Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new Vip3A in the product Bollgard III

APVMA product number 69656

JANUARY 2016

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

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PREFACE

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

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

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

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the APVMA website at www.apvma.gov.au.

This public release summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a public release summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **BOLLGARD III** should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into

account in deciding whether to grant the application. These matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **Tuesday 16 February 2016** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be ***confidential commercial information (CCI)***[1] contained in submissions will be treated confidentially.

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

Case Management and Administration Unit (CMAU)
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4701
Fax: (+61 2 6210 4721
Email: enquiries@apvma.gov.au

[1] A full definition of 'confidential commercial information' is contained in the Agvet Code.

Further information

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

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

1 INTRODUCTION

1.1 Applicant

Monsanto Australia Ltd.

1.2 Purpose of application

Monsanto Australia Ltd., has submitted an application seeking to gain registration for Bollgard III cotton expressing the three insecticidal *Bt* proteins Cry1Ac, Cry2Ab and Vip3A as an insecticidal product produced *in planta* in *Gossypium hirsutum* for use against the lepidopteran cotton pests, native budworm *Helicoverpa punctigera* and cotton bollworm, *H. armigera*.

The new genetically modified (GM) cotton, Bollgard III, proposed for registration is similar to another registered GM cotton line, Bollgard II with the addition of a third gene *Vip3A* and is intended to have increased protection against insect resistance developing in the target pests of cotton. Bollgard III has been derived from conventional plant crossing of Bollgard II and a Syngenta cotton line containing (used under licence agreement) the Vip3A gene.

Bollgard III has been assessed by the Office of the Gene Technology Regulator (OGTR) and the Regulator issued a licence for the intentional, commercial scale release of Bollgard III into the environment (this commercial release followed field trial work conducted under a previous licence). Following consultation with a range of experts, agencies and authorities and the general public the OGTR published its final Risk Assessment and Risk Management Plan (RARMP) in June 2014. The RARMP concluded that, *'…the commercial release* [of Bollgard III] *poses negligible risks to human health and safety and the environment, either in the short or long term, and no specific risk treatment measures are required.'* To maintain on-going regulatory oversight of the commercial release, the OGTR licence contains various conditions that the licence holder must adhere to, which includes an obligation to report any un-intended effects. (OGTR, RARMP, DIR 124, 2014).

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of **Bollgard III**, and approval of the new active constituent, Vip3A.

1.3 Product claims and use pattern

The new GM cotton is intended to be grown in areas where cotton, both GM and conventional, is currently grown in Australia and the intention is that this product with three insect resistant proteins expressed will require fewer pesticide applications per growing season than a conventional non-insecticidal cotton. Under high pest pressure additional insecticidal control would be necessary.

Cotton growers will need to be party to a Bollgard III Technology User Agreement with Monsanto Australia Ltd. in order to grow this cottonseed and must agree to practise preventative insect resistance management strategies.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

COMMON NAME:	*Bacillus thuringienis* strain AB 88 Exotoxin, VIP3A, as produced by vip3A(a) Gene Technical Active
IUPAC NAME:	NA
CAS NAME:	NA
CAS REGISTRY NUMBER:	NA
MINIMUM PURITY:	NA
MOLECULAR FORMULATION:	NA
MOLECULAR WEIGHT:	NA
STRUCTURE:	NA
FAMILY:	Bacillaceae
MODE OF ACTION:	A line of transgenic cotton that produces a vegetative insecticidal protein, VIP3A, against several lepidopteran species including *Helicoverpa zea* (cotton bollworm), *Heliothis virescens* (tobacco budworm), *Pectinophora gossypiella* (pink bollworm) et al.

2.2 Product

DISTIGUISHING NAME:	Bollgard III
FORMULATION TYPE:	NA
ACTIVE CONSITUENT CONCENTRATION:	*Bacillus thuringiensis* subsp. Kurstaki delta endotoxins as produced by the Cry1Ac and Cry2Ab genes and their controlling sequences. *Bacillus thuringiensis* strain AB88 exotoxin as produced by the Vip3A(a) gene and its controlling sequence.

2.3 Recommendation

Based on a review of the chemistry and manufacturing details, registration of Bollgard III is supported.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Bollgard III is a genetically modified (GM) cotton event primarily expressing three *Bacillus thuringiensis* genes encoding the *in planta* insecticidal proteins Cry1Ac, Cry2Ab and Vip3A. The three introduced genes are derived from the soil bacterium *B. thuringiensis* sub-species *kurstaki* and provide protection against the Cotton Bollworm (*Helicoverpa armigera*) and Native Budworm (*Helicoverpa punctigera*) by disrupting their normal gut function, causing insect death.

The Bollgard III event was created by crossing the GM cotton lines known as COT 102 (contains a *vip3A (a)* gene) and MON 15985 (contains *Cry1Ac* and *Cry2Ab* genes - also known as the Bollgard II event).
The APVMA has previously considered the toxicity of Cry1Ac and Cry2Ab, through the assessment of the Bollgard II cotton event. It was concluded that the Bollgard II posed negligible risk to human safety. It was subsequently registered in July 2003.

Vip3A is novel insecticidal protein, secreted by B. *thuringiensis* during the vegetative stage of growth has, specific activity against the Lepidopteran insect pests, *Helicoverpa armigera* and *Helicoverpa punctigera* and targets a different receptor than the Cry proteins, Cry1Ac and Cry 2Ab. The Vip3A protein is non-toxic to mammals and has limited potential to be allergenic.

The combined risks posed to human health of the three insecticidal proteins (Cry1Ac, Cry2Ab and Vip3A), and the associated selectable markers and genetic regulatory elements comprising the Bollgard III event, have previously been considered by other Australian Government regulators, namely the Office of the Gene Technology Regulator (OGTR) and Food Standards Australia New Zealand (FSANZ). These regulators concluded that the Bollgard III event posed negligible risk to human health and approved its release into the environment on a commercial scale and food derived from it when sold, respectively.

3.2 Biochemistry

Active constituents

ACTIVE CONSTITUENT(S)/COMMON NAMES(S)/SPECIFIC NAME(S):	• Cry1Ac/Crystal protein 1Ac • Cry2ab/Crystal protein 2Ab • Vip3a/Vip3Aa19, Vegetative insecticidal protein 3Aa19
BIOCHEMICAL CLASS:	• Cry1Ac: Insecticidal δ-endotoxin protein • Cry2Ab: Insecticidal δ-endotoxin protein • Vip3A: Insecticidal β-exotoxin protein

The active constituents will be produced by farmed cotton plants and any aberrant forms of the actives are expected to be degraded *in planta*.

3.3 Public health standards

Poisons scheduling

Given the low toxicity of Cry1Ac, Cry2Ab and Vip3A scheduling in the SUSMP (Standard for the Uniform Scheduling of Medicines and Poisons) is not considered necessary.

ADI/ARfD

No ADI (Acceptable Daily Intake) or ARfD (Acute Reference Dose) values are required for Cry1Ac, Cry2Ab and Vip3A as the assessment of the toxicological data available for Cry1Ac, Cry2Ab and Vip3A does not indicate a risk to human health and safety.

NOEL

While the NOEL (No Oberservable Effects Limit) for the three active constituents is unknown, it is not considered necessary as Cry1Ac, Cry2Ab and Vip3A are of low very toxicity to humans and expression within the cotton plant significantly limits exposure.

3.4 Conclusions

Based on the outcomes of the previous APVMA, FSANZ and OGTR considerations and the evaluation of the data submitted in this application indicating that there were no new toxicological concerns for human health and safety, it was concluded that Bollgard III poses negligible risk to human health.

4 RESIDUES ASSESSMENT

Bacillus thuringiensis subsp. *kurstaki* delta endotoxins Cry1Ac and Cry2Ab as produced by the cry1Ac and cry2Ab genes and their controlling sequences are currently registered in recombinant cotton MON 15985 (Bollgard II Cotton, product number 55786). The risk associated with '*Bacillus thuringiensis* subsp. *kurstaki* delta endotoxins Cry1Ac and Cry2Ab' has not changed and no further consideration of those proteins was required. '*Bacillus thuringiensis* var.*kurstaki* exoprotein Vip3A' has however not been previously considered.

The toxicological assessment of the Vip3A protein concluded that it posed a negligible risk to human health when used in cotton and an ADI or ARfD were not required.

In June 2006, FSANZ completed its evaluation of food derived from insect-protected cotton line COT102, containing the Vip3A gene that produces the Vip3A protein that binds to specific receptors and disrupts the digestive processes and cause death of the insect. The FSANZ evaluation stated that 'A number of studies demonstrate that the Vip3A protein is non-toxic to mammals, and have limited potential to be allergenic' and that 'comparative analyses do not indicate that there are any compositional differences in cottonseed from transgenic cotton line COT102, compared to the non-GM control that would lead to food safety or nutritional problems'.

It is noted that the FSANZ evaluation of the Vip3A protein focused on cotton seed, which may be consumed as oil by humans, but did not investigate Vip3A levels in forage and fodder that may be consumed by livestock. Because protein such as Vip3A is rapidly degraded in gastric fluid and because Vip3A in non-toxic to mammals, no finite residues of any proteins expressed by Bollgard III are expected in animal tissues for human consumption from the feeding of cotton containing Bollgard III to animals.

As the Vip3A protein is non-toxic to mammals and as seed produced GM cotton plants (Bollgard III) that contain the Vip3A gene that produces the Vip3A protein has no significant compositional differences to non-GM cotton, it is concluded that MRLs should not be required for the Vip3A protein. It is recommended that a Table 5 entry be established for *Bacillus thuringiensis kurstaki* exoprotein Vip3A as an Insecticide expressed in recombinant cotton in the MRL standard. [Note: Table 5 exists for situations where residues do not or should not occur in foods or animal feeds or are otherwise of no toxicological significance.]

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Finite residues are not expected to be present in any human food commodities as a result of the use of this product. Therefore, it is not expected that there will be any undue prejudice to trade with other countries with regards to residues in exported food commodities.

Genetically modified BT cotton has been registered for use in Australia since Ingard (single insecticidal generating gene, Cry1Ac) was registered in 1996 and approximately 30 per cent of Australia's cotton crop is GM cotton. To the APVMA's knowledge, there has been no prejudice to Australia's trade as a result of this use of GM cotton. As Bollgard III (three genes) is very similar to Bollgard II (two genes) and Ingard (one gene) with regard to the genetic modification, it is not expected that produce from Bollgard III cotton will result in undue prejudice to Australia's trade with other countries.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Product use pattern

The product will exist as seeds through to cotton plants of all growth stages, limited to certain products (cotton plant trash and cotton seeds) of those plants.

6.2 Occupational exposure

Plant breeders, seed distributors, farm workers and those associated with cotton gin processing will be the main occupations exposed to the product. Direct exposure is unlikely to occur except if damaged cotton plant material is extensively handled or ingested. In such a scenario the amount of exposure to the intact active constituents is expected to be negligible.

As the toxicity of the active constituents is very low, and the exposure of employees in occupations working directly with cotton plants and their raw products to the active constituents is expected to be minimal, no risk management measures are required. Therefore, no first aid instructions or safety directions are warranted.

6.3 Bystander/re-entry/re-handling

The general public is not expected to be exposed to unprocessed cotton material. The introduced genes and expressed proteins are not present in cotton products such as cottonseed oil, fibres and linters.

The active constituents are contained within plant material and readily degraded in the external environment.

Therefore, re-entry/re-handling exposure to plant breeders, seed distributors, farm workers and those associated with cotton gin processing will be minimal.

6.4 PPE based acute hazards

No acute risks have been identified. Therefore, no safety directions or PPE are warranted.

6.5 Risk from repeat exposure

The risks associated with repeat exposure are negligible, especially as the toxicity of the active constituents is very low and their allergenic potential is very low.

6.6 Re-entry and re-handling

The risks associated with exposure with re-entry and re-handling are negligible as the toxicity of the active constituents is very low, and the active constituents are readily degraded. Therefore, no risk management measures are required.

6.7 Conclusion

There are no concerns on human health and safety grounds to the registration of Bollgard III event in cotton, which encodes the *B. thuringiensis*-derived insecticidal proteins Cry1Ac, Cry2Ab and Vip3A as active constituents.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Monsanto Australia Ltd is seeking registration of a biological agricultural product Bollgard® III, which produces three insecticidal Bt-proteins. Including both proteins from Bollgard® II Cotton Event MON15985 (Cry1Ac and Cry2Ab proteins as produced by the c*ry1Ac* and *cry2Ab genes* and their controlling sequences, as expressed in cotton (*Gossypium hirsutum)* event 15985) and the Vip3A protein, produced by the *Vip3A(a)* gene, from *Bacillus thuringiensis* strain AB88 as expressed in transgenic cotton plants derived from Cotton Event COT102.

The primary application is stated to be for the control of two target pests *Helicoverpa armigera* and *Helicoverpa punctigera.*

7.2 Environmental fate

Biodegradation

Soil Metabolism

The accumulation of Vip3A(a) in soil was assessed in four live soils (three from different agricultural regions of Brazil; one from Illinois, USA) and one artificial soil. Vip3Aa19 was tested at two concentrations, 16 mg and 4 mg/g dry wt. equivalent soil (corresponding to ca. 58 and 14 µg Vip3Aa19/g dry wt. equivalent soil, respectively). The soil mixtures were sampled over a 29-day period and tested for bioactivity against larvae of a target lepidopteran pest of maize, the black cutworm (*Agrotis ipsilon*). The loss of bioactivity in the soil samples, as defined by a decrease in insect mortality, was used to estimate the DT50 (time to dissipation of 50 per cent of the initial bioactivity) for each soil.

The estimated DT50 values ranged from 6.0–12.6 days at the 16 mg/g test concentration. Although the characteristics of the various soils tested were diverse there were no substantial differences in the rates at which bioactivity declined among the soil types. All had negligible effect on the rate of dissipation of bioactivity. These results indicate that any Vip3A19 protein residues that may be incorporated into agricultural soils from plants expressing Vip3Aa19 protein (eg, via post-harvest tillage) will likely not persist or accumulate, but will degrade rapidly.

Mobility

In general, kinetic and metabolism data are not relevant for microbial agents and other living organisms unless the organism produces a mammalian toxin. If the organism produces, or is suspected of producing, a toxin or toxic metabolite, then these should be identified, and also isolated if possible. As the VIP3A protein has been demonstrated to be non-toxic to mammals, metabolism and toxicokinetic studies are not required.

7.3 Environmental effects

Avian

No apparent toxicity was observed in mice or quail at doses of 2700 mg or 400 mg Vip3A protein/kg body weight, respectively, over 14 days of examination.

Aquatic invertebrates

Based on the results of toxicity studies conducted with Vip3A, Bollgard III is classified as nontoxic (LC50>752.6 µg/L Vip3Aa20) to *Daphnia magna.*

Terrestrial invertebrates

VIP3A protein was shown to not be toxic to bees with oral of LC50 was greater than 83.8 µg Vip3Aa19/g pollen and a NOEC> 730 µg Vip3A/g sucrose for brood development and the survival of adult worker bees in hives of the honeybee.

Acute toxicity tests for earthworms showed Vip3A proteins were non-toxic with an LC50>3.60 mg Vip3Aa19 protein/kg dry soil, the highest rate tested.

The non-target arthropod species Predatory Bug (*Orius insidiosus,* green lacewing (*Chrysoperla carnea*) ladybird beetles (*Coccinella septempunctata*) and ladybird beetles (*Coleomegilla maculate*) were exposed to Vip3A protein resulting in an LC50 >7.25 mg Vip3Aa19/g diet, the highest rate tested.

28-Day Survival and Reproduction of Collembola showed Vip3A proteins to be non-toxic with an LC50 >43.4µgVip3Aa19/g diet, the highest rate tested.

A field study was conducted by CSIRO between 2010 and 2012 to establish whether Bollgard® III alters the structure of the invertebrate communities in comparison to Bollgard® II alone. Findings indicate that overall there was little difference in communities of invertebrates in any of the *Bt* cottons in the trials. When comparing individual taxa responses, differences between *Bt* and non-*Bt* cotton invertebrate communities were largely driven by changes in the abundance of lepidopteran larvae. Taxa showing significant differences between crop types were several generalist predators and some pests including several spider families; many of these are more common in non-*Bt* cotton most probably due to prey preferences. In suction samples, there were differences observed in small dipterans between *Bt* and non-*Bt* plants. It was not clear why these insects were shown to be more common on non-*Bt* plants although the authors speculated these populations may have been influenced by prolonged vegetative growth caused by insect damage in non-*Bt* cotton. There was no overall significant difference between Bollgard® II and III communities, despite the addition of the Vip gene in Bollgard® III.

Microorganisms

Numerous published studies indicate that exposure to Cry protein produced in *Bt* crop plants does not adversely affect soil microorganisms (Sanvido *et al*. 2007; Oliveira *et al*. 2008). In addition, *Bacillus thuringiensis* toxin released from root exudates and biomass of *Bt* corn has no apparent effect on

earthworms, nematodes, protozoa, bacteria, and fungi in soil (Saxena and Stotzky 2001). Other research findings conclude no *Bt*-related risks have evolved from the decomposition of *Bt*-corn leaves for the meso- and macrofauna soil community (Hönemann *et al*. 2008). Although a minimal transient increase and shift in microbial populations may result from the presence of transgenic plant tissue in soil, no adverse effects have been attributed to the Cry protein.

Terrestrial plants

Toxicity test to non-target plants are not applicable however gene transfer is of considerable importance.

Out-crossing was very rare (less than 0.01 per cent) or was not detected at a distance of 10 m from GM cotton plants and no outcrossing was detected at 20 m. Gene transfer to naturalised cotton populations is thought to be unlikely because of the geographic distances between these naturalised populations and the cotton growing regions of NSW and QLD. Gene transfer from GM insecticidal cottons to native cottons is prevented not only by genetic incompatibility but also by geographic constraints to cross-pollination. Most of the Australian *Gossypium* species have limited distributions and occur at considerable geographic distance from cultivated cotton fields in NSW and QLD (the centre of native *Gossypium* diversity in Australia).

7.4 Environmental risk assessment

The APVMA is satisfied that the proposed use of this product is unlikely to have an unintended effect that is harmful to animals, plants or things or the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Introduction

The applicant, Monsanto Australia Ltd., has submitted an application seeking to gain registration for Bollgard III cotton expressing the three insecticidal *Bt* proteins Cry1Ac, Cry2Ab and VIip3A as an insecticidal product produced *in planta* in *Gossypium hirsutum* for use against the lepidopteran cotton pests, native budworm *Helicoverpa punctigera* and cotton bollworm, *H. armigera*.

The new genetically modified (GM) cotton, Bollgard III, proposed for registration is similar to another registered GM cotton line, Bollgard II with the addition of a third gene *vip3A* and is intended to have increased protection against insect resistance developing in the target pests of cotton. Bollgard III has been derived from conventional plant crossing of Bollgard II and a Syngenta cotton line containing (used under licence agreement) the Vip3A gene.

8.2 Product use

The new GM cotton is intended to be grown in areas where cotton, both GM and conventional, is currently grown in Australia and the intention is that this product with three insect resistant proteins expressed will require fewer pesticide applications per growing season than a conventional non-insecticidal cotton. Under high pest pressure additional insecticidal control would be necessary.

Bollgard III has been approved for intentional, commercial scale release in Australia by the Office of the Gene Technology Regulator (OGTR) and a licence has been issued (June 2014). The Regulator concluded that the commercial release poses negligible risks to human health, safety and the environment, and the release is subject to general licence conditions for ongoing auditing, monitoring and reporting.

Cotton growers will need to be party to a Bollgard III Technology User Agreement with Monsanto Australia Ltd. in order to grow this cottonseed and must agree to practise preventative insect resistance management strategies.

8.3 Field and laboratory trial results

Data were submitted from Australian and United States field and laboratory studies comparing the efficacy, agronomic characteristics, *Helicoverpa* species abundance and crop safety of Bollgard III cotton. The trials were replicated and randomised and compared Bollgard III and Bollgard II technology with conventional cotton.

In the 2011–12 cotton season six sites in the Australian eastern states were planted with Bollgard III cotton and compared to control lines. Efficacy data were obtained from four sites: Cecil Plains in the Darling Downs, Narrabri, Emerald and St. George by recording damage to terminals, squares and bolls throughout the season. When data from the sites were combined and analysed there were no significant differences between Bollgard III and Bollgard II in the percentage of damage to terminals, squares and bolls. Addition of

the *vip3A* gene did not have a negative impact on Bollgard II cotton; Bollgard III was as efficacious as Bollgard II for control of *Helicoverpa* in cotton.

Protein determinations were also carried out on field grown leaf material to confirm that the transgenic plants were expressing the *Bt* insecticidal proteins at the appropriate levels. All three insecticidal proteins were detected in field grown material of leaves, pollen and seed of Bollgard III with the highest levels found in leaf tissue (the feeding preference for *Helicoverpa* larvae) and lower levels found in seed and pollen. Levels detected varied depending on the year, time of season and site location as environmental conditions can affect protein expression.

Laboratory insect feeding bioassays were also conducted to test that the leaf material from Australian field grown transgenic plants were producing the *Bt* proteins that inhibited the growth and development of susceptible *Helicoverpa* larvae. The leaf bioassays were conducted over 7 days and insect mortality, survival and developmental stages reached were recorded. In these trials the Bollgard III cotton performed similarly to Bollgard II cotton. Percentage mortality of both *H. armigera* and *H. punctigera* larvae was significantly higher in the Bollgard III leaf material than in the non-*Bt* cotton leaf material. Survival of insect larvae to the third instar stage and above was significantly lower in the Bollgard III leaf material than on the non-*Bt* cotton leaf material. The trials indicated that the addition of the Vip3A protein did not have any negative effects on efficacy in leaf bioassays.

8.4 Crop safety and phytotoxicity

In the Australian field trials agronomic characteristics such as plant stand (early and late stand count), plant height, plant vigour, nodes above first white flower (NAWF), seed cotton weight, total seed per boll and fibre quality characteristics important for cotton processing (micronaire, strength and length) were measured and recorded. When combined data from the sites were analysed there were no significant differences between the agronomic or quality characteristics of Bollgard III cotton plants.

Extensive analyses of agronomic, phenotypic, fibre quality characteristics and disease resistance were also undertaken on Bollgard III cotton that was grown at several sites in the US. The Bollgard III cotton performed similarly to the Bollgard II cottons and conventional reference cottons and the agronomic and fibre quality parameters measured fell within the accepted variability of the reference range. Bollgard III cotton had similar disease rankings to non-*Bt* cotton with respect to common cotton diseases and the addition of the Vip3A trait did not alter disease susceptibility.

There was no evidence of phytotoxicity in either the Australian or US trials and the product can be considered safe to use if used according to the label recommendations.

8.5 Resistance management

The cotton industry Transgenic and Insecticide Management Strategies Committee (TIMS) has considered and accepted the Bollgard III Resistance Management Plan (RMP) submitted by the Applicant.

Cotton growers will need to be party to a Bollgard III Technology User Agreement with Monsanto Australia Ltd. in order to grow this cottonseed and must agree to practise preventative insect resistance management strategies.

8.6 Conclusions

Efficacy data provided for Bollgard III cotton demonstrated that it was not significantly different from Bollgard II in field performance. In combined data from the Australian field trials there were no significant differences in damage to terminals, squares or bolls by *Helicoverpa* species between Bollgard III and Bollgard II lines.

There were significant differences in numbers of Heliothis insects on non-*Bt* cotton compared to that observed on Bollgard III and Bollgard II cotton with higher numbers on the non-*Bt* lines confirming that Bollgard III and Bollgard II provide protection against *Helicoverpa* species under Australian conditions.

Assays on leaf material collected from the Australian field trials confirmed that the *Bt* proteins were expressed under Australian field conditions.

The APVMA is satisfied that the data presented supports the label claims for efficacy of the Bollgard III technology in cotton and that claim the product can considered safe to use provided it is used according to the label recommendations and resistance preventative management plan.

9 LABELLING REQUIREMENTS

READ BEFORE OPENING THIS BAG
Cottonseed in this bag contains the Bollgard III technology by Monsanto

BOLLGARD III

ACTIVE CONSTITUENTS:
***Bacillus thuringiensis* subsp. *kurstaki* delta endotoxins**
as produced by the *Cry1Ac* and *Cry2Ab* genes and their controlling sequences
***Bacillus thuringiensis* strain AB88 exotoxin**
as produced by the *Vip3A(A)* gene and its controlling sequence

GROUP	11C	INSECTICIDE

For in-built protection of cotton against the Cotton Bollworm and Native Budworm

APVMA APPROVAL NO. XXXX

DIRECTIONS FOR USE

Cotton containing the Bollgard III technology must be grown in accordance with the directions prescribed in the endorsed Resistance Management Plan and with the conditions set out in the current Bollgard III Technology User Agreement. Read before planting.

Control of Cotton Bollworm and Native Budworm (Heliothis pests)
Cotton containing the Bollgard III technology expresses *Bacillus thuringiensis* subsp. *kurstaki* delta endotoxin proteins and a *Bacillus thuringiensis* strain AB88 exotoxin protein for the control of the following Lepidopteran cotton insect pests:

Cotton Bollworm *Helicoverpa armigera*
Native Budworm *Helicoverpa punctigera*

Cotton containing the Bollgard III technology will provide significant protection of cotton against the Cotton Bollworm and Native Budworm. Supplemental insecticide control may still be required under conditions of high pest pressure or high plant stress to maintain Heliothis populations below economically damaging levels.

Monitor crops regularly and apply insecticide treatments if necessary. Insecticide selection should comply with the Insecticide Resistance Management Strategy for Conventional Cotton for the current year. For optimum efficacy, manage crops and inputs to avoid plant stress. Note that eggs and very small larvae (neonates/first instar) will be observed in the crop, as larvae must feed before being controlled by the Bollgard III technology.

The Bollgard III technology is not registered to control other pests. Other pests should be monitored and treated using the recommended thresholds.

Resistance management

Preventative resistance management is designed to keep *Helicoverpa* resistance to non-detectable levels and so extend the benefits of Bollgard III cotton into the future. Growers must practise preventative resistance management as detailed in the 'Resistance Management Plan for Bollgard III Cotton' (the Plan) **for the current year**, as endorsed by the cotton industry and included in the Bollgard III Technology User Agreement. Note that separate Plans apply in different geographic regions. Additional copies of the current year Plan may be obtained from any Monsanto Technology Service Provider or from Monsanto.

Crop management

Always grow a Bollgard III cotton variety that is appropriate for the local area. Use the best agronomic and crop management practices for the area. For optimum efficacy, manage agronomic inputs to avoid plant stress and to achieve early plant maturity. Follow integrated pest management principles and utilise crop management practices that minimise pest incidence.

IMPORTANT NOTICE

The Bollgard III technology by Monsanto is registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) under the Agricultural and Veterinary Chemicals Code. Bollgard III technology is protected under license in Australia of Patent Nos 638438 and 762748. This seed may only be used by growers who have a current Bollgard III Technology User Agreement with Monsanto Australia Limited governing the use of the Bollgard III technology. Any use of the Bollgard III technology that contravenes the Agreement will be subject to claims of patent infringement and/or breach of Agreement.

LIMIT OF WARRANTY AND LIABILITY

Buyers and all users are deemed to have accepted the terms set out in the Technology User Agreement upon opening this bag of cottonseed containing the Bollgard III technology.

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ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour

ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council

NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

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