study. Males and females at 20 ppm and above showed a small but statistically significant reduction in RBC, Hb and/or Hct, with increases in MCV and reticulocyte counts, indicative of mild haemolytic anaemia. Histopathology revealed increased haemosiderin in the liver at 200 ppm (males) and 100 ppm (females), and increased haemosiderin and/or erythrocytic hyperplasia in the spleen of male rats at 50 ppm and above and female rats at 20 ppm and above, with an increased incidence of bone marrow hyperplasia (female rats at 50 ppm and above). The NOEL was 8 ppm for males and females (0.56 mg/kg/day for males and 0.68 mg/kg/day for females).

Dogs were fed diets containing 0, 40, 80, 160 or 640 ppm indoxacarb for 90 days. In females at 640 ppm, food consumption was reduced during the first 8 weeks and body weight and/or body weight gain was reduced sporadically throughout the study. Mild anaemia (decreased RBC, Hb and Hct, increased serum bilirubin, Heinz bodies) was seen in both sexes at 160 and 640 ppm. Microscopically, haemosiderin was present in the spleen and liver of male and female dogs at 40 ppm and above, and in the kidneys and bone marrow (with erythrocytic hyperplasia of the spleen and bone marrow) of females at 40 ppm and males at 80 ppm. A NOEL could not be established in this study, due to evidence of haemolysis at the lowest doses (1 mg/kg/day for both sexes).

### **Long-Term Studies**

Mice were fed indoxacarb in the diet at 0, 20, 100 or 200 ppm for 18 months; the concentration of indoxacarb in the diet at the highest dose level was reduced to 150 ppm at 4 months and then to 125 ppm at 9 months, because of excessive deaths. Clinical signs suggestive of neurotoxicity, including abnormal gait/mobility and head tilt, were observed in males at 200/150/125 ppm and females at 100 ppm and above, with histological evidence of neuronal degeneration. Body weights or body weight gain were significantly decreased in the two highest dosage groups. In mice dying during the study, the cause of death was attributed to CNS disorder or heart inflammation/necrosis (males only). At the end of the study, male mice fed 200/150/125 ppm indoxacarb had red fluid in the pleural cavity, with necrotic, haemorrhagic, inflammatory heart lesions. In male and female mice (200/150/125 ppm), lymphoid depletion in the spleen was noted. There were no treatment-related neoplastic changes in any group. The NOEL in this study was 20 ppm for males and females, equivalent to 2.63 mg/kg/day for males and 3.99 mg/kg/day for females, based on decreased body weight gain and food efficiency at the higher dose levels.

Rats were fed indoxacarb in the diet at 0, 10 (females only) 20, 40, 60, 125 or 250 (males only) ppm for 24 months. There was no difference in survival between treated groups and controls at the end of the study; however, in 125 ppm females a small but statistically significant increase in deaths (7/70) of undetermined cause occurred during the first year of the study; these rats had bone marrow atrophy, splenic lymphoid depletion and/or thymic necrosis. Female rats at 125 ppm had an increased incidence of hair loss. Food consumption and body weight gain were decreased in males at 125 and 250 ppm and in females at 60 and 125 ppm, especially during the first year. Female rats at 40 ppm and above had mild haemolytic anaemia, consisting of decreased RBC, Hb and Hct, with minimal increases in reticulocyte counts and erythrocyte macrocytosis in these groups. In males and females dosed at 125 ppm and above, increased spleen weights, splenic congestion and increased haemosiderin in macrophages of the spleen and liver were noted at necropsy. There were no treatment-related neoplastic changes in any group. The NOEL in this study was 60 ppm (2.4 mg/kg/day) for males and 20 ppm (1.04 mg/kg/day) for females, based on decreased body weight gain and food consumption and haemolysis at the higher dose levels.

Dogs fed indoxacarb in the diet at 0, 40, 80, 640 or 1280 ppm for 52 weeks, showed no treatment-related clinical signs and there were no deaths during the study. Food consumption and body weight gain were decreased in the 1280 ppm group, especially during the first 3 months. Throughout the study, there was a dose-related decrease in indicators of circulating erythrocytic mass (RBC, Hb and Hct) in the 640 and 1280 ppm groups, with increased numbers of Heinz bodies and increased mean reticulocyte counts. Other haematologic changes secondary to haemolytic anaemia in these groups included increased MCV, decreased MCHC, erythrocyte morphologic changes (Howell-Jolly bodies, polychromasia and hypochromasia) and/or increased mean platelet counts, and increased serum bilirubin. Minor haemolytic effects were also seen at 40 ppm (males) and at 80 ppm (males and females). Mean absolute and relative liver weights in the 640 ppm males and 1280 ppm groups were increased. Increased haemosiderin deposits were observed in the liver, spleen, kidneys and/or bone marrow of all treated groups. There was evidence of extramedullary haemopoiesis in the spleen and minimal to mild bone marrow hyperplasia, consistent with a secondary physiological response to indoxacarb-induced haemolysis. A NOEL could not be established in this study due to the presence of haemolytic anaemia at the lowest dose level (40 ppm, equivalent to 1.1 mg/kg/day for males and 1.3 mg/kg/day for females).

### **Reproduction and Developmental Studies**

Male and female rats were fed indoxacarb (0, 20, 60 or 100 ppm) in the diet from at least 70 days before mating until 21 days after parturition, throughout two generations. Parental body weight gain and food consumption was reduced in males at 100 ppm and females at 60 and 100 ppm, and absolute and relative spleen weights were increased in these groups.

Reproduction and fertility indices were unaffected by treatment. The weights of pups in the 60 and 100 ppm groups were reduced during the lactation period, possibly as a result of maternal weight loss. Absolute and relative spleen weights were increased in F<sub>1</sub> females at 100 ppm. Microscopic examination of 4 rats from the 100 ppm group showed mild to moderate splenic extramedullary haematopoiesis and haemosiderin pigmentation. The NOEL for parents and offspring in this study was 20 ppm (approximately 1.25 mg/kg/day in males and 1.5 mg/kg/day in females) based on reduced food consumption and body weight gain at the higher dose levels.

In a pilot study, pregnant rats were administered indoxacarb (0, 20, 40, 80 or 160 mg/kg) by gavage on gestation days 7 to 21. All rats in the 40, 80 and 160 mg/kg/day groups died and, in the 20 mg/kg group, 5/8 rats died. All deaths were preceded by clinical signs of toxicity (ataxia, diarrhoea, head shake, hunched appearance, salivation, stained/wet fur) and marked decrease in body weight and food consumption. The 3 surviving dams had similar litter size and numbers of viable foetuses to controls. The live foetuses were extremely small, but no treatment-related alterations were seen.

Pregnant rats were administered indoxacarb (0, 0.5, 1, 2 or 4 mg/kg) by gavage from days 7 to 21 of gestation. Maternal body weight gain and food consumption was reduced at 4 mg/kg/day. Hair loss was noted in rats from each of the 2 and 4 mg/kg/day groups. In the 4 mg/kg/day group there was a significant decrease in mean foetal weight (4.79 g) compared with controls (5.12 g), but no other effect on foetal development, including the incidence of foetal alterations. The maternal and developmental NOEL in this study was 2 mg/kg/day, based on lower maternal and foetal body weight at the higher dose level.

Pregnant rats were administered indoxacarb (0, 10, 100, 500 or 1000 mg/kg) by gavage from days 7 to 21 of gestation. Maternal deaths and decreases in body weight gain and food consumption occurred at doses of 100 mg/kg/day and above, and clinical signs of hair loss, abnormal gait/mobility, weakness, hunched posture and distension, haemorrhage, and white/yellow/orange pasty contents in the gastrointestinal tract were noted. At 100 mg/kg and above, there was a significant reduction in the number of foetuses per litter, and mean foetal weight was significantly reduced at 500 and 1000 mg/kg. The NOEL for maternal and foetal toxicity in this study was 10 mg/kg, based on lower maternal and foetal body weight, maternal clinical signs and reduced number of live foetuses at the higher dose level.

Pregnant rabbits were administered indoxacarb (0, 250, 500 or 1000 mg/kg) by gavage from days 7 to 28 of gestation. At 1000 mg/kg/day, there were no deaths but maternal body weight gain and food consumption were reduced throughout the dosing period. Mean foetal weight was significantly reduced at 1000 mg/kg and there was a significant increase in retarded sternebral ossification. There was no effect of treatment on the foetal viability or sex ratio. The maternal and developmental NOEL in this study was 500 mg/kg/day, based on lower maternal and foetal body weight and retarded foetal ossification at the higher dose level.

### **Genotoxicity**

Indoxacarb was not genotoxic in the following assays: *S. typhimurium* and *E. coli* reverse mutation assays at concentrations up to 5000 µg/plate (with and without metabolic activation); *in vitro* mammalian (human peripheral lymphocyte) cytogenetics assay at up to 1000 µg/mL (with and without metabolic activation); mammalian gene mutation (CHO/HGPRT) assay at up to 1000 µg/mL (with and without metabolic activation); unscheduled DNA synthesis in primary rat hepatocytes (up to 200 µg/mL); and a mouse bone marrow micronucleus assay (1000-4000 mg/kg).

### **Other Studies**

Two neurotoxicity studies were conducted in rats. Single doses of up to 100 mg/kg (females) or 200 mg/kg (males) indoxacarb by oral gavage produced reduced body weight gain and food consumption at the highest doses. Females at 50 mg/kg showed hair loss, pallor and at 100 mg/kg, slightly reduced motor activity. Toxicity in male rats included reduced forelimb grip strength and decreased foot splay (200 mg/kg). Administration of indoxacarb in the diet

to young adult rats, at up to 200 ppm (males) and 100 ppm (females) for 90 days, resulted in 3/12 deaths in females (100 ppm) between days 9-11 but no dose-related clinical signs in surviving rats from any group. Hair loss was noted in some females at 50 and 100 ppm. Males at 100 and 200 ppm and females at 50 and 100 ppm showed reduced body weight gain associated with reduced food consumption and food efficiency. There were no treatment-related effects on any of the parameters evaluated in motor activity or functional observational battery assessments. There was no histopathological evidence of neurotoxicity in either study.

The occurrence of Heinz bodies and increases in methaemoglobin concentration suggest that the haematological effects produced by indoxacarb are the result of oxidant effect on red blood cells. The oxidant effects likely involve an arylamine metabolite and are dependent on the biotransformation of the arylamine to its N-hydroxylamine. Species differences in susceptibility to oxidant stress have been reported for a number of haemolysins. In general, the red cells of dogs have been shown to be more sensitive to oxidant stress than those of humans. The increased susceptibility of the dog compared to human may be related to the lower concentration of reduced glutathione in canine erythrocytes and/or to lower activity of the erythrocyte pentose phosphate pathway.

## **Public Health Standards**

### ***Poisons Schedule***

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

The NDPSC recommended that indoxacarb be listed in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first-aid directions on the draft product label.

### ***NOEL/ADI***

The lowest NOEL was 1.04 mg/kg/day (females) in a rat 2-year study. However, in the dog 12-month study, a NOEL could not be established. The presence of histopathological changes (indicating a regenerative response secondary to haemolysis) at the lowest dose level (1.1 mg/kg/day in males) in the 12-month dog study, indicates that an additional safety factor of 10 is warranted. Although it is likely that the dog is more sensitive than most humans to the oxidant effect of indoxacarb on red blood cells, the presence of a highly susceptible human subpopulation justifies retention of the additional 10-fold safety factor. Using a safety factor of 1000, an ADI of 0.001 mg/kg/day was chosen for indoxacarb.

## RESIDUES ASSESSMENT

Data concerning residues in cotton, metabolism in plants and animals, environmental fate and chemistry were considered as part of the residue evaluation of the application.

### Metabolism

In cotton and lettuce the radioactive residues were almost exclusively due to the presence of the parent compound. In lettuce the parent compound generally accounted for greater than 80% of the total radioactive residues (TRR). There was some chromatographic evidence of polar compounds however these were not present at significant levels. In cotton plants, greater than 90% of the TRR was typically extracted and parent compound generally accounted for more than 80% of the TRR in the extract. No transformation products of the parent compound were identified in lettuce or cotton.

In rats, indoxacarb was extensively eliminated in urine (35 – 45% of total dose) and faeces (33 – 47% of total dose) following a single oral dose. The TRR in tissues at sacrifice accounted for 3.4 – 12.9% of the dose. <sup>14</sup>C residues were highest in fat (1.8-8.8% of total dose) with the demethoxy carbonyl metabolite (IN-JT333) accounting for up to 90% of the TRR.

In hens indoxacarb was extensively eliminated in excreta (87.0 – 87.6% of total dose). Less than 2% of the total dose was present in tissues at sacrifice, with fat accounting for 0.84 – 0.88% (0.46 – 0.51 ppm parent equivalents) of the dose. The TRR in individual egg collections was in the range equivalent to 0.02 – 0.10 ppm parent equivalents and 0.01 – 0.33 ppm parent compound equivalents for whites and yolks respectively.

In lactating cows indoxacarb was extensively eliminated in faeces (53.3 – 60.2% of total dose) and urine (19.3 – 19.8% of total dose). Less than 1% of the total dose was present in tissues at sacrifice with liver accounting for 0.447 – 0.517% (0.537 – 0.689 ppm parent equivalents) of the dose. <sup>14</sup>C residues in the total milk output accounted for 0.7 – 0.8% of the total dose. The TRR in individual milk collections was in the range equivalent to 0.023 – 0.18 ppm parent equivalents. Parent compound was the major residue component in milk (25 – 49.1% of TRR, up to 0.028 ppm, 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 perirenal fat (66.7 – 80.5% of TRR, up to 0.89 ppm). The demethoxy carbonyl metabolite (IN-JT333), which was stated to be insecticidally active, was only detected in perirenal fat (5.2-7.7% of TRR, up to 0.08 ppm). Indoxacarb residues in cream were concentrated by up to 20× compared to the residue levels in skim milk. The concentration of bile residues was high (up to 4.9 ppm) however the residues accounted for only 0.11 – 0.13% of the dose.

### Analytical methods

A validated analytical method for determination of indoxacarb residues in various crop matrices (including cotton seed) was provided. The practical Limit Of Quantitation (LOQ) in all sample types was 0.01 mg/kg. Indoxacarb was determined by GC-MSD as a single chromatographic peak following ethyl acetate extraction and SPE clean-up. HPLC-UV methods for determination of indoxacarb residues in crop samples (including cotton seed,

cotton forage, cotton trash, cotton hulls, cotton meal and cotton oil) and animal tissues (muscle, fat, kidney, liver, milk, skim milk and cream) were also provided. Samples were extracted with various organic solvents with clean-up on SPE cartridges. Determination was by HPLC-UV using an automated column switching arrangement. Practical LOQs were 0.01 mg/kg in all samples.

### **Storage stability (of residues)**

Indoxacarb residues in apples were shown to be stable for at least 18 months when stored at ~20°C. Storage stability data were also provided for grapes, grape wet pomace, wine, lettuce, tomatoes, soil and apple juice. Indoxacarb residues in these commodities were shown to be stable for at 6 – 18 months when stored frozen. Residues in cotton hulls, meal and refined oil were shown to be stable for at least 7 months when stored frozen. The maximum frozen storage interval for residue trial samples was 9.5 months a period that was covered by the storage stability trials on various crops.

Residues of indoxacarb and metabolite IN-JT333 were stable for at least 60 days in whole milk, 82 days in muscle, 90 days in fat and 90 days in liver. The maximum period between tissue collection and analysis was 42 days while the maximum period for milk samples was 77 days.

### **Residue definition**

The parent compound is considered adequate for the purposes of monitoring Good Agricultural Practice. The residue definition (MRL Standard, Table 3) will therefore be as follows:

<b>Compound</b>	<b>Residue</b>
Indoxacarb	indoxacarb

### **Residue trials**

The proposed maximum application rate is 850 mL product/ha. This is equivalent to 170 g indoxacarb/ha which gives a dose rate of 127.5 g S-isomer/ha. A ±30% tolerance extends Australian GAP to 119 – 221 g indoxacarb/ha. The applicant provided residue data from 5 Australian trials and 11 US trials that were considered to comply with proposed Australian GAP.

In trials conducted according to proposed Australian GAP (119 – 221 g indoxacarb/ha, 28 – 33 day PHI) residues in cotton seed were (median underlined): <0.02, <0.02, <0.05, 0.027, 0.067, 0.075, 0.12, 0.14, 0.14, 0.16, 0.18, 0.20, 0.28, 0.28, 0.36 and 0.46 ppm. Taken as a whole the residue data support the establishment of a MRL of 1 mg/kg for cotton seed.

### **Processing studies**

In a US trial processed fractions were obtained from cotton treated with four consecutive applications (5 day intervals) of indoxacarb at 1000 g indoxacarb/ha. The processing factors for hulls, meal and refined oil were 0.026, <0.01 and 0.036 respectively.

### **Animal feed commodity MRLs**

Based on an MRL of 1 mg/kg for cotton seed and the appropriate experimental processing factors the expected residues (dry weight basis) in cotton hulls and meal are 0.029 mg/kg and 0.0011 mg/kg respectively [ $1 \times 0.026 \times 100/90$  and  $1 \times 0.001 \times 100/88$ ]. The practical LOQ of the analytical method (as used by the Australian residue testing laboratory) was 0.05 mg/kg. An MRL of \*0.05 mg/kg is recommended for cotton seed meal and hulls.

The applicant has proposed a grazing restraint for cotton forage, stubble and trash. Consequently, no MRLs will be recommended for these items at this time.

### **Animal commodity MRLs**

In the animal transfer study the 1× feed level was equivalent to 8.42 ppm in the diet (approximately 0.3 mg/kg bw/day based on a 550 kg animal consuming 20 kg DM/day). At this feed level the maximum residues in fat, milk and offal (kidney and liver) were 0.24 mg/kg, 0.026 mg/kg and <0.01 mg/kg respectively. Residues in meat [in the fat], milk and offal would be 0.032 mg/kg, 0.0035 mg/kg (<LOQ) and <0.01 mg/kg respectively as a result of feeding 100% cotton seed containing indoxacarb at the MRL. It is recommended that animal commodity (mammalian products) MRLs be based directly on the 1× dose group in the feeding study. The appropriate MRLs are meat [in the fat] 0.5 mg/kg, edible offal \*0.01 mg/kg and milk 0.05 mg/kg.

### **Estimated dietary intakes**

The chronic dietary risk is estimated by the National Estimated Daily Intake calculation encompassing all registered and/or temporary uses of the chemical and dietary intake data from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with the *Guidelines for Predicting Dietary Intake of Pesticide Residues (revised)* (WHO, 1997). The calculation has been revised to reflect the *expected* residue levels in commodities (STMRs) rather than the *maximum* residue levels (MRLs). This is consistent with the principles for assessing chronic dietary intake which is considered to occur through a lifetime of exposure.

The refined NEDI for indoxacarb is equivalent to less than 1% of the ADI. It is concluded that the chronic dietary exposure is small and the risk is acceptable.

### **Bioaccumulation potential**

The pure active enantiomer of indoxacarb has a log P<sub>OW</sub> value of 4.65. The racemic technical material has a log P<sub>OW</sub> value of 4.6. According to the FAO definition<sup>#</sup> the compound should therefore be designated as fat soluble.

In the 28-day animal transfer study residues in whole milk plateaued by day 14. The mean concentration factor of residues in cream relative to whole milk was approximately 10×. In tissues indoxacarb was found to be preferentially distributed in the fat. Residues in muscle and offal were not detectable at the 1× dose level.

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<sup>#</sup> FAO Manual on the Submission and Evaluation of Pesticide Residues Data, Food and Agriculture Organisation of the United Nations, Rome, 1997, p 36.

Residues in milk, muscle, liver and kidney were not detectable when a 15-day depuration period was observed following 28 days dosing at 75 ppm in the diet. The residue in fat was 0.079 mg/kg after the same depuration period.

Tissue residues (mg/kg) were not magnified when compared to the dose rates (mg/kg bw) administered in the feeding study.

**Recommended amendments to the MRL Standard:**

<b>Table 1</b>		
<b>Compound</b>	<b>Food</b>	<b>MRL (mg/kg)</b>
<b>DELETE:</b>		
<b>Indoxacarb</b>	SO 0691 Cotton seed	T 3
	MM 0095 Meat (mammalian) [in the fat]	T 0.2
	ML 0106 Milks [in the fat]	T 0.5
	MO 0105 Edible offal (mammalian)	T *0.01
<b>ADD:</b>		
<b>Indoxacarb</b>	SO 0691 Cotton seed	1
	MM 0095 Meat (mammalian) [in the fat]	0.5
	ML 0106 Milks	0.05
	MO 0105 Edible offal (mammalian)	*0.01

T = Temporary

\* = At or about the LOQ

<b>Table 4</b>		
<b>Compound</b>	<b>Animal Feed Commodity</b>	<b>MRL (mg/kg)</b>
<b>ADD:</b>		
<b>Indoxacarb</b>	Cotton seed meal and hulls	*0.05

The MRL recommendations indicated above will be conveyed to the Australia and New Zealand Food Authority (ANZFA) for consideration for incorporation into Standard A14 of the Food Standards Code and consequent adoption into the State/Territory food legislation.

**Withholding periods:**

Harvest

Cotton: DO NOT harvest for 28 days after application.

Grazing

Cotton: DO NOT allow livestock to graze crops, stubble or gin trash that may have been treated with Steward Insecticide.

## ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

### Commodities exported and main destinations

Australian exports of cotton seed and related products are summarised below:

Commodity	Amount exported (1998/99) <sup>1</sup>	Major destinations <sup>2</sup>
Cotton seed	359.94 kt	USA, Japan, Korea
Cotton seed oil	1.35 kt	Japan, Korea, India
Meal	29.97 kt <sup>3</sup>	Korea
Hulls	No figure available	Korea, Japan

1. Figures from ABARE, Australian Commodity Statistics 1999
2. Information provided by Cargills Australia (major oilseed merchant)
3. Combined total of sunflower seed meal and cotton seed meal.

Australian exports of beef/veal and live cattle in 1998/99 were 855.3 kt and 511.2 kt respectively. Major export markets for beef/veal were US (285.2 kt) and Japan (320.9 kt). The value of beef/veal exports to these two markets alone was worth over \$2 billion in 1998.

### Overseas registration status

DuPont has advised that indoxacarb is currently registered for use in the following countries: USA, Columbia, Hungary, Romania, Turkey, Uzbekistan, Mali, Burkina, Benin, Chad, Cameroon, South Africa, Pakistan, Korea and Indonesia. Registration of indoxacarb is being pursued for a range of crops in Mexico, Central America, Brazil, Canada, Ecuador, Peru, Venezuela, Netherlands, Italy, Spain, France, Greece, Germany, Poland, Balkans, Egypt, Saudi Arabia, Israel, Lebanon, Jordan, Morocco, Kenya, India, Thailand, Malaysia, Taiwan, Philippines, Vietnam, China, New Zealand and Japan. The expected registration date for most countries is towards the end of 2000.

DuPont advised that the following cotton-related MRLs were *proposed* in relation to registration of indoxacarb in the US and EU:

Country	Commodity	MRL (proposed)
EU	Cotton seed	0.02
US	Cotton seed	3
	Cotton gin trash	15
	Meat	0.02 (0.75*)
	Milk	0.10 (0.75*)
	Cattle kidney	0.05

\* Based on combined residue of indoxacarb and metabolite IN-JT333

### CODEX Alimentarius Commission MRLs

Indoxacarb has not been considered by CODEX.

### Potential risk to Australian export trade

Finite residues are unlikely to occur in cotton seed meal, oil or hulls. The risk to trade from the export of these processed fractions is expected to be minimal.

Treated cotton seed may contain finite indoxacarb residues (MRL 1 mg/kg, STMR 0.14 mg/kg). The US is the only major destination for Australian cotton seed where a suitable MRL (3 mg/kg) has been proposed. It is noted that the US MRL is only a proposal (at the time of publication indoxacarb has just been registered for use in the US). Indoxacarb is registered for use in Korea and registration is pending in Japan, however no cotton seed MRLs have been proposed or established. Based on information provided by the applicant, Australia's main trading partners for cotton seed do not appear to have MRLs established for indoxacarb. As such the export of produce containing finite residues of indoxacarb may prejudice Australia's export trade.

To further reduce residues in cotton seed the applicant has proposed that application of *DuPont Steward Insecticide* be limited to crops where fewer than 30% of bolls are open. In residue trials where the last application of indoxacarb was made at <30% bolls open residues were <0.02 (5% open), <0.05 (0%), 0.067 (20%) and 0.14 mg/kg (25 – 35%). In trials where the last application was at >30% bolls open residues were 0.027 (70% open), 0.075 (50%), 0.12 (70%), 0.14 (90%), 0.16 (80%), 0.18 (50%), 0.28 (95%), 0.28 (90%), 0.36 (100%) and 0.46 (100%). Percentage of bolls open at last application was not specified for 2 trials. It is considered that application at <30% bolls open combined with normal bulking and blending of seed will reduce the risk of quantifiable residues in exported cotton seed to an acceptable level.

The likelihood of finite tissue residues occurring in cattle as a result of feeding treated cotton products is considered to be small. Cotton meal, hulls and oil are not expected to contain finite residues of indoxacarb. A grazing restraint will apply to cotton forage and trash. The only feed item that needs to be considered is cotton seed. Residues in fat are predicted to be 0.032 mg/kg (LOQ 0.01 mg/kg) if cotton seed containing indoxacarb residues at the MRL is fed to cattle at 100% of the diet. Residues in milk and offal should be <LOQ. This scenario is likely to be exaggerated as cotton seed would not normally comprise 100% of the diet. If cotton seed containing indoxacarb residues at the STMR level is fed to cattle at 25% of the diet finite residues are not expected to occur in any tissue.

It is considered that grazing of pasture contaminated by spray drift is likely to pose the greatest risk in relation to animal tissue residues. The applicant has met with Meat & Livestock Australia to discuss the residue implications of spray drift. It is expected that the risk to trade can be effectively managed through the use of buffer zones in cotton crops. Provided that residues on neighbouring pasture grazed by livestock can be limited to  $\leq 0.5$  mg/kg dry weight then the risk of finite residues in animal tissues will be small. Modelling data indicate that a buffer zone of 600m when applied aerially (200m from ground application), would be adequate to reduce off-target deposition to  $\leq 0.5$  mg/kg dry weight at the buffer edge. Provided a suitable buffer zone is established the risk to Australia's export trade in meat products from the use of indoxacarb on cotton is considered to be acceptably low.

Accordingly the NRA does not consider evaluation of depletion data for adventitious exposure of cattle to indoxacarb and the determination of a slaughter withholding period to be

necessary in this case. Comment on the acceptability and practicality of this mitigation strategy (buffer zones) is welcome.

## OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Indoxacarb is not currently included in the NOHSC *List of Designated Hazardous Substances*. However, the applicant has determined indoxacarb to be a hazardous substance, in accordance with NOHSC *Approved Criteria for Classifying Hazardous Substances*, based on its acute oral toxicity and skin sensitisation effect. The following risk and safety phrases has been assigned by the applicant:

Risk phrases:

- R22: Harmful if swallowed  
R43: May cause sensitisation by skin contact

Safety phrases:

- S24: Avoid contact with skin  
S28: After contact with skin, wash immediately with plenty of soap and water  
S36/37: Wear suitable protective clothing and gloves

Substances containing indoxacarb at concentrations  $\geq 1\%$  are classified as skin sensitiser.

Indoxacarb will be manufactured overseas as a white to off white powder with faint ethyl acetate odour. Indoxacarb has low to moderate acute oral toxicity, low acute dermal and inhalation toxicity. It is not a skin irritant but a moderate eye irritant. Indoxacarb is a strong skin sensitiser.

*DuPont Steward Insecticide* is a suspension concentrate formulation.

The applicant has classified the product, *DuPont Steward Insecticide*, as a hazardous substance, in accordance with NOHSC criteria, based on its acute oral toxicity and skin sensitisation effect. Steward has low acute oral, dermal and inhalation toxicity. It is a slight eye and skin irritant, and a strong skin sensitiser.

### Formulation, transport, storage and retailing

*DuPont Steward Insecticide* containing 200 g/L indoxacarb (equivalent to 150 g/L active S-isomer) will be formulated overseas and imported in bulk containers where it will be repacked into containers ranging from 1L to 208L. Transport and storage workers will handle the packaged product and can only be exposed if the packaging is breached.

Advice on safe handling of the active or product during routine application is provided in the Material Safety Data Sheet (MSDS) for *DuPont Steward Insecticide*.

### Use and exposure

*DuPont Steward Insecticide* will be applied either by ground rig (blanket or banded spray) or by aerial application to cotton. The draft product label states that application may occur up to a maximum of three spray applications per field per cotton growing season, but with no more than two consecutive sprays per field per season. Depending on pest pressure, the proposed application rate is 650 or 850 mL indoxacarb/ha in a minimum spray volume of 100 L water/ha (0.10 or 0.13% indoxacarb and 0.65 or 0.85% EUP).

The main routes of exposure to *DuPont Steward Insecticide* will be dermal, ocular and inhalational. Workers may become contaminated with the product during mixing, loading, spraying, cleaning up spills, maintaining equipment, human flagging or at re-entry.

There are no worker exposure studies submitted for indoxacarb and *DuPont Steward Insecticide*. The UK Predictive Operator Exposure Model (POEM) is used by NOHSC to estimate mixer/loader and applicator exposure to *DuPont Steward Insecticide* during ground (boom) spray. The risk assessment indicated that *DuPont Steward Insecticide* is safe for use at the proposed rates, provided overalls and gloves are worn during mixing/loading operations and ground application.

As exposure to flaggers cannot be quantified, the use of human flagging is not supported unless flaggers are protected by engineering controls such as vehicles with cabs.

### **Entry into treated areas or handling treated crops**

Re-entry into treated areas is possible when checking the effectiveness of the insecticide. Acute toxicity studies conducted on *DuPont Steward Insecticide* suggest that the substance can cause sensitisation in contact with skin. The low concentration of *DuPont Steward Insecticide* in the prepared spray is not expected to pose undue risk to workers who will be examining the treated crops, once the spray has dried.

### **Recommendations for safe use**

Users should follow the instructions and Safety Directions as proposed on the draft product label. Safety Directions include the use of cotton overalls buttoned to neck and wrist and a washable hat and elbow length PVC gloves when opening the container, preparing and using the spray.

The Personal Protective Equipment recommended should meet the relevant *Standards-Australia* document specified below:

AS 2161.2-1998	Occupational Protective Gloves
AS 3765-1990	Clothing for protection against hazardous chemicals

### **Product Labelling**

Re-entry: DO NOT allow entry into treated areas until the spray has dried. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrist and a washable hat and chemical resistant gloves. Clothing must be laundered after each day's use.

Precaution: Human flagging is not supported unless flaggers are protected by engineering controls such as vehicles with cabs.

### **Active constituent label**

Indoxacarb should be labelled in accordance with NOHSC *National Code of Practice for the Labelling of Workplace Substances*.

### **Material Safety Data Sheet**

Manufacturers and importers should produce an MSDS for *DuPont Steward Insecticide*. These should contain information relevant to Australian workers, as outlined in the NOHSC National Code of Practice for the Preparation of Material Safety Data Sheets. Employers should obtain the MSDS from the supplier and ensure that their employees have ready access to it.

### **Conclusion**

NOHSC supports the registration of *DuPont Steward Insecticide* containing 200 g/L indoxacarb (150g/L as the active S-isomer) as a suspension concentrate, for the control of *Helicoverpa* spp. in cotton. *DuPont Steward Insecticide* 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 MSDS for *DuPont Steward Insecticide*

## ENVIRONMENTAL ASSESSMENT

### Environmental Exposure

*DuPont Steward Insecticide*, containing the technical grade active constituent indoxacarb at 150 g a.i./L present as the active S isomer (and 50 g/L of the inactive R isomer), is proposed for the control of cotton bollworm and native budworm (*Helicoverpa* spp.) in cotton. The product may be used at either 650 or 850 mL/ha, equivalent to 97.5 or 127.5 g a.i./ha, depending on the pest pressure. A maximum of three ground band and/or aerial sprays per cotton growing season are allowed with no more than two consecutive sprays per field per season. In response to a question from Environment Australia, the company has included a statement on the draft label: “Applications must be a minimum of seven days apart”.

### Environmental Chemistry and Fate

#### *Abiotic transformation*

Indoxacarb hydrolyses quickly at pH 9 with a half-life of 1 d, moderately at pH 7 (38 d half-life) and very slowly at pH 5 (half-life > 400 d); the main hydrolysis product is IN-KT413. In aqueous solution, photolysis half-lives were 3.2 – 4.0 d in pH 5 and natural creek waters assuming 12 h of sunlight per day with a range of metabolites found. Photolysis was slower on soil with a mean half-life equivalent to 139 d of summer sunlight.

#### *Biotic transformation*

In three studies using a total of five soils, aerobic metabolism was generally rapid initially, with DT<sub>50</sub> values of 3 – 23 d, followed by a slow lag phase; however, the DT<sub>50</sub> was >120 d in one soil which is moderately persistent to persistent. The applicant commented that there is apparently no correlation between pH and degradation rate in aerobic soils and that microbial degradation is the determining factor. Main metabolites were IN-JT333, IN-KG433, IN-ML437 hydroxide, IN-JU873, IN-MK638 and IN-MK643. The insecticidally active IN-JT333 was more persistent with DT<sub>50</sub> and DT<sub>90</sub> values of 24 – 27 and 97 – 224 d, respectively, and a possible reversal in enantiomeric ratio. In soil flooded with water, the half-life in water was 6 d (nondetectable by 31 DAT) with a DT<sub>50</sub> of 26 – 35 d for the whole water-soil system and main metabolites of IN-JT333 and IN-KT413; parent compound partitioned quickly to soil and the S and R isomers degraded at an equal rate. In two systems, the DT<sub>50</sub> values in natural water, sediment and whole system were 2, 28 – 39 and 10 – 17 d, respectively, with the same major metabolites identified as in anaerobic soil-water. Initially, the radioactivity moved from the water to the sediment (35 – 51% in sediment at 0 DAT) with the polar metabolites appearing in the water and the nonpolar metabolites in the sediment.

#### *Mobility*

In conventional batch equilibrium studies, parent indoxacarb was slightly mobile to nonmobile in four soils based on K<sub>OC</sub> values of 2500 – 9600 while the metabolite IN-JT333 showed even lower mobility. The maximum leaching of aged residues was 16% of parent travelling 5 cm through a loam soil column.

### ***Field dissipation***

DT<sub>50</sub> values were variable with 16 – 17 d in two US soils while two others showed 82 and 114 d. Dissipation was biphasic with rapid initial loss followed by a relatively long lag phase. Parent compound remained mostly in the top 15 cm of soil with the metabolite IN-JT333 detected intermittently in the top 15 cm. In a second study using two of the same soils, DT<sub>50</sub> values of 60 – 63 d were intermediate with the majority of detections in the top 15 cm. IN-JT333 peaked at 14 d after treatment and was only found in the top 15 cm. In three European soils, DT<sub>50</sub> values calculated by two methods were relatively short at 6-18 d but DT<sub>90</sub> values of 60 – 111 d again showed a lag phase. Parent compound and IN-JT333 were not detected deeper than 10 cm while IN-KG433 was never detected.

### ***Accumulation***

If *DuPont Steward Insecticide* were directly applied to a 15 cm body of water at the maximum application rate of 127.5 g a.i./ha and closest three spray schedule, the resulting concentration would be 0.085 mg a.i./L. Using best and worst case DT<sub>50</sub> values of 2 – 39 d, the resulting peak concentrations in water, whole system and sediment are 0.09, 0.17 mg a.i./L and 0.21 mg a.i./kg sediment, respectively. After one year, there is no residue remaining and therefore no annual carryover.

In the worst case application rate of 127.5 g a.i./ha, the concentration of indoxacarb in the top 5 cm of soil would be 0.196 mg a.i./kg soil. Following an application schedule of weekly applications for the first two weeks, no application in the third week and then a final application in the fourth week, soil concentrations would peak at 0.38, 0.52 and 0.55 mg a.i./kg soil in the best, moderate and worst cases, respectively, after the final application. These calculations use the best, moderate and worst case field soil dissipation DT<sub>50</sub> values of 16, 60 and 114 d.

### ***Bioconcentration***

The bioconcentration factor (BCF) in whole bluegill sunfish was 1130 – 1560 with a maximum of 22000 in whole fish lipids. The active S isomer had the lowest BCF of 76 – 104 compared to the inactive R isomer's BCF of 2000 – 2500. The company commented that the disparity in BCF values between isomers is most likely due to differential metabolism rather than any difference in the physical properties of the enantiomers.

## **Environmental Toxicology**

### ***Birds***

The active S isomer of indoxacarb was moderately toxic to northern bobwhite quail as the TGAC, the proposed 150SC formulation as *DuPont Steward Insecticide* and a 30WG formulation (identical to the EUP Avatar submitted for registration separately) in single dose acute toxicity studies. One of the main metabolites IN-JT333 was slightly toxic as a single dose. The TGAC was moderately and slightly to practically nontoxic to bobwhite and mallard ducks in 5-d dietary exposures with LC<sub>50</sub> values of 881 (675, 1152) and >4969 mg a.i./kg food, respectively. Chronic one-generation dietary exposures to bobwhite determined NOEC and LOEC values of 118 and 613 mg a.i./kg food, respectively, while the chronic

NOEC to mallards was >613 mg a.i./kg food.

### ***Fish***

Indoxacarb was highly toxic to rainbow trout as the TGAC but highly to very highly toxic as a 30WG formulation. Bluegill sunfish was similarly sensitive to the TGAC and 30WG formulation with highly toxic 96-h LC<sub>50</sub> values of 0.89 (0.65, 1.7) and 0.35 (0.27, 0.48) mg a.i./L, respectively. However, the proposed *DuPont Steward Insecticide* formulation of 150SC caused no mortality or sublethal effects to bluegills at mean measured concentrations up to 0.85 mg a.i./L.

The metabolite IN-JT333 was also very highly toxic to trout with a 96-h LC<sub>50</sub> of 24 (12, 220) µg/L and an EC<sub>50</sub> of 5.8 (2.0, 8.4) µg/L based on sublethal responses. The single concentration of IN-KT413 tested of 1.06 mg/L caused no adverse effects to trout and is at worst moderately toxic. The minor metabolite IN-JU874 likely had a 96-h LC<sub>50</sub> between 13 and 21 mg/L, the concentrations causing 0 and 85% mortality, respectively, which is slightly toxic. The analog IN-KT094 had a 96-h LC<sub>50</sub> of >0.25 mg/L, the highest concentration tested and near the water solubility limit.

A single early life stage study on trout found 90-d NOEC and LOEC values of 0.12 and 0.20 mg a.i./L, respectively, with a maximum acceptable toxicant concentration of 0.15 mg a.i./L. This was considered only slightly toxic and the acute to chronic ratio is also low at 3.4.

### ***Aquatic invertebrates***

Indoxacarb as the TGAC or formulated as the proposed *DuPont Steward Insecticide* or a 30WG was highly toxic to daphnids in acute exposures with 48-h EC<sub>50</sub> values of about 410 – 500 µg a.i./L. The metabolite IN-JT333 was very highly toxic (48-h EC<sub>50</sub> = 0.69 µg/L) when assessed on the sublethal effect of causing lethargy. The single concentration of IN-KT413 tested of 0.967 mg/L caused 15% immobility resulting in a 48-h EC<sub>50</sub>>0.967 mg/L. Daphnids were apparently less sensitive in chronic 21-d exposures with NOEC and LOEC values of 31 and 67 µg a.i./L, respectively, for transient immobility of neonates. This resulted in an acute to chronic ratio of about 11. However, indoxacarb was moderately toxic to the marine invertebrate mysid shrimp with 28-d NOEC and LOEC values of 14.5 and 32.2 µg a.i./L, respectively, and a 28-d LC<sub>50</sub> of 49.7 (42.4, 56.6) µg a.i./L based on survival of first generation mysids.

### ***Aquatic plants***

The green alga *Pseudokirchneriella subcapitata* was not affected by indoxacarb at the single concentrations tested in the various Tier I limit studies chosen to reflect a variety of application rates and solubility limits. The 120-h NOEC to the TGAC was 78 µg a.i./L while the 72-h NOEC and LOEC values to the proposed *DuPont Steward Insecticide* formulation were <620 and 620 µg a.i./L, respectively. The metabolite IN-JT333 had a 120-h NOEC of 17 µg/L. The macrophyte duckweed was also insensitive to the TGAC with a 14-d NOEC of 63.2 µg a.i./L.

### *Terrestrial invertebrates*

Both the TGAC and metabolite IN-JT333 were slightly toxic to earthworms with 14-d LC<sub>50</sub> values of >945 mg a.i./kg soil and >987 mg/kg soil, respectively. IN-KG433 was very slightly toxic with a 14-d LC<sub>50</sub>>1000 mg/kg soil. However, the proposed *DuPont Steward Insecticide* was highly toxic to honey bees in 48-h oral (LD<sub>50</sub> = 0.24 (0.21, 0.26) µg a.i./bee) and contact (0.15 < LD<sub>50</sub> < 0.30 µg a.i./bee) laboratory experiments. By contrast, other studies showed the 48-h LC<sub>50</sub> was >478 mg a.i./L (which could not be compared as the dose in terms of µg a.i./bee was unknown) and 7.2 (5.1, 9.8) µg a.i./bee when administered in a honey solution which is moderately toxic. Other contact toxicity studies found LD<sub>50</sub> values of 0.099 (no confidence limits) and 0.41 (0.33, 0.50) µg a.i./bee indicating high toxicity. However, semifield studies showed direct spraying of actively foraging bees at 50 g a.i./ha had only transient adverse effects. It is unknown what effect would result from applications at the maximum proposed rate for *DuPont Steward Insecticide* of 127.5 g a.i./ha.

A series of laboratory and semifield studies on predatory mites showed mixed results. Application rates of up to 100 g a.i./ha of various formulations (including the proposed *DuPont Steward Insecticide*) had no adverse effect on adult survival, number of eggs produced, egg hatch. As further data could not be provided to allow assessment of absolute numbers of mites, rather than only proportions, these results should be treated with caution. A field study with grapevines sprayed three times with up to 44.5 g a.i./ha showed no differences in mite abundance with control vines. Similarly, six applications of 70.0 – 77.4 g a.i./ha with a 30WG formulation on apple trees at 10-12 d intervals showed no adverse effect on predatory mites. However, juvenile mite mortality and the number of eggs laid per female were adversely affected when apple leaves were treated with a 30WDG at 61.7 g a.i./ha (2.1× lower than the proposed application rate for *DuPont Steward Insecticide*), but not the following year when trees were treated at 50 g a.i./ha.

Adult and larval hoverflies showed no statistically significant adverse effect when exposed to cabbage plants treated one, three or six times (10-d intervals) at 50.1 g a.i./ha with a 30WDG formulation, despite the trend of increasing larval mortality with increasing number of applications. A repeat of this experiment using a 30WG formulation showed similar results in addition to no difference in hatching success when mite eggs were directly sprayed.

Indoxacarb (as the proposed *DuPont Steward Insecticide* or a 30WG formulation) sprayed onto glass plates at 5-100 g a.i./ha was clearly harmful to parasitic wasps with 93 – 100% mortality after 48 h. When cotton seedlings were treated at 50 and 100 g a.i./ha with the same formulations, wasp mortality was ≥98%. A different species of wasp experienced 35-88% mortality after exposure to cabbage plants sprayed one, three and six times at 50 g a.i./ha, with the highest mortality and reduced fecundity with the single spray.

Significant differences between treatment of cotton fields (three sprays at 75 or 127.5 g a.i./ha of the proposed *DuPont Steward Insecticide*) and controls in NSW were seen for various arthropods at various single sampling times, but mean differences were only significant for ants, pirate bugs, predatory bugs (not identified to species) and unspecified predators at 127.5 g a.i./ha. Only the density of beetles and predatory bugs at some sampling times was significantly lower than controls in another field study on cotton in Qld when 127.5 g a.i./ha of *DuPont Steward Insecticide* was applied with a surfactant.

### ***Soil nitrification and respiration***

A sandy loam treated at 0.23 mg a.i./kg soil (approximately equivalent to an application rate of 177 g a.i./ha) showed no lasting adverse effect on microbial nitrification or respiration processes although nitrate concentrations at 28 DAT were tolerable with a 23% deviation from control. A loamy sand treated at 0.132 and 1.32 mg a.i./kg soil dw (equivalent to 0.78× and 7.8× the application rate for *DuPont Steward Insecticide*) showed deviations from controls of <10% at 28 DAT indicating negligible effect. The metabolite IN-JT333 at 0.08 mg/kg soil (equivalent to 60 g/ha) also caused a tolerable effect on nitrification at 42 DAT and negligible effect on respiration by 28 DAT. IN-KG433 at 0.0756 mg/kg soil caused negligible deviations of <16% from controls at 28 DAT.

### **Environmental Hazard**

#### ***Estimated Environmental Concentrations***

After a single application of *DuPont Steward Insecticide* at 127.5 g a.i./ha, the EEC in the top 5 cm of soil would be 0.196 mg a.i./kg soil (plus approximately 33% if accounting for the inactive R isomer for a total of 0.262 mg indoxacarb/kg soil) presuming a soil bulk density of 1.3 g/mL. Following weekly applications for the first two weeks, no application in the third week (another insecticide with a different mode of action must be used) and then a final application in the fourth week, soil concentrations would peak at 0.38, 0.52 and 0.55 mg a.i./kg soil (or 0.51, 0.69 and 0.73 mg indoxacarb/kg soil) in the best, moderate and worst cases (DT<sub>50</sub> values of 16, 60 and 114 d), respectively, after the final application. By the next season one year later, no residues would remain in the best case but the concentration in the moderate and worst cases would be 0.009 and 0.065 mg a.i./kg soil (or 0.014 and 0.094 mg indoxacarb/kg soil), respectively.

In a worst-case scenario of a direct overspray of a 15 cm deep body of water with the maximum single application rate of 127.5 g a.i./ha, the EEC would be 0.085 mg a.i./L (or 0.113 mg indoxacarb/L from an application rate of 170 g indoxacarb/ha accounting for the inactive R isomer). If this were repeated in the same application intervals as above, the expected dissipation shows peak concentrations in water, whole system and sediment of 0.09, 0.17 mg a.i./L and 0.21 mg a.i./kg sediment (or 0.11, 0.22 mg indoxacarb/L and 0.28 mg indoxacarb/kg sediment), respectively. After one year, there is no residue remaining and therefore no annual carryover.

#### ***Hazard to Terrestrial Organisms***

There is no expected hazard to bobwhite quail, mallard ducks, earthworms, terrestrial plants or soil microbial processes from either acute or chronic exposures to indoxacarb residues. However, the hazard to honey bees, parasitic wasps (*Aphidius colemani* and *Diaeretiella rapae*), ants, pirate bugs, beetles and other arthropods (unspecified as to species in submitted studies) is unacceptable unless mitigated by restricted use or label warnings of the hazard to users. The hazard of the proposed use of *DuPont Steward Insecticide* to predatory mites and hoverflies could not be assessed and the hazard is unknown.

The hazard of various metabolites could only be assessed for those organisms for which ecotoxicity studies were submitted. IN-JT333 is not expected to be a hazard to birds, earthworms and soil microbial processes. IN-KG433 is not expected to be a hazard to earthworms but presents an unknown hazard to soil microbes.

### ***Hazard to Aquatic Organisms***

The direct overspray of a 15 cm deep water body with *DuPont Steward Insecticide* at the maximum application rate of 127.5 g a.i./ha (or 170 g indoxacarb/ha accounting for both S and R isomers) represents an unacceptable acute hazard to fish, invertebrates and algae. However, the likelihood of direct repeated oversprays of natural waterways is minimal particularly if best management practices are followed. The more likely exposure through spray drift (worst case of 10% drift) reduces the hazard from the parent compound to an acceptable level for fish, invertebrates and aquatic plants in both acute and chronic exposures. Any run-off from treated areas would likely involve chemical strongly bound to soil particles (given its high  $K_{OC}$  values) and not bio-available for uptake by organisms. Leaching to groundwater with subsequent recharge to surface water is not expected due to the strong adsorption and low mobility in soil.

If minimum buffer zones of 100 and 300 m as specified by the cotton best management practices manual are used for ground and aerial applications respectively, the hazard to fish and aquatic invertebrates from IN-JT333 is expected to be acceptably low. IN-KT413 poses an acceptable hazard to rainbow trout and daphnids (and is similarly expected to aquatic plants) in the worst case of a direct overspray.

### ***Desirable Vegetation***

Terrestrial plants are not expected to be adversely affected as *DuPont Steward Insecticide* is proposed for use on cotton and indoxacarb is proposed for use on other plants in other EUPs.

### ***Conclusions***

Du Pont Australia Ltd has applied for the registration of a new end use product (EUP) *DuPont Steward Insecticide* containing the technical grade active constituent (TGAC) indoxacarb at 150 g a.i. (active ingredient)/L present as the active S isomer. The EUP also contains 50 g/L of the inactive R isomer. This product is proposed for the control of cotton bollworm and native budworm in cotton at a maximum application rate of 127.5 g a.i./ha. A maximum of three applications per growing season are allowed with a minimum spray interval of seven days and no more than two consecutive sprays per field per season; the application of another insecticide with a different mode of action is required in the cotton industry's integrated pest management and resistance strategy.

There is no expected hazard to bobwhite quail, mallard ducks, earthworms, terrestrial plants, soil microbial processes, fish, aquatic invertebrates or terrestrial/aquatic plants from the proposed use of *DuPont Steward Insecticide* provided cotton best management practices application techniques and Good Agricultural Practice are followed, including the avoidance of direct overspray of water bodies and minimising spray drift. However, the hazard to honey bees, parasitic wasps (*Aphidius colemani* and *Diaeretiella rapae*), ants, pirate bugs, beetles and other arthropods (unspecified as to species in submitted studies) is unacceptable and must

be mitigated by restricted use or users warned of the hazard. The hazard to predatory mites and hoverflies could not be assessed and is unknown.

## EFFICACY AND CROP SAFETY ASSESSMENT

### Justification for use

Indoxacarb is the first member of a new insecticide group the oxadiazines, effective against resistant populations of *H. armigera* and less disruptive to beneficial insect species than traditional broad-spectrum groups. Indoxacarb has a novel mode of action with no known cross-resistance to existing chemical groups in *Helicoverpa* species. This will significantly contribute to user ability to effectively rotate chemical groups, essential for the successful implementation of Insecticide Resistance Management (IRM). Indoxacarb will be an extremely useful management tool in cotton, both in terms of IPM and IRM.

Efficacy data were gathered from a range of laboratory and field trials, typified by good experimental design and analysis. The trials were carried out under a range of pest pressures, different populations of *Helicoverpa* species, various weather conditions and in soil types typical of those experienced during the Australian cotton season.

The statistical analysis of laboratory data (Probit analysis) and field trial data (Analysis of Variance, Duncan's New Multiple Range Test and Fisher's Protected Least Significant Difference Test) was good. The analysis (and in some cases transformation) of data are appropriate, thorough and clearly laid out in the submission.

In-house trials, and those performed by contract researchers were well designed and executed. The range of locations and stages during the cotton season under which the trials were performed adequately tested the product against insecticide resistant and susceptible *Helicoverpa* species.

The trial data give a thorough indication of the efficacy of the product. Data also supported the use of *DuPont Steward Insecticide* in combination with amitraz, and this use pattern is also consistent with IPM compatibility.

*DuPont Steward Insecticide* alone shows no phytotoxicity to cotton in the submitted trial data. Limited (acceptable) phytotoxicity to cotton was reported in one of the trials with *DuPont Steward Insecticide* in mixture with amitraz. Greater selectivity of this product to a range of beneficial insect species common in cotton growing systems, compared with broad-spectrum alternatives (such as endosulfan and bifenthrin), is consistent with a good potential fit for *DuPont Steward Insecticide* in cotton IPM.

### Conclusions

This is an important product for the control of *Helicoverpa* species in Australia supported by a high quality submission. *DuPont Steward Insecticide* would provide clear benefits for Integrated Pest Management (IPM) and Insecticide Resistance Management (IRM) in Australian cotton. The efficacy data support the label claims.

## **LABELLING REQUIREMENTS**

The draft label is present on the following pages. It includes all risk mitigation options identified by this assessment.

{Main panel}

# POISON

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



# Steward™

## insecticide

ACTIVE CONSTITUENT: 200 g/L INDOXACARB (25:75)  
(equivalent to 150 g/L active S-isomer)



For the control of *Helicoverpa armigera* (cotton bollworm) and *H. punctigera* (native budworm) in cotton.

Read the attached leaflet before using this product.

CONTENTS: 1L, 2L, 3.8L, 4L, 4.5L,  
5L, 10L, 20L, 55L, 56.7L, 110L,  
200L, 208L.

## SHAKE WELL BEFORE USE

Du Pont (Australia) Limited  
A.C.N. 000 716 469  
168 Walker Street, North Sydney NSW 2060  
Customer Service: 1 800 257 169  
™ DuPont Trademark

## **{Ancillary panel one}**

### **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 container 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 container 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. **{For 1L, 2L, 3.8L, 4L, 4.5L, 5L, 10L, 20L, 55L, 56.7L recyclable containers only}**

Empty contents fully into application equipment. Close all valves and return to point of supply for refill or storage. **{For 110L, 200L, 208L returnable minibulks}**.

## {Ancillary panel two}

### PRECAUTION

Human flagging is not supported unless flaggers are protected by engineering controls such as vehicles with cabs.

### RE-ENTRY PERIOD

**DO NOT** allow entry into treated areas until spray has dried. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrists, a washable hat and chemical resistant gloves. Clothing must be laundered after each day's use.

### SAFETY DIRECTIONS

Harmful if swallowed. Will irritate the eyes and skin. Avoid contact with eyes and skin. Repeated exposure may cause allergic disorders. Sensitive workers should use protective clothing. Wash hands after use. When opening the container, preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrists, a washable hat and elbow-length PVC gloves. After each day's use wash, gloves and contaminated clothing.

### FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (ph 13 11 26).

Additional information is listed in the Material Safety Data Sheet that can be obtained from the supplier.

IN A MEDICAL EMERGENCY CALL  
1800 674 415 All hours

### NOTICE TO BUYER

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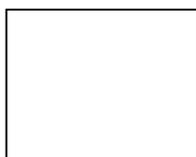
NRA Approval number: [not yet determined]

Barcode number for each individual pack:

SAP number

Batch number and date of manufacture

**Barcode : 9 3 1 4 0 4 2 0 0 5 2 4 (4 Litre pack)**



*{drumMUSTER eligible container logo: 1L, 2L, 3.8L, 4L, 4.5L, 5L, 10L, 20L, 55L, 56.7L recyclable containers only}*

{Label leaflet}

**POISON**

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



# Steward<sup>TM</sup>

## insecticide

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**ACTIVE CONSTITUENT: 200 g/L INDOXACARB (25:75)  
(equivalent to 150 g/L active S-isomer)**

For the control of *Helicoverpa armigera* (cotton bollworm) and *H. punctigera* (native budworm) in cotton.

Important: Read this leaflet before using this product.

Du Pont (Australia) Limited  
A.C.N. 000 716 469  
168 Walker Street, North Sydney NSW 2060  
Customer Service: 1 800 257 169  
<sup>TM</sup> DuPont Trademark

## DIRECTIONS FOR USE

### RESTRAINTS

**DO NOT** apply if rain is expected within 2 hours of application, or if heavy dew is present on cotton.

**DO NOT** apply more than three (3) applications per field in any one cotton growing season and no more than two (2) consecutive sprays per field per season. Applications must be a minimum of seven days apart.

**DO NOT** treat cotton plants with greater than 30% open bolls.

**DO NOT** apply within 600m (aerial) or 200m (ground), of neighbouring arable land.

CROP	PEST	STATE	RATE	CRITICAL COMMENTS
Cotton	Cotton bollworm ( <i>Helicoverpa armigera</i> )  Native budworm ( <i>H. punctigera</i> )	NSW, NT, Qld and WA only	650mL/ha or 850mL/ha	<p><b>Use the lower rate of Steward™ when:</b></p> <p>(1) <i>H. armigera</i> specific field levels are less than or equal to 60% prior to treatment application AND</p> <p>(2) 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</p> <p>(3) where preservation of beneficial insects is desirable.</p>
				<p><b>Use the higher rate of Steward™ when:</b></p> <p>(1) <i>H. armigera</i> specific field levels are greater than 60% prior to treatment application AND</p> <p>(2) 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</p> <p>(3) where preservation of beneficial insects is desirable.</p>
			650mL/ha + 2L/ha Ovasyn ® insecticide (or 200g amitraz /L EC formulation such as DuPont amitraz EC)	<p><b>Use Steward™+ Ovasyn® or DuPont Amitraz EC when:</b></p> <p>(1) egg and larvae pressure ARE AT 15-20 brown eggs and 2 very small (first instar) or small larvae (second instar) larvae per 10 terminals AND</p> <p>(2) where limited preservation of beneficial insects is required.</p>

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

### WITHHOLDING PERIODS:

DO NOT HARVEST FOR 28 DAYS AFTER APPLICATION.

DO NOT ALLOW LIVESTOCK TO GRAZE CROPS, STUBBLE OR GIN TRASH THAT MAY HAVE BEEN TREATED WITH STEWARD INSECTICIDE.

### GENERAL INSTRUCTIONS

Steward™ should be applied after careful field monitoring of pest populations for eggs and larvae to determine the need for application, the correct timing of the initial application and of any subsequent applications. Subsequent applications are dependent on economic thresholds, as well as the growth rate of new unprotected cotton terminals.

Spray applications should be timed to coincide with egg hatching and before larvae are entrenched in protected feeding sites.

Steward™ has been specifically designed for use in Integrated Pest Management schemes. The active ingredient, indoxacarb enters insects primarily by ingestion of treated foliage, or through penetration of the insect cuticle. After ingesting indoxacarb, the larvae cease feeding and die three to five days later. Steward™ does not give traditional larval “knockdown” control but controls *Helicoverpa* spp larvae giving superior cotton square protection.

## INSECTICIDE RESISTANCE WARNING

GROUP	22	INSECTICIDE
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Indoxacarb, the active ingredient in Steward™, is an oxadiazine insecticide, and a sodium channel antagonist with a unique mode of action. No cross-resistance has been recorded between Steward™ and other insecticide groups. Steward™ is expected to control *Helicoverpa* species with known resistance to other registered insecticides.

Strategies to minimise the risk of insecticide resistance are available. To help prevent the development of resistance to Steward™ insecticide observe the following instructions:

- Use Steward™ in accordance with the current Insecticide Resistance Management (IRM) strategy for your region.
- Cultivate all cotton fields as soon as possible after picking to destroy overwintering pupae of *Helicoverpa armigera*.

Consult your farm chemical supplier, consultant, local Department of Agriculture or Primary Industries, or local DuPont Representative for more details.

### PRODUCT USE

**Strategies outlined in the cotton industry's Best Management Practice Manual must be observed to minimise spray drift during both ground and aerial application.** The interaction of equipment and weather-related factors determines the potential for spray drift. The applicator must consider all these factors when making application decisions and determining off-target drift risks near the application.

APPLYING LARGER DROPLETS (volume median diameter (VMD) 150 – 250 microns) REDUCES DRIFT POTENTIAL, BUT WILL NOT MINIMISE DRIFT IF APPLICATIONS ARE MADE IMPROPERLY OR UNDER UNFAVOURABLE ENVIRONMENTAL CONDITIONS. Larger droplets may reduce the effects of evaporation.

### Mixing

Agitate or shake the container immediately before use. Use only clean water. Half fill the spray tank with water and add the appropriate amount of Steward™ directly to the spray tank, agitate and add Ovasyn® or amitraz 200g/L EC, (if applicable), then completely fill the tank. Mix thoroughly and continue mechanical or hydraulic agitation.

### Storage of spray mixture

Use the prepared spray immediately. If unforeseen conditions prevent immediate use of the Steward™ spray mix, the mix may be stored up to 72 hours. Before use, thoroughly agitate the spray mix until fully resuspended. Mixtures of Steward™ plus Ovasyn® or amitraz 200g/L EC should not be stored.

### Application

Application equipment should be calibrated to apply at least sixty (60) **droplets** per cm<sup>2</sup> of target cotton foliage. Droplet VMD should be in the range of 150 – 250 microns.

### Ground application

Apply either as a *blanket* spray or as a *banded* spray over the cotton plants. Apply in a minimum spray volume of 100L/ha. Ensure thorough spray coverage on the cotton foliage. This can be maximised by using appropriate sized hollow cone nozzles to deliver 100L spray volume per hectare. Increase the number of hollow cone nozzles per cotton row as the plant size increases. A minimum spray pressure of 275 kPa (40psi) should be used with hollow cone nozzles.

**Higher pressure reduces droplet size, DOES NOT improve canopy penetration and may increase drift potential.** WHEN HIGHER FLOW RATES ARE NEEDED, USE A HIGHER-CAPACITY NOZZLE INSTEAD OF INCREASING PRESSURE.

### **Aerial application**

Steward™ must only be applied with aircraft fitted with accurately calibrated equipment. Apply a minimum total spray volume of 30L/ha with either Micronaire® rotary atomisers or conventional hydraulic nozzles set to spray droplets with a VMD in the range of 150 – 250 microns. A strategy as per the cotton industry's Best Management Practice Manual should be employed at all times to minimise spray drift during aerial application. **DO NOT apply Steward™ using Ultra Low Volume (ULV) methods.**

### **Compatibility**

Steward™ is compatible with Ovasyn® insecticide and amitraz EC formulations. Steward™ is not compatible with ultra low volume (ULV) formulations.

### **Spray Equipment Cleanout**

Only apply product using clean, well-maintained equipment. Immediately following application, thoroughly clean all spray equipment to reduce risk of deposits forming that might become difficult to remove.

Drain spray equipment into a disposal pit designed for this purpose. Thoroughly rinse sprayer and flush hoses, boom, and nozzles with clean water. Fill the sprayer with clean water and household ammonia (one litre of 3% active for every 100 L of water). Flush hoses, boom, and nozzles. Turn off boom and top off the tank with clean water. Circulate through the spraying system for at least 15 minutes. Flush the hoses, boom and nozzles and drain the tank. Remove and clean nozzles, screens, and strainers in a bucket of fresh ammonia and water. Thoroughly rinse the sprayer, hoses, boom and nozzles with clean water several times. Clean all other associated contaminated application equipment.

### **PROTECTION OF LIVESTOCK**

**Dangerous to bees.** **DO NOT** apply when bees are actively foraging. Avoid direct application or drift of the spray mix onto bee hives. After the spray has dried, bees can safely forage flowering crops.

**AVOID SPRAY DRIFT ONTO ADJOINING PROPERTIES OR STOCK AREAS.** Keep animals out of operational areas during treatment.

### **PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT**

**DO NOT** contaminate streams, rivers or waterways with the chemical or used containers. **Retain irrigation water** and **DO NOT** allow the chemical to enter adjacent paddocks, crops or water supplies.

### **PROTECTION OF NON-TARGET BENEFICIAL INSECTS**

Beneficial insects contribute to control of secondary pest outbreaks. Steward™ applications are unlikely to affect spiders and lacewings. Applications MAY temporarily reduce populations of predatory beetles, transverse ladybirds, ants and pirate bugs, but populations quickly recover.

### **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 non-target plants/crops, cropping lands or pastures.

Refer to the Product Use section above and cotton industry's Best Management Practice Manual to manage spray drift during application.

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NRA Approval number: [not yet determined]

## GLOSSARY

<b>Active constituent (or TGAC)</b>	The substance that is primarily responsible for the effect produced by a chemical product.
<b>Acute</b>	Having rapid onset and of short duration.
<b>Carcinogenicity</b>	The ability to cause cancer.
<b>Chronic</b>	Of long duration.
<b>Codex MRL</b>	Internationally published standard maximum residue limit.
<b>Desorption</b>	Removal of an absorbed material from a surface.
<b>Efficacy</b>	Production of the desired effect.
<b>Formulation</b>	A combination of both active and inactive constituents to form the end use product.
<b>Genotoxicity</b>	The ability to damage genetic material
<b>Hydrophobic</b>	Water repelling
<b>Leaching</b>	Removal of a compound by use of a solvent.
<b>Log P<sub>ow</sub></b>	Log to base 10 of octanol water partitioning co-efficient.
<b>Metabolism</b>	The conversion of food into energy
<b>Photodegradation</b>	Breakdown of chemicals due to the action of light.
<b>Photolysis</b>	Breakdown of chemicals due to the action of light.
<b>Subcutaneous</b>	Under the skin
<b>Toxicokinetics</b>	The study of the movement of toxins through the body.
<b>Toxicology</b>	The study of the nature and effects of poisons.

## References

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