Australian Government
Department of Health
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan for

DIR 145

Commercial release of cotton genetically modified for insect resistance and herbicide tolerance

(Bollgard® 3 XtendFlex™ (SYN-IR102-7 x MON 15985-7 x MON-88913-8 x MON 88701-3)

and

XtendFlex™ (MON-88913-8 x MON 88701-3) cotton)

Applicant: Monsanto Australia Limited

December 2016

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Summary of the Risk Assessment and Risk Management Plan

for

Licence Application DIR 145

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this application for the intentional, commercial scale release of insect resistant and herbicide tolerant genetically modified (GM) cottons in Australia. A Risk Assessment and Risk Management Plan (RARMP) for this application was prepared by the Regulator in accordance with requirements of the *Gene Technology Act 2000* (the Act) and corresponding state and territory legislation, and finalised following consultation with a wide range of experts, agencies and authorities, and the public. The RARMP concludes that this commercial release poses negligible risks to human health and safety and the environment and no specific risk treatment measures are imposed. However, general licence conditions have been imposed to ensure that there is ongoing oversight of the release.

The application

Application number	DIR 145
Applicant	Monsanto Australia Limited (Monsanto)
Project title	Commercial release of cotton genetically modified for insect resistance and herbicide tolerance (Bollgard® 3 XtendFlex™ (SYN-IR102-7 x MON 15985-7 x MON-88913-8 x MON 88701-3) and XtendFlex™ (MON-88913-8 x MON 88701-3) cotton)
Parent organism	Cotton (*Gossypium hirsutum L.*)
Introduced genes and modified traits	**Three insect resistance genes:** • *vip3A* synthetic gene from *Bacillus thuringiensis* (Bt) • *cry1Ac* gene from Bt • *cry2Ab* gene from Bt **Three herbicide tolerance genes:** • *cp4 epsps* gene (two copies) from *Agrobacterium sp*. strain CP4 (glyphosate tolerance) • *bar* gene from *Streptomyces hygroscopicus* (glufosinate tolerance) • *dmo* gene from *Stenotrophomonas maltophilia* (dicamba tolerance) **Four selectable marker genes:** • *nptII* gene from *Escherichia coli* (antibiotic resistance) • *aph4* gene from *E. coli* (antibiotic resistance) • *uidA* gene from *E. coli* (reporter) • *aad* gene from *E. coli* (antibiotic resistance)
Proposed locations	Australia-wide
Primary purpose	Commercial release of the GM cotton

Risk assessment

The risk assessment concludes that risks to the health and safety of people or the environment from the proposed dealings, either in the short or long term, are negligible.

The risk assessment process considers how the genetic modification and activities conducted with the GMO might lead to harm to people or the environment. Risks were characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application, relevant previous approvals, current scientific knowledge and advice received from a wide range of

experts, agencies and authorities consulted on the preparation of the RARMP. Both the short and long term impacts were considered.

Credible pathways to potential harm that were considered included: toxic and allergenic properties of the GM cottons; potential for increased weediness of the GM cotton relative to unmodified plants; and vertical transfer of material to other sexually compatible plants.

The principal reasons for the conclusion of negligible risks are: the GM cottons have been produced by conventional breeding from GM parental cotton lines. Two of the three GM parent cottons have been approved for commercial release and the third has been approved for field trial in Australia. The risks associated with these cottons and combinations thereof, have been assessed previously as negligible. One of the GM parental lines (individually and in combination with another parental GM line) currently makes up over 90% of Australian commercial cotton production, without reports of adverse effects on human health or the environment. The genes and their products have been assessed as posing no increased risk of toxicity or allergenicity to humans or animals, or toxicity to other beneficial organisms. GM cotton has limited capacity to spread and persist in undisturbed environments and can be controlled using integrated weed management in agricultural and high intensity use areas. In addition, food made from the GM parental cotton lines has been approved by Food Standards Australia New Zealand (FSANZ) as safe for human consumption and this approval also covers food from offspring produced by conventional breeding.

Risk management

The risk management plan describes measures to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan is given effect through licence conditions.

As the level of risk has been assessed as negligible, specific risk treatment is not required. However, the Regulator has imposed licence conditions to ensure that there is ongoing oversight of the release and to allow the collection of information to verify the findings of the RARMP. The licence also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.

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Abbreviations

aad	*3"(9)-O-aminoglycoside adenyltransferase* gene
Act2	Actin2
aph4	*hygromycin B phosphotransferase* gene
APVMA	Australian Pesticides and Veterinary Medicines Authority
bar	*bialaphos resistance* (*phosphinothricin N-acetyltransferase*) gene
BGII	Bollgard® II GM cotton
BG2 RRF	Bollgard® II Roundup Ready Flex® GM cotton
BG3	Bollgard® 3 GM cotton
BG3 RRF	Bollgard® 3 Roundup Ready Flex® GM cotton
BG3 XF	Bollgard® 3 XtendFlex™ GM cotton
Bt	*Bacillus thuringiensis*
CaMV	Cauliflower mosaic virus
cp4 epsps	*epsps* gene from *Agrobacterium sp*. strain CP4
CP4 EPSPS	EPSPS protein from *Agrobacterium sp*. strain CP4
CRDC	Cotton Research and Development Corporation
Cry	Crystal protein
cry1Ac	*cry1Ac* gene from *B. thuringiensis*
Cry1Ac	Cry1Ac crystal protein from *B. thuringiensis*
cry2Ab	*cry2Ab* gene from *B. thuringiensis*
Cry2Ab	Cry2Ab crystal protein from *B. thuringiensis*
CSD	Cotton Seed Distributors
CSIRO	Commonwealth Scientific and Industrial Research Organisation
ctp	Chloroplast transit peptide
DAFWA	Department of Agriculture and Food, Western Australia
DIR	Dealing involving Intentional Release
dmo	*dicamba monooxygenase* gene from *Stenotrophomons maltophilia*
DMO	Dicamba monooxygenase
DNA	Deoxyribonucleic acid
EPSPS	5-enolpyruvylshikimate-3-phosphate synthase
FMV	Figwort mosaic virus
FSANZ	Food Standards Australia New Zealand (formerly ANZFA)
GM	Genetically Modified
GMO	Genetically Modified Organism
GTTAC	Gene Technology Technical Advisory Committee
GUS	β-glucuronidase protein
ha	Hectare
HGT	Horizontal gene transfer
Hsp	Heat shock protein
IPM	Integrated Pest Management
IWM	Integrated Weed Management
LGA	Local government area
m	metre
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
nptII	Neomycin phosphotransferase II
NSW DPI	New South Wales Department of Primary Industries
OGTR	Office of the Gene Technology Regulator
PAT	phosphinothricin N-acetyl transferase
PRR	Post release review
QDAF	Queensland Department of Agriculture and Fisheries
RARMP	Risk Assessment and Risk Management Plan
RMP	Resistance Management Plan for cotton
TFA	Total Fatty Acids

aad	*3"(9)-O-aminoglycoside adenyltransferase* gene
TGA	Therapeutic Goods Administration
the Regulations	Gene Technology Regulations 2001
the Regulator	Gene Technology Regulator
TUA	Technology User Agreement
RRF	Roundup Ready Flex® GM cotton
Ubi3	Ubiquitin3
USDA-APHIS	United States Department of Agriculture Animal and Plant Health Inspection Service
US EPA	United States Environmental Protection Agency
Vip	Vegetative insecticidal protein
vip3Aa	*vip3Aa* gene from *B. thuringiensis*
Vip3Aa	Vip3Aa crystal protein from *B. thuringiensis*
XF	XtendFlex™ GM cotton

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.

2. The Act in conjunction with the Gene Technology Regulations 2001 (the Regulations), an inter-governmental agreement and corresponding legislation in States and Territories, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

3. This chapter describes the parameters within which potential risks to the health and safety of people or the environment posed by the proposed release are assessed. The risk assessment context is established within the regulatory framework and considers application-specific parameters (Figure 1).

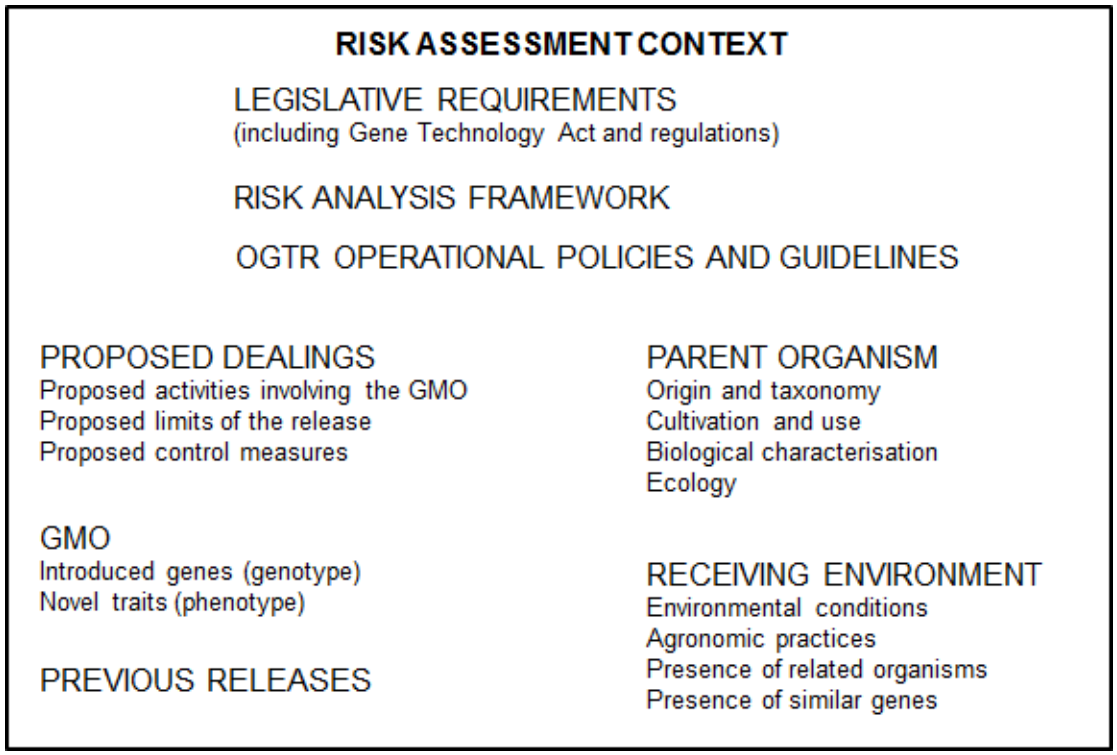

Figure 1 Summary of parameters used to establish the risk assessment context

Section 2 Regulatory framework

4. Sections 50, 50A and 51 of the Act outline the matters which the Gene Technology Regulator (the Regulator) must take into account, and who must be consulted, in preparing the Risk Assessment and Risk Management Plans (RARMPs) that inform the decisions on licence applications. In addition, the Regulations outline further matters the Regulator must consider when preparing a RARMP.

5. Since this application is for commercial purposes, it cannot be considered as a limited and controlled release application under section 50A of the Act. Therefore, under section 50(3) of the Act, the Regulator was required to seek advice from prescribed experts, agencies and authorities on

matters relevant to the preparation of the RARMP. This first round of consultation included the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government authorities or agencies prescribed in the Regulations, all Australian local councils[1] and the Minister for the Environment. A summary of issues contained in submissions received is given in Appendix A.

6. Section 52 of the Act requires the Regulator, in a second round of consultation, to seek comment on the RARMP from the experts, agencies and authorities outlined above, as well as the public. Advice from the prescribed experts, agencies and authorities in the second round of consultation, and how it was taken into account, is summarised in Appendix B. Seven public submissions were received and their consideration is summarised in Appendix C.

7. The Risk Analysis Framework (OGTR 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the legislative requirements. Additionally, there are a number of operational policies and guidelines developed by the Office of the Gene Technology Regulator (OGTR) that are relevant to DIR licences. These documents are available from the OGTR website.

8. Any dealings conducted under a licence issued by the Regulator may also be subject to regulation by other Australian government agencies that regulate GMOs or GM products, including FSANZ, Australian Pesticides and Veterinary Medicines Authority (APVMA), Therapeutic Goods Administration (TGA) and the Department of Agriculture and Water Resources. These dealings may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

Section 3 The proposed release

9. Monsanto Australia Ltd (Monsanto) proposes commercial cultivation of two types of GM cotton. The first type, XtendFlex™ cotton, contains three introduced genes that confer herbicide tolerance. The second type, Bollgard® 3 XtendFlex™ cotton, contains three introduced genes that confer insect resistance, in addition to the three herbicide tolerance genes.

10. For the remainder of the document XtendFlex™ will be referred to as XF and Bollgard® 3 XtendFlex™ as BG3 XF.

11. XF cotton is a result of conventional crossing between Roundup Ready Flex® (RRF) cotton and MON 88701 cotton. RRF is a herbicide tolerant GM cotton which has been approved for commercial release and MON 88701 is a herbicide tolerant GM cotton that has been approved for limited and controlled release.

12. The BG3 XF cotton was produced by conventional crossing between MON 88701 and a Bollgard® 3 Roundup Ready Flex™ (BG3 RRF), a GM cotton approved for commercial release. BG3 RRF is a product of conventional crosses between three GM cottons: Bollgard® II (BGII), COT 102 and RRF. Details can be found in RARMPs for DIR 059/2005, DIR 066/2006 and DIR 124.

13. GM cotton lines are identified by OECD unique identifiers; SYN-IR102-7 (COT102), MON-15985-7 (BGII), MON-88913-8 (RRF) and MON-88701-3 (MON 88701):

- XF is identified as MON-88913-8 x MON-88701-3

[1] Monsanto is seeking approval for unrestricted commercial release of the GM cottons in all cotton growing areas of Australia. Cotton may be grown over a significant proportion of Australian agricultural land, and viable cottonseed may be transported out of the cotton growing areas. Therefore, the Regulator decided to consult with all of the local councils in Australia, except for those that have requested not to be consulted on such matters.

- BG3 XF is SYN-IR102-7 x MON-15985-7 x MON-88913-8 x MON-88701-3.

14. The applicant is seeking approval for the release to occur Australia-wide, subject to any moratoria imposed by States and Territories for marketing purposes. The GM cottons could be grown in all commercial cotton growing areas, and products derived from the GM plants would enter general commerce, including use in human food and animal feed.

15. The dealings involved in the proposed intentional release are:

(a) conducting experiments with the GMO
(b) making, developing, producing or manufacturing the GMO
(c) breeding the GMO
(d) propagating the GMO
(e) using the GMO in the course of manufacture of a thing that is not the GMO
(f) growing, raising or culturing the GMO
(g) transporting the GMO
(h) disposing of the GMO
(i) importing the GMO

and the possession, supply or use of the GMO for the purposes of, or in the course of, any of the above.

Section 4 The parent organism

16. The parent organism is upland cotton (*Gossypium hirsutum* L.), the most commonly cultivated cotton species worldwide. Cotton is exotic to Australia and is grown as an agricultural crop in New South Wales (NSW) and Queensland (Qld), with occasional trial or small-scale cultivation in Victoria (Vic.), northern Western Australia (WA) and in the Northern Territory (NT).

17. Cotton is grown as a source of textile and industrial fibre, cottonseed oil and linters for food use, and cottonseed meal for animal feed. A brief description of relevant biological information about the parent organism is provided in the following sections. More detailed information is contained in a reference document, *The Biology of* Gossypium hirsutum *L. and* Gossypium barbadense *L. (cotton)* (OGTR 2016), which was produced to inform the risk assessment process for licence applications involving GM cotton plants. The document is available from the OGTR website or on request from the OGTR.

18. In establishing the risk context, details of the parent organism form part of the baseline for a comparative risk assessment (Figure 1, OGTR 2013). Non-GM cotton is the standard baseline for biological comparison, while noting that over 98 % of the Australian commercial cotton crop is GM cotton (ABARES 2016).

19. Cotton with stacked insect resistance and herbicide tolerance constituted over 95% of the Australian cotton crop by 2012 (James 2013). Currently, BGII and RRF, individually and in combination, constitute approximately 93% of the Australian cotton crop (data supplied by applicant). Thus, data for BGII RRF cotton is also relevant for purposes of comparative risk assessment.

4.1 Cotton as a crop

20. Cotton is a domesticated crop that grows best under agricultural conditions. It prefers soils with high fertility and responds well to irrigation. Cotton has been commercially cultivated in Australia since the 1860s (OGTR 2016). It is a perennial plant that is cultivated as an annual.

21. A summary of climatic data and production systems for past and potential cotton growing areas can be found in the RARMP for DIR 066/2006. This provides a general overview of abiotic factors relevant to release in commercial cotton growing areas, including consideration of potential areas of development north of latitude 22°South.

22. Areas where cotton can be grown in Australia are mainly limited by water availability, the suitability of the soil, temperature and the length of the growing season. For further detail see discussion in RARMPs for DIR 066/2006 and DIR 124. Commercial cultivation of cotton is also extensively reviewed in *The Biology of* Gossypium hirsutum *L. &* Gossypium barbadense *L. (cotton)* (OGTR 2016).

23. Based on 2014/15 and 2015/16 estimates of commercial cropping areas and production volume in Australia cotton is ranked ninth in area of production and fifth in total production among Australian crops. Estimated production area for 2015/16 was 270,000 ha (ABARES 2016).

4.1.1 Management of pests in cotton crops

24. Prior to the introduction of GM insect resistant cotton, crops were sprayed 8 to 12 times per season to control *Helicoverpa spp.* and these sprays also controlled other insect pests (OGTR 2016). Since 2002, the number of sprays per season has been reduced.

25. Currently Integrated Pest Management (IPM) is preferred to control insect pests. This involves using a range of tactics throughout the season to manage pest and beneficial insect populations in and around farms. Use of insecticides is only one part of this system and use of IPM is important to slow the development of insecticide resistance (CottonInfo 2016).

4.1.2 Cotton and herbicide resistance

26. Issues regarding herbicide use and resistance most appropriately fall under the Agricultural and Veterinary Chemicals Code Act 1994, and as such are the responsibility of the APVMA. The APVMA assesses all herbicides used in Australia and sets their conditions of use, including for resistance management.

27. A number of agricultural practices are used to control weeds in fields prepared for the planting of cotton and also to manage cotton volunteers. These practices include cultivation or the application of herbicide treatments (OGTR 2016). In addition, integrated weed management (IWM) practices are used to avoid selection of resistant weed biotypes (CropLife Australia 2012). The Australian cotton industry uses such weed management practices to decrease the possibility that herbicide tolerant weeds will become a problem (CRDC 2013b).

28. Over 30 weed species from around the world are reported to have resistance to glyphosate of which 12 species are found in Australia (source: Australian Glyphosate Sustainability Working Group database; (Heap 2016). No glufosinate-resistant or dicamba-resistant weed species have been reported in Australia (Heap 2016).

4.2 Non-GM cotton outside cultivation – weediness

29. In the context of this RARMP, characteristics of cotton when present as a volunteer in the relevant agricultural land uses, in intensive use areas such as roadsides and in nature conservation areas are examined.

30. The Standards Australia National Post-Border Weed Risk Management Protocol rates the weed risk potential of plants according to properties that strongly correlate with weediness for each relevant land use (Standards Australia Ltd et al. 2006). These properties relate to the plants' potential to cause harm (impact), to its invasiveness (spread and persistence) and to its potential distribution (scale). The weed risk potential of volunteer cotton has been assessed using methodology based on the National Post-Border Weed Risk Management Protocol (OGTR 2016).

4.2.1 Potential to cause harm

31. In summary, as a volunteer (rather than as a crop), non-GM cotton is considered to exhibit the following potential to cause harm:

- low potential to negatively affect the health of animals and/or people
- low potential to reduce the establishment or yield of desired plants
- low potential to reduce the quality of products or services obtained from all relevant land use areas
- low potential to restrict the physical movement of people, animals, vehicles, machinery and/or water
- some potential to act as a reservoir for a range of pests and pathogens
- low potential to adversely affect soil salinity and the water table

32. With respect to the potential to negatively affect the health of people, it should be noted that workers in gins may develop byssinosis, an allergy to cotton (OGTR 2016).

33. Mammals, including people, can be fatally poisoned when ingesting cotton plant parts, due to the presence of natural toxins in cotton. These are gossypol and the cyclopropenoid fatty acids (malvalic acid, sterculic acid and dihydrosterculic acid), all of which are found in seeds and certain other plant tissues (Bell 1986). These compounds limit the use of cottonseed meal in human food and animal feed.

4.2.2 Invasiveness

34. With regard to invasiveness, non-GM cotton has:

- low ability to establish amongst existing plants
- low tolerance to average weed management practices in cropping and intensive land uses
- high tolerance in nature conservation areas, as they are not specifically targeted for weed management or because weed management is not applied in the area where cotton is present
- a short time to seeding (less than one year)
- low annual seed production
- the ability to reproduce sexually, but not by vegetative means
- some ability for long distance spread by natural means (wind dispersal)
- high ability for spread long distance by people from dryland and irrigated cropping areas, as well as from intensive land uses such as road sides
- low ability for spread by people from or to nature conservation areas

4.2.3 Management of volunteer cotton

35. The control of cotton volunteers is usually achieved by mechanical means or use of a range of herbicides, preferably as part of IWM practices. Control of volunteer cotton by herbicides is most effective on seedling cotton and there are no herbicides currently registered for control of volunteer cotton larger than nine nodes in size (CottonInfo 2015).

36. However, considering the widespread use of GM glyphosate-tolerant cotton crops use of glyphosate to control cotton volunteers is not generally an option at any stage. This is also true for glufosinate ammonium where tolerance to this herbicide is included in GM cotton lines. Currently dicamba is not registered for use in controlling volunteer cotton (CottonInfo 2015). For the most recent information, consult the APVMA website.

4.2.4 Spread

37. Seed may be spread off-farm, primarily through irrigation runoff into common drainage lines and during transport to gins. In 2012 and 2013, Queensland Department of Agriculture and Fisheries

(QDAF) conducted a survey of cotton plants outside crop areas in Qld and northern NSW. This study showed that plants were generally localised just beyond the farm gate and very little cotton had moved into the broader agricultural landscape. Densities were highest adjacent to cotton farms, within a 5 km radius and in close proximity to ginning facilities (CRDC 2013a).

4.2.5 Potential distribution

38. Modelling to predict the areas suitable for long-term survival of *G. hirsutum* cotton outside cultivation areas in Australia indicated that the areas of greatest potential were north eastern coastal regions (Rogers et al. 2007), which is consistent with reported naturalised populations in Australia (Australia's Virtual Herbarium).

39. A number of limiting factors including dry stress, cold temperatures and soil fertility were important in predicting this distribution. However, establishment in these areas would be further limited by canopy conditions of the natural vegetation, as well as fire regimes and weed competition (Rogers et al. 2007). Thus although there are some naturalised populations in relatively natural areas of northern Australia, there is limited potential for *G. hirsutum* populations to spread and persist in undisturbed nature conservation areas.

40. Naturalised populations are thought to have been derived from cottons planted in the early 19th century in northern Qld and the NT (Brubaker & Craven pers. comm., 2002, *cited in* (OGTR 2014) or from cottons planted before the current commercial types (Eastick 2002).

4.3 Sexually compatible plants

41. In the natural environment, for successful hybridisation to occur, parent plants have to occur in close proximity, flower at the same time, have pollen from one plant deposited on the stigma of the other, fertilisation must occur and progeny must survive to sexual maturity. Any progeny seed would have to be viable. Cotton is largely self-pollinating and no self-incompatibility mechanisms exist. Where cross-pollination does occur it is likely facilitated by honeybees.

42. Baseline information on vertical gene transfer associated with non-GM cotton plants can be found in *The Biology of* Gossypium hirsutum *L. and* Gossypium barbadense *L. (cotton)* (OGTR 2016). In summary, cotton is predominantly self-pollinating with no self-incompatibility mechanisms present. It does not reproduce by asexual mechanisms, although root cuttings can be propagated under laboratory conditions.

43. The other species of cultivated cotton, *G. barbadense*, is sexually compatible with G. *hirsutum*.

44. There are 17 native species of *Gossypium* in Australia, most of which are found in the NT and the north of WA (OGTR 2016). However, the likelihood that *G. hirsutum* could hybridise successfully with any of the native Australian cottons is extremely low, due to genetic incompatibility. This is discussed in greater detail in *The Biology of* Gossypium hirsutum *L. and* Gossypium barbadense L.*(cotton)* (OGTR 2016) and in the RARMP for DIR 124.

Section 5 The GM parental cottons

5.1 Introduction to the GM parents

45. The GM cottons proposed for release are:

- XtendFlex™ (XF) cotton. XF cotton is a result of conventional crossing between Roundup Ready Flex® (RRF) cotton and MON 88701 cotton
- Bollgard® 3 XtendFlex™ (BG3XF) cotton. BG3 XF cotton was produced by conventional crossing between MON 88701 and Bollgard® 3 Roundup Ready Flex™ (BG3 RRF).

46. Both RRF and BG3 RRF have been extensively evaluated in previous RARMPs for limited and controlled release and have been approved for commercial release throughout Australia under the following DIRs:

- RRF under DIR 059/2005 and DIR 066/2006
- BG3 RRF under DIR 124

47. Therefore, given the thorough risk assessment already undertaken, this section will provide only brief summary information for these GM parental cottons.

48. The dicamba and glufosinate tolerant GM cotton MON 88701 was evaluated for limited and controlled release under DIR 120, individually and in combination with the other parental cottons. It has not been approved for commercial cultivation in Australia and has few commercial approvals worldwide. Thus, the current RARMP will focus mainly on MON 88701, including the *dmo* gene, the DMO protein and its metabolites.

5.1.1 Details of the introduced genetic elements

49. Table 1 shows the genes present in each of the GMOs proposed for release, as well as the parental cotton lines used to generate the GMOs. Further details of the individual genetic elements are provided in Table 2, which also identifies which parental GM cottons contain each element.

Table 1: Genes present in the GMOs proposed for release

GM cotton	Parental GM cotton	Glyphosate tolerance	Dicamba tolerance	Glufosinate tolerance	Insect resistance	Antibiotic resistance
XF	RRF	*cp4 epsps*[a]		-	-	-
	MON 88701	-	*dmo*	-	-	-
		-	-	*bar*	-	-
BG3 XF	BG3 RRF		-	-	*cry1Ac*	*aad*
			-	-	*cry2Ab*	*uidA, nptII*
			-	-	*vip3Aa19*	*aph4*
		cp4 epsps	-	-		
	MON 88701	-	*dmo*		-	-
				bar		

[a] two copies of this gene are inserted

Table 2: Details of introduced genetic elements

Gene (Source)	Protein produced	Function	Promoter (source)	Terminator (source)	Additional elements (source)	Present in
cry1Ac (*Bt*)	Crystal protein 1Ac	Insect Resistance	35S (CaMV)	7S 3' *(Glycine max*)		BGII; BG3; BG3 RRF
cry2Ab *(Bt)*	Crystal protein 2Ab2	Insect resistance	35S (CaMV)	nos (*A.tumefaciens*)	PetHSP70 (*Petunia x hybrida*), Ctp2 (*Arabidopsis thaliana*)	BGII; BG3; BG3 RRF
vip3A (*Bt*)	Vegetative insecticidal protein 3A	Insect resistance	actin2 (A. thaliana)	nos *(A.tumefaciens)*		COT102; BG 3; BG3 RRF
cp4 epsps[a] *(Agrobacterium sp.* strain CP4)	5-enolpyruvylshikimate-3-phosphate synthase	Tolerance to glyphosate	P-FMV/TSF2 (Figwort mosaic virus/A. thaliana) P-35S/ACT8 (CaMV/A.thaliana)	rbcs-E9 (*Pisum sativum* – pea) rbcs-E9 (*P. sativum*)	Ctp2 (*A. thaliana*) Ctp2 (*A. thaliana*)	RRF; BG3 RRF
bar[a] *(Streptomyces hygroscopicus)*	Phosphinothricin N-acetyl transferase (PAT)	Tolerance to glufosinate	35S (CaMV)	nos *(A.tumefaciens)*	HSP70 (*P. x hybrida*)	88701
dmo[a] *(Stenotrophomonas maltophilia)*	Dicamba monooxygenase	Tolerance to dicamba	PC1SV[a] (Peanut chlorotic streak caulimovirus)	E6 3' (*Gossypium barbadense*)	TEV (tobacco etch virus) Ctp2 (*A. thaliana*)	88701
aad *(E. coli)*	3"(9)-O-aminoglycoside adenyltransferase.	Marker - Antibiotic resistance (streptomycin)	Tn7 (*E.coli*)			BGII; BG3; BG3 RRF
nptII	Neomycin phosphotransferase type II	Marker - Antibiotic resistance (kanomycin)	35S (CaMV)	nos *(A.tumefaciens)*		BGII; BG3; BG3 RRF
uidA *(E. coli)*	beta-glucuronidase (GUS)	Selective marker (colour reaction)	35S (CaMV)	nos *(A.tumefaciens)*		BGII; BG3; BG3 RRF
aph4 *(E. coli)*	Hygromycin B phosphotransferase	Marker - Antibiotic resistance (hygromycin)	ubiquitin 3 (A. thaliana)	nos *(A.tumefaciens)*	ubi3 intron	COT102; BG 3; BG3 RRF

5.2 GM RRF cotton

50. As noted above (Section 5.1), RRF cotton has undergone extensive evaluation for limited and controlled release (DIR 055/2004) and has been approved for commercial release under a number of DIR licences (DIR 059/2005, DIR 066/2006, DIR 124).

5.2.1 Genetic modification and introduced genes

51. A detailed description of the genetic modification is available in the RARMP for DIR 035/2003. This information was extensively reviewed in the RARMP for DIR 124.

52. Roundup Ready Flex® cotton contains two copies of the 5-enolpyruvylshikimate-3-phosphate synthase (*cp4 epsps*) gene from the soil bacterium *Agrobacterium* sp. strain CP4 (Barry et al. 1992). Unlike plant EPSPS enzymes, the CP4 EPSPS enzyme can function in the presence of glyphosate, the active constituent of a number of herbicides including Roundup Ready® herbicide. Expression of *cp4 epsps* in Roundup Ready Flex® GM cotton confers tolerance to glyphosate (Barry et al. 1992).

53. Previous risk assessments for RRF (cited above) include extensive discussion of the method of genetic modification, molecular stability, the introduced genes and regulatory elements and the proteins encoded by the introduced genes. This includes discussion of potential toxicity/allergenicity to humans, animals and non-target arthropods, effects on soil microorganisms, the presence of identical or similar genes and proteins in the environment. These risk assessments concluded that there was negligible risk of harm to people, other beneficial organisms or the environment from the *cp4 epsps* gene or its expression in GM cotton.

5.2.2 Experience with RRF cotton and its products

Australian experience from cultivation of RRF cotton

54. RRF GM cotton has previously been described and assessed for commercial release (refer to RARMPs for DIR 059/2005, DIR 066/2006 and DIR 124. These assessments of RRF, individually or in combination with BGII and BG3 concluded that it poses negligible risks to human health and safety and the environment.

55. The RRF trait also combined with insect resistance traits in BGII RRF, which accounted for approximately 87% of Australian commercial plantings in the 2015/16 growing season (data supplied by applicant). As such experience with BGII RRF is important to the risk context for this RARMP.

56. To date, the Regulator has not received reports of adverse effects on human health, animal health or the environment caused by RRF cotton (alone or in combination with BGII) as a crop. There are no scientific studies showing adverse effects of RRF cotton grown as a crop on human health or the environment in Australia.

57. Approval from FSANZ has been granted for the use of oil and linters derived from RRF *G. hirsutum* and RRF *G. barbadense* (pima cotton) in food (FSANZ 2005). These approvals cover material derived from RRF cotton and GM cotton lines produced by conventional breeding with RRF.

International experience with RRF cotton

58. A number of countries have approved RRF cotton for environmental release, as well as food and feed use (Table 3). All countries listed have also approved BGII RRF or BGII – see table notes for detail. However, regulatory systems in some countries, for example the USA and Canada, do not require separate authorisation for environmental release of GMOs produced by conventional crossing between previously authorised GMOs.

59. Some countries have also approved RRF for *G. barbadense*. Please refer to the International Service for the Acquisition of Agri-biotech Applications (ISAAA) GM approval database for further details.

Table 3: International approvals of RRF cotton[a]

Country	Food - direct use or processing	Feed - direct use or processing	Cultivation - domestic or non-domestic use
Brazil[b]	2011	2011	2011
Canada	2005	2005	
China	2007	2007	
Colombia	2009	2008	
Costa Rica			2009
EU	2015	2015	
Japan	2005	2006	2006
Mexico	2006		2006
New Zealand	2006		
Philippines	2005	2005	
Singapore	2014		
South Africa			2007
South Korea	2006	2006	
Taiwan	2015		
USA	2005	2005	2004

[a] Source: ISAAA GM approval database; accessed March 2016
[b] Countries underlined have also approved BG II and BGII RRF. All others listed here have also approved BGII.

5.3 GM BG3 RRF cotton

60. The BG3 and BG3 RRF cottons were approved for commercial release in Australia in 2014 in DIR 124. To date, no widescale commercial planting of these cottons has occurred in Australia. Approximately 19,000 ha of BG3 cotton was planted in the 2015/16 season, mainly for seed production for wider scale commercial release in 2016/17 (CSD 2016). BG3 RRF cotton is a product of the conventional crossing of BG3 and RRF cottons.

61. The previous generation of GM cottons, BGII and BGII RRF *G. hirsutum,* were approved for commercial release in previous licences DIR 059/2005 and DIR 066/2006. These cottons in combination with COT102 were also approved (as BG3 and BG3 RRF) for commercial release in DIR 124.

62. Tables 1 and 2 (Section 5.1) list the genetic elements present in BG3 and BG3 RRF. BG3 RRF cotton contains genes conferring insect resistance (*cry1Ac*, *cry2Ab*, *vip3Aa*), glyphosate herbicide tolerance (*cp4 epsps*), antibiotic resistance genes, a reporter gene and regulatory elements.

63. The following discussion of BG3 and BG3 RRF is summarised from DIR 124 unless otherwise stated.

5.3.1 Genetic modification

64. The RARMP for DIR 124 includes information regarding the molecular stability and expression levels of the inserted genes in BG3 and BG3 RRF. The risk assessment for DIR 124 and those from earlier DIR licences (DIR 012/2002, DIR 059/2005, DIR 066/2006, DIR 101) discussed the genetic elements inserted in BG3 and BG3 RRF.

65. In addition to the *cp4 epsps* gene discussed in section 5.2, BG3 RRF contains the *cry1Ac*, *cry2Ab* and *vip3Aa* genes from *B. thuringiensis,* which confer resistance to Lepidopteran pests of cotton. The RARMPs from commercial releases (DIR 059/2005, 066/2006 and DIR 124) and for earlier limited and controlled releases for COT 102 (DIR 017/2002, DIR 025/2002, DIR 034/2003, DIR

036/2003, DIR 058/2005, DIR 065/2006 and DIR 073/2007) discuss the details of these genes and their products. These RARMPs also discuss the marker genes and the regulatory elements.

66. This GM cotton expresses proteins toxic to certain insects in the order Lepidoptera, including the most important insect pests of cotton crops in Australia. It is also tolerant to the herbicide glyphosate. Accordingly, agricultural management of BG3 RRF cotton differs from non-GM cotton in the application of insecticides and herbicides.

67. Recent publications have reviewed studies conducted to determine Cry toxin specificities and potential activity against other insect orders (van Frankenhuyzen 2013; Hilbeck & Otto 2015). One of these concludes that there is sufficient information to indicate that Cry1Ac is also active against a Dipteran species (tsetse flies) and an Hemipteran species (*Acyrthosiphon pisum,* 'pea aphid') (van Frankenhuyzen 2013) while the other suggests that further examination of Cry toxins, particularly stacks of Cry toxins needs further testing (Hilbeck & Otto 2015). However, in a recent review the National Academies of Science (US) concluded that comparisons of Bt crops and non-Bt crops showed an increase in insect biodiversity in Bt crops compared to non-Bt crops sprayed with insecticide (National Academies of Sciences 2016).

68. Additionally, field trials in Australia comparing insect populations in non-GM, BGII and BG 3 cotton found differences in insect communities only when sufficient lepidopteran larvae were present to exert direct and indirect effects on other insect species. No differences in insect numbers were found between BGII and BG3 crops. The authors concluded that compared to BGII, BG 3 has no additional effect on cotton invertebrate communities (Whitehouse et al. 2014).The RARMP for DIR 124 concluded that there was negligible risk to people, other beneficial organisms or the environment from the release of this cotton.

69. FSANZ assessed each of the GM parent cottons for BG3 and BG3 RRF as being as safe as those produced from other conventional cotton varieties (FSANZ 2002; FSANZ 2004; FSANZ 2005) and approval of the parental cottons includes approval of cotton products from conventional crosses of the parental lines.

70. BG3 RRF cotton meets the definition of an agricultural chemical product under the Agricultural and Veterinary Chemicals Code Act 1994, due to its production of insecticidal substances. As such, it needs to comply with an approved insect resistance management plan (RMP) and any other relevant conditions that may be imposed by the APVMA. For GM cotton, the Transgenic and Insect Management Strategy (TIMS) committee, facilitated by Cotton Australia manages RMPs. The RMP includes mandatory growing of refuges to produce susceptible insects, defined planting windows, restrictions on the use of foliar *Bt* sprays, mandatory cultivation of crop residues and the control of volunteer plants following cropping and in refuge crops.

5.3.2 Previous releases of BG3 and BG3 RRF

71. To date, there have been few international approvals for the commercial release of BG3 and BG3 RRF cottons. However, regulatory systems in some countries, including Canada and the US, do not require separate authorisation for environmental release of GMOs produced by conventional crossing between other already authorised GMOs. This would be the case for BG3 and BG3 RRF cottons.

72. BG3 was approved for direct use or processing in food in Japan and Mexico in 2014. BG3 RRF was approved for direct use or processing in food in Japan (2014), South Korea (2015) and Taiwan (2016), as well for direct use or processing in feed in South Korea (2016).

5.4 GM MON 88701 cotton

73. GM MON 88701 cotton was approved by the Regulator for limited and controlled release under DIR 120, but has not been approved for commercial release in Australia and has had only a few approvals worldwide.

74. MON 88701 has been modified for tolerance to the herbicides dicamba and glufosinate. Thus, agricultural management of MON 88701 cotton will differ from non-GM cotton in that these herbicides can be applied for control of weeds.

5.4.1 The introduced genes, regulatory elements and encoded proteins

75. MON 88701 contains a copy of the codon-optimised *dmo* gene, which encodes a protein that confers tolerance to dicamba herbicide (2-methoxy-3,6-dichlorobenzoic acid).

76. The *dmo* gene and encoded protein have previously been described in the RARMP for limited and controlled release application DIR 120. The gene was derived from the bacterium *Stenotrophomonas maltophilia* (formerly *Pseudomonas maltophilia*) strain DI-6 (Herman et al. 2005). *S. maltophilia* is an aerobic, environmentally ubiquitous gram negative bacterium which is generally considered safe.

77. MON 88701 also contains the bialaphos resistance (*bar*) gene, isolated from *Streptomyces hygroscopicus* (Thompson et al. 1987), a common saprophytic, soil-borne microorganism that is not considered to be a pathogen of plants, humans, or other animals (OECD 1999). The *bar* gene encodes a phosphinothricin N-acetyl transferase (PAT) protein that confers tolerance to glufosinate ammonium (Thompson et al. 1987), the active component in a number of herbicides.

78. The *bar* gene and the PAT protein has been assessed in other RARMPs (DIR 062/2005, DIR 091), as well as in scientific literature. It has been assessed in canola (DIR 021/2002, DIR 62/2005, DIR 108, DIR 138) in Australia and in corn and soybean in other countries. The environmental safety of the PAT protein present in biotechnology-derived crops, either alone or in combination with other GM traits, has also been extensively assessed by regulatory authorities worldwide (CERA 2011). Data presented and assessed for DIR 120 suggests that there is no toxicity or allergenicity associated with the PAT protein or the products produced in the presence of glufosinate.

79. MON 88701 also contains regulatory elements derived from plants, *A. tumefaciens* and from three plant viruses (caulimovirus, peanut chlorotic streak caulimovirus and tobacco etch virus).

5.4.2 The DMO protein

80. The introduced *dmo* gene encodes for dicamba mono-oxygenase (DMO) that rapidly demethylates dicamba to 3,6-dichlorosalicylic acid (DCSA), which has no herbicidal activity, and formaldehyde. Data presented and assessed for DIR 120 suggests that there is no toxicity or allergenicity associated with the DMO protein or the products produced in the presence of dicamba.

81. MON 88701 DMO was found to be specific to dicamba when tested using structurally similar endogenous substrates as well as exogenous herbicide substrates representing a wide range of herbicide modes-of-action (Monsanto 2012).

82. The GM 88701 plants and non-GM control plants (Coker 130, a near-isogenic line) were treated with a range of herbicides from a range of mode of action groups. The only differences between MON 88701 and non-GM controls were seen for dicamba, where GM plants showed little or no damage while control plants showed high levels of damage (Monsanto 2012), indicating that GM plants did not have differing response to any other herbicides.

83. FSANZ found that food derived from cotton line MON 88701 in *G. hirsutum* and *G. barbadense* is as safe for human consumption as food derived from conventional cotton cultivars (FSANZ 2013). This assessment also includes foods derived from cotton lines generated by conventional crosses

with MON 88701. In addition FSANZ noted that as the cotton components used in food were highly refined it is likely that dietary exposure to DMO (and PAT) will be negligible (FSANZ 2013).

5.4.3 Genetic modification and molecular characterisation

84. MON 88701 was produced using *Agrobacterium*–mediated transformation. This method has been widely used in Australia and overseas for introducing genes into plants. More information can be found on the Risk Assessment References page on the OGTR website. Data presented in the RARMP for DIR 120 indicate the introduced gene was stably incorporated, with no unintended sequences in MON 88701.

5.4.4 Germination and dormancy

85. Characteristics affecting germination and dormancy have the potential to affect the persistence of seed in the environment and therefore the potential for weediness.

86. Laboratory germination trials were conducted in the United States (US) using seed collected from field test sites, using MON 88701 as the test line. Non-GM Coker 130 was the control line. Four commercial non-GM cottons per site were used as reference lines, selected from a group of nine used across the trial sites.

87. Seeds were collected from three field sites with four replicates per site. Germination was tested in a laboratory under six controlled temperature treatments. Three were constant temperatures and three were alternation between two temperatures.

88. Measures included percentage of germinated seed, percentage of viable hard seed, percentage of viable firm swollen seed and percentage of dead seed. The percentage of viable hard seed was included as a measure of dormancy and potentially an indicator of weediness. Data were analysed within sites and across all sites.

89. For one site there were significant ($p < 0.05$) differences, with higher percentage of normal germinated seed and lower percentage of abnormal germinated seed for MON 88701 at the 20 °C/30 °C regime. This was the only temperature regime for which this assessment was made. At the same site MON 88701 had a lower percentage of dead seed at the 10 °C/20 °C regime. However, these differences were not seen in other sites and were not significant in combined site analysis. The means for each measure also fell within the reference range for these measures.

90. For one treatment, statistically significant ($p < 0.05$) differences were seen between MON 88701 and control for the combined-site data. MON 88701 had a higher percentage germinated seeds and significantly lower percentage of dead seeds at 30 °C. However, these differences were small and were within the reference range.

91. Considering these results it is unlikely that there are changes to germination and dormancy which would increase the weediness of MON 88701 cotton compared to non-GM cotton.

5.4.5 Approvals of MON 88701 cotton and its products

Australian approvals of MON 88701 cotton

92. MON 88701 has been approved for field trials in Australia, alone and in combination with the other GM parental cottons (DIR 120). FSANZ assessed food from MON 88701 cotton as being as safe for consumption as food derived from conventional cotton (FSANZ 2013).

International approvals of MON 88701 cotton and its products

93. MON 88701 cotton has been approved internationally for cultivation, for food or for food and feed (including direct use and processing in each use). These are summarised in Table 4.

Table 4: International approvals of MON 88701 cotton[a]

Country	Food - direct use or processing	Feed - direct use or processing	Cultivation - domestic or non-domestic use
Canada	2014	2014	
Japan	2013	2015	2015[b]
Mexico	2014		
New Zealand	2014		
South Korea	2015	2015	
Taiwan	2016		
USA	2013	2013	2015

[a] Source: ISAAA GM approval database; accessed March 2016

[b] Type 1 use - 'for conveyance and cultivation of food, feed etc. Approved only when the LMOs are judged not to cause adverse effects on biological diversity.'

94. In addition, two crops containing a *dmo* gene derived from *S. maltophilia* have also received nonregulated status in the US (USDA-APHIS): dicamba tolerant soybean (2015), glufosinate and dicamba tolerant maize (USDA-APHIS 2015; USDA-APHIS 2016).

Section 6 The GMOs

6.1 Introduction to the GMOs

95. The GM cottons proposed for release are produced by conventional crossing of RRF cotton with MON 88701 cotton for XF and of BG3 RRF cotton with MON 88701 cotton for BG3 XF.

96. Tables 1 and 2 list all of the genetic elements present in the GM cottons used to produce the GM cottons under consideration.

97. As with the GM parents of XF and BG3 XF cotton, the GM plants are phenotypically similar to non-GM cotton. They will be limited by the same abiotic factors as non-GM cotton, sexually compatible with the same plants and their products used identically to non-GM cotton. The difference between XF cotton or BG3 XF cotton and non-GM cotton is that the GM cotton are tolerant to glyphosate, glufosinate and dicamba herbicides and in the case of BG3 XF cotton, resistant to Lepidopteran insect pests of cotton.

98. Agricultural management of the GM cottons differs from non-GM cotton with respect to insect pest management and in the application of herbicides to control weeds in the crop. Any XF or BG3 XF cotton volunteers in subsequent crops would need to be controlled by mechanical means or use of herbicides other than those to which the crop is tolerant.

99. The RARMP for DIR 120 identified additional information that may be required to assess an application for a large scale or commercial release of BG3 XF and XF cottons, or to justify a reduction in containment conditions. This includes:

- additional data on the potential toxicity and allergenicity of plant materials from the GM cottons
- additional phenotypic characterisation of the GM cotton lines, particularly with respect to traits that may contribute to weediness, including tolerance to environmental stresses and disease susceptibility
- additional molecular and biochemical characterisation of the GM cotton lines
- additional information on pollen mediated gene flow in cotton in the absence of a pollen trap

100. Subsequent to release of DIR 120, BG3 and BG3 RRF cottons have been approved for commercial release under DIR 124, which included some of the additional information and

Monsanto has provided additional information for MON 88701, alone and in combination with BG3 and BG3 RRF (discussed below).

6.2 Characterisation of the GMOs

101. The applicant has provided data from both Australian and US field trials. Data supplied for Australian lines were generated using plants produced by conventional crossing between three of the four GM parental cotton lines – BGII x RRF x MON 88701. Data from US trials were generated for BG3 XF cotton, in a background that is not available in Australia.

102. Field trials in Australia provided protein expression data and phenotypic data. In the US, separate field trials were conducted for protein expression, cottonseed composition and phenotypic measures. Material from field trials was also used for glasshouse germination trials in the US (see Section 6.2.3).

6.2.1 Molecular Stability

103. Southern blotting analysis was used to confirm the identity of inserts for each gene in BG3 XF cotton. The BG3 XF cotton was analysed together with each of the GM parental lines, positive and negative controls. Results of this analysis confirmed that BG3 XF contains the DNA inserts of each of the parental GM lines.

6.2.2 Protein expression

104. In the US trials, concentrations of expressed proteins from the introduced genes in BG3 XF and GM parental lines were measured in leaves, roots and seeds samples (Table 5). Data are shown as the mean ± standard deviation, followed by the range of values recorded.

Table 5: Protein expression for BG3 XF and GM parental cotton lines in US field trials

Protein	Line[a]	Leaf[b] (µg/g fw)	Root (µg/g fw)	Seed (µg/g fw)
DMO	BG3 XF[c]	31 ± 14	15 ± 3.5	18 ± 6.8
		12 - 70	9.6 - 22	8.6 - 33
	MON 88701	55 ± 16	19 ± 5.7	21 ± 6.0
		26 - 81	11 - 32	9.6 - 34
PAT	BG3 XF	0.61 ± 0.20	0.47 ± 0.11	3.6 ± 0.99
		0.32 - 0.96	0.34 - 0.75	2.5 - 6.1
	MON 88701	0.94 ± 0.36	0.61 ± 0.19	7.0 ± 1.8
		0.39 - 1.6	0.32 - 1.1	3.5 - 12
CP4 EPSPS	BG3 XF	210 ± 61	46 ± 10	150 ± 26
		120 - 300	25 - 77	89 - 200
	RRF	210 ± 88	60 ± 10	170 ± 30
		97 - 360	37 - 71	120 - 230
Cry1Ac	BG3 XF	2.6 ± 1.0	0.38 ± 0.054	2.8 ± 0.96
		1.2 - 4.5	0.29 - 0.48	1.8 - 5.3
	BGII	4.7 ± 1.8	0.49 ± 0.15	6.1 ± 1.7
		1.7 - 7.9	0.30 - 0.73	2.5 - 8.5
Cry2Ab2	BG3 XF	29 ± 12	17 ± 2.3	70 ± 12
		13 - 66	13 - 21	55 - 91
	BGII	50 ± 16	30 ± 4.4	110 ± 7.0
		17 - 75	22 - 37	93 - 120
Vip 3Aa19	BG3 XF	6.6 ± 1.4	2.0 ± 0.49	1.9 ± 0.59
		4.8 - 9.4	1.2 - 3.3	1.1 - 3.2
	COT102	7.1 ± 2.8	2.4 ± 0.72	0.66 ± 0.23
		2.3 - 12	1.6 - 3.8	0.33 - 1.0

[a] For each protein expression in the test line (BG3 XF) was compared to the appropriate GM parental cotton, listed in the table

[b] Leaf – OSL1, collected at 2 -3 leaf stage; root collected at late/peak bloom stage; seed collected after harvest

[c] BG3 XF plants were "treated" – sprayed with dicamba, glufosinate, glyphosate

105. In the US trials, the concentrations of most expressed proteins are lower in all tissues tested in the BG3 XF cotton than in the comparable GM parental line. The exception is Vip3Aa19 in seed.

106. Although there are differences in protein expression between BG3 XF and parental lines, the means for most proteins in BG3 XF are within the ranges observed for the parental lines. The exceptions are Cry2Ab2 in root and seed tissues (lower than parental line) and Vip3Aa19 (higher than parental line) in seed tissue.

107. Data for protein expression were also collected from Australian field trials. In 2013/14 season samples were obtained from a single site, while in 2014/15 samples were collected from five sites in northern NSW and southern Qld. In each year, each site had three plots per site in a randomised complete block design.

108. Expressed protein concentrations were collected in the Australian trial from BGII x RRF x MON 88701 cotton. Leaf samples (Over season leaf - OSL) were collected at four stages throughout plant development from stage V2-V3 to cutout (OSL1 – OSL4).

109. In Australian trials in 2013/14 the highest concentration of each of proteins involved in insect resistance and herbicide tolerance was seen in OSL2. In 2014/15 this was also true. In the case of Cry1Ac the concentration in OSL1, equal to that for OSL1 and for DMO the concentration in OSL4 was very similar to OSL2. In general the concentration of expressed protein peaks at OSL2 then declines in later samples, but is expressed throughout the season. Concentrations of all proteins were lower in 2014/15 than in 2013/14, except the DMO protein, which had concentrations equal to or higher than those recorded for 2013/14.

110. A single pollen sample was analysed in the 2013/14 season. In season 2014/15 no data for pollen are supplied. Expression levels of all proteins except Cry1Ac was lower in pollen than leaf tissues. However, with only a single sample analysed the pollen data are not robust.

111. The concentrations of Cry2Ab and CP4 EPSPS proteins in leaf and pollen samples reported here are similar to those recorded for parental GM cottons BG3 and BG3 RRF grown under Australian conditions from 2010 to 2012, reported in the RARMP for DIR 124. However, leaf and pollen concentrations of Cry1Ac are higher than those reported for BG3 and BG3 RRF samples in the DIR 124 RARMP. Expressed protein concentrations were lower in pollen than in leaf tissues (except Cry1Ac), as observed for the single sample in 2013/14 field trials.

6.2.3 Phenotypic characterisation of the GM cottons

Australian characterisation of the GM cotton phenotype

112. Phenotypic analysis of BGII x RRF x MON 88701 has been generated from field trials in Australia. Details of the treatments in the Australian trials are as follows:

- all treatments were sprayed with glyphosate
- Test unsprayed: BGII x RRF x MON 88701 (15985 x 88913 x 88701), no glufosinate and dicamba spray
- Test sprayed: BGII x RRF x MON 88701 with glufosinate and dicamba spray
- Control: BGII RRF (15985 x 88913) in a similar background line
- Reference: two BGII RRF cotton lines in backgrounds adapted for local climatic conditions
- due to issues with germination, at some sites the test lines were planted at higher seeding rates

113. Samples were collected from the same sites as samples for expression data. Details of plot setup and replication are given with discussion of that data in Section 6.2.2.

114. Measures assessed were:

- stand counts - early (21 days after planting - DAP), final (seven days prior to harvest)
- plant vigour rating
- plant height (every 21 days from 21 DAP)
- number of nodes (every 21 days from 21 DAP)
- nodes above white flower (NAWF) – three samples, taken weekly from seven days after flowering (DAF)
- cotton seed weight per plot and as kg/ha
- lint yield per plot and kg lint/ha
- fibre quality measures - length, uniformity, short fibre index, strength, elongation and micronaire
- seed measures - seed index (g/100 seeds), seed number per 50 bolls on acid-delinted seed (boll sample collected 4 days prior to harvest)

115. Data from the single site in 2013/14 season were analysed independently, while both pooled data (five sites) and individual site data were analysed for 2014/15.

116. There were few significant differences between test (sprayed or unsprayed) and control plants in either season or for pooled or individual site data in 2014/15. Differences were:

- Plant stand counts (plants/m) were higher for test plants at two of the sites in 2014/15, but no significant difference was apparent for pooled data
- unsprayed test plants were significantly shorter than controls at some later stages of plant growth
- both sprayed and unsprayed test plants were taller than reference lines.

- yield (kg lint/plot or kg lint/ha) was significantly lower in unsprayed test plants compared to control plants (strongly influenced by significant differences at two of the five sites in 2014/15)

117. The applicant suggests that some of the differences at individual sites may have been influenced by competition between plants for light, water or nutrients in plots the sites where seeding rates were increased for test plants. However, there were not consistent differences within the sites or across the two sites with higher seeding rates.

118. These results do not provide clear results, due to issues with seed germination in 2013/14 and differences in seeding rates for 2014/15. However, there do not appear to be clear differences in phenotype that indicate an increased risk of weediness for the test lines containing MON 88701.

119. No germination trials were performed in Australia, however lower germination rates were noted in the 2013/14 season for the test line (BGII x RRF x MON 88701). This observation influenced an adjustment in the sowing rates of this seed in some test sites in the 2014/15 season. However, there were higher than expected germination rates for some of these sites in 2014/15, based on the earlier observations.

120. Australian agronomic and phenotypic data provided for DIR 124 included BG3 and BG3 RRF, which contain the *vip3Aa* gene expressing Vip3Aa protein, which is not present in the lines presented for the current application. These were compared to BGII and BGII RRF as well as RRF and non-GM cotton. There were no consistent differences between the BG3 or BG3 RRF and the BGII or BGII RRF lines with respect to agronomic and phenotypic characteristics. In that study, non-GM plants had significant insect damage which was consistent with lower yields for these plants.

United States characterisation of the GM cotton phenotype

121. The applicant has provided phenotypic and environmental interactions measures for a single season in the US.

122. The US expression studies consisted of five sites, each with four replicates of the test line (BG3 XF) and the control lines. Control lines were BGII, COT102, RRF and MON 88701. Plots of test and control lines were set up as a randomised complete block design.

123. The US composition studies consisted of five sites, each with four replicates of the test line (BG3 XF) and the control line (non-GM Coker 130 cotton, a comparative line). Plots of test and control lines were set up as a randomised complete block design.

124. The US phenotypic studies compared BG3 XF to the control (non-GM Coker 130) and commercial non-GM reference lines. Four reference lines were planted at each site, chosen from a group of nine possible commercial lines used across all sites. Eight sites set up as a randomised block design, with four replicates per site. Table 6 provides a list of the phenotypic measures collected in US field trials.

Table 6: Phenotypic measures collected for US field trials of BG3 XF

Measure class	Measure
Plant growth and Development	stand counts [a] plant height [a] plant vigour [a] NAWF [a] yield
Plant mapping	mainstem nodes nodes to first fruiting branch total bolls total first position bolls total vegetative bolls,

Measure class	Measure
	% retention first position bolls
	% first position bolls
Seed measures	seed index
	mature seed per boll
	immature seed per boll
Boll and fibre measures	boll weight
	micronaire
	elongation per cent
	fibre strength
	fibre length
	fibre uniformity
Abiotic stressors [b]	drought
	hail injury
	heat,
	mineral microtoxicity
	nutrient deficiency
	soil compaction
	sun scald
	wet soil
	wind
Disease stressors [c]	blights, rots, rusts, spots and nematodes
Arthropod stressors	nine non-lepidopteran arthropods

[a] these measures collected more than once throughout a season
[b] biotic, disease and arthropod measures were by observation
[c] thirteen disease stressors assessed

125. Data were analysed from individual sites and across five sites combined. For some parameters, there were significant differences ($p < 0.05$) at individual sites, but not for combined site analyses. Likewise, a significant difference found for combined site data may not mean that each site showed a significant difference when analysed individually. Thus, in the following summary where the comments reflect results from combined site analyses, the number of individual sites with significant differences is also shown in brackets:

- lower plant heights at 30 DAP and harvest for treatment plants (four)
- higher total number of bolls (two)
- higher number of first position bolls (two)
- higher per cent retention of first position bolls (two)
- lower seed index (five)
- higher seeds per boll (four)
- higher per cent fibre elongation (two)

126. For combined site data, test and control means for all measures were within the range for reference material across all sites. This indicates that although there were some statistically significant differences in these parameters, there were no biologically meaningful differences.

127. There were no differences in the number of sites with observations of abiotic, disease or arthropod stressors.

Compositional analysis

128. Cotton seed was analysed for proximates (five measures), amino acids (18), fatty acids (22), carbohydrates by calculation, calories by calculation, fibre (four), minerals (nine), vitamin E (α-tocopherol) and anti-nutrients (gossypol and cyclopropenoid fatty acids), as well as moisture.

129. There were statistically significant ($p < 0.05$) differences between BG3 XF and control line for 40 of the measures. However, the means for all measures (and the entire range of values for all but two measures) were within the ranges available from the International Life Sciences Institute (ISLI) Crop Composition Database (accessed 28 April 2016) and/or within ranges cited in literature. One exception to this was dihydrosterculic acid for which the mean (0.30 % of total fatty acid -TFA) was significantly ($p < 0.001$) higher than the control mean (0.23 % TFA). The mean was within the range of the ISLI database (0.031 – 0.325 % TFA), but outside the range seen for reference lines in this study (0.18 - 0.27 % TFA).

130. In summary, the differences in cottonseed composition between BG3 XF and conventional cotton are generally within the range of expected variation between lines and locations.

131. FSANZ has assessed each of the GM parental cotton lines and stated that food derived from these lines is considered to be as safe for human consumption as food derived from conventional cotton cultivars. FSANZ approval includes foods produced from cotton lines generated by conventional crossing of approved GM lines, therefore BG3 XF and XF are included in these approvals.

Agricultural management

132. Any differences in agricultural management of BG3 XF and XF compared to non-GM cotton relate to the inserted genes in these lines for insect resistance and/or herbicide tolerance. These will influence only the management of insect pests and weeds in the cotton crop.

133. The applicant has also stated that growers wishing to purchase the seed will have to undergo training, sign a Technology User Agreement (TUA) and manage crops according to the terms of this agreement.

134. Individually and in combination, BGII and RRF cottons currently make up over 90% of the Australian commercial cotton crop. In addition to the introduced genes in BGII and RRF, BG3 XF contains the *vip3Aa* insect resistance gene and/or the *dmo* and *bar* genes for dicamba and glufosinate tolerance respectively.

135. The introduction of the *dmo* and *bar* genes means that, if appropriate approvals were obtained from APVMA, broadleaf weeds in cotton crops could be sprayed with glufosinate and dicamba, which has not been an option previously.

136. As mentioned in Section 4.2, glyphosate and glufosinate are not registered for use on volunteer cotton after nine nodes, thus can only be used on young cotton seedlings and are not suitable for use in controlling GM cotton volunteers expressing glyphosate or glufosinate tolerance. Dicamba is not registered for use in controlling volunteer cotton, although it is currently used for application prior to planting to control weeds (CottonInfo 2015) or for application in rotation crops (CRDC 2013b).

137. Management of volunteer cotton following growing of XF or BG3 XF crops would need to rely on cultivation and/or herbicide spraying using herbicides other than glyphosate, glufosinate or dicamba.

138. Integrated weed management (IWM) consists of using a number of integrated and complementary methods to control weeds, reducing the reliance on any single method (CRDC 2013b; CottonInfo 2015). Selection of crop variety, crop rotations, cultivation practices and rotation of herbicide classes are among the many components of this system (CRDC 2013b; CottonInfo 2015). The three herbicides to which XF and BG3 XF cottons are tolerant are from different mode of action groups. Glyphosate is from Group M, glufosinate Group N and dicamba Group I (CropLife Australia 2015). IWM is currently recognised as best practice for controlling weeds in cotton crops for a number of reasons including effective weed control, managing herbicide use, managing herbicide

resistance and minimising costs (CRDC 2013b). IWM can be tailored for use in managing GM herbicide tolerant crops (CropLife 2015).

Effects of the GMOs on desirable invertebrates in Australia

139. The potential for harmful effects of the three insect resistant GM parental cottons and BG3 on non-target organisms were reviewed in the RARMP for DIR 124. BG3 XF differs from BG3 RRF in the introduction of two genes for herbicide tolerance (MON 88701). No data additional to that previously considered under DIR 124 were supplied regarding the toxicity of BG3 XF cotton on non-target organisms in Australia. However, based on toxicity data provided for the DMO and PAT proteins (Section 5.4.1 and 5.4.2), and the known mechanism of action of these proteins, no adverse effects of BG3 XF on non-target invertebrates would be expected.

140. Synergistic, additive and antagonistic interactions between the Cry toxins were reviewed in previous RARMPs (DIR 059/2005, DIR 066/2006 and DIR 124), with the conclusion that Cry 1Ac and Cry2Ab acted independently without any consistent evidence of any of these effects. In addition a recent study examining interactions between Cry and Vip proteins in their effects on Lepidopteran species found no evidence of any interactions between Cry1Ac and Vip3Aa (Lemes et al. 2014).

6.2.4 Experience from cultivation of GM cottons

141. Field data from trials conducted in Australia have been discussed in earlier sections of this Chapter (Section 5.5 and Section 6.2). These data are for a GM line including BGII, RRF and MON 88701 (i.e. not including COT 102).

142. The applicant states that no adverse consequences have been recorded for COT102, MON 15985, MON 88913 or MON 88701 in any of the trials listed above or any uses overseas.

6.2.5 Approvals of the GM cottons proposed for release

143. As mentioned previously, FSANZ has approved use of oil and linters from each of the parental cottons and these approvals cover material from lines generated by conventional crossing of the parents, hence XF and BG3 XF cottons are included.

144. Approval will be required from the APVMA for application of glyphosate, glufosinate and dicamba for control of weeds in BG3XF and XF cotton crops.

145. The parental GM lines for XF and BG3 XF cotton have received nonregulated status from United States Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS) in the US. As mentioned previously, separate approval for lines produced by conventional crossing of GM lines is not required in some countries, including the US.

146. Approvals have been given for GM lines produced by crossing MON 88701 with other GM lines. For example a cross of MON 88701 and MON 88913 (RRF) has been approved for food (including direct and processing uses) in Japan and Mexico in 2015, and for feed (including direct and processing uses) and cultivation in Japan in 2015 (ISAAA GM approval database; accessed March 2016).

147. Likewise a cross between MON 88701, MON 88913 (RRF) and MON 15985 (BGII) has been approved for cultivation in Japan (2015). It has also been approved for food (including direct and processing uses) in Japan (2015), Mexico (2014) and South Korea (2015), for feed (including direct and processing uses) in Japan and South Korea in 2015 (ISAAA GM approval database; accessed March 2016).

148. More recently, a cross between all four GM lines (MON 15985 (BGII), COT102, MON 88913 (RRF) and MON 88701) has been approved for food, feed and cultivation in Japan and for food and feed in South Korea (ISAAA GM approval database; accessed November 2016).

Section 7 Other relevant considerations for the Australian environment

7.1 Other relevant plants

149. A number of insect resistant and/or herbicide tolerant GM cotton lines have been approved for commercial release in Australia (Table 7). These form part of the risk context for this DIR licence application.

Table 7: Australian approvals for the commercial release of insect resistant and or herbicide tolerant GM cotton lines.

GM cotton	Genes	DIR licence number[a]	Comment
MON 15985 (BGII)	*cry1Ac* *cry2Ab*	012/2002; 059/2005; 066/2006; 124	Approved individually and in combination with an herbicide tolerance trait
MON 88913 (RRF)	*cp4 epsps*	059/2005; 066/2006; 124	Approved individually and in combination with insect resistance and/or other herbicide tolerance trait
COT102 (VIP3A)	*vip3Aa19*	124	Approved individually and in combination with other insect resistance and/or herbicide tolerance trait
Liberty Link®	*bar*	062/2005	Glufosinate herbicide tolerance
Widestrike™	*cry1Ac* (synthetic) *cry1F* (synthetic) *pat*	091	Insect resistance and glufosinate herbicide tolerance

[a] This table lists licences for commercial release. For a list of all licences relating to the genes inserted in BG3 XF and XF see Table 3 (Section 5.1)

150. To date, the Regulator has not received any reports of adverse effects caused by these authorised releases.

151. Two other GM cottons (GlyTol® and GlyTol TwinLink Plus®) are currently under evaluation for commercial release in Australia under DIR 143, with a decision expected in December 2016. GlyTol® cotton contains the *2mepsps* gene for glyphosate tolerance and GlyTol TwinLink Plus® contains this gene and the *bar* gene for glufosinate tolerance as well as the *cry 1Ab*, *cry 2Ae* and *vip3Aa19* (*vip3Aa*) genes for insect resistance.

Chapter 2 Risk assessment

Section 1 Introduction

152. The risk assessment identifies and characterises risks to the health and safety of people or to the environment from dealings with GMOs, posed by or as the result of, gene technology (Figure 2). Risks are identified within the context established for the risk assessment (see Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

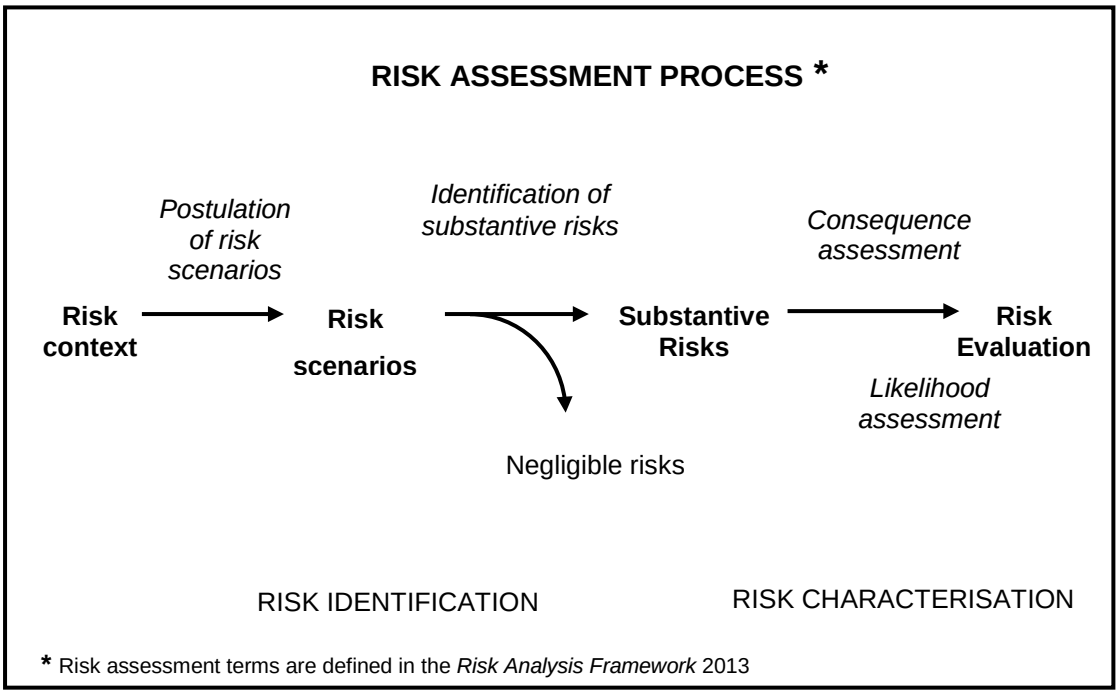

Figure 2 The risk assessment process

153. Initially, risk identification considers a wide range of circumstances whereby the GMO, or the introduced genetic material, could come into contact with people or the environment. Consideration of these circumstances leads to postulating plausible causal or exposure pathways that may give rise to harm for people or the environment from dealings with a GMO (risk scenarios) in the short and long term.

154. Postulated risk scenarios are screened to identify substantive risks that warrant detailed characterisation. A substantive risk is only identified for further assessment when a risk scenario is considered to have some reasonable chance of causing harm. Pathways that do not lead to harm, or could not plausibly occur, do not advance in the risk assessment process.

155. A number of risk identification techniques are used by the Regulator and staff of the OGTR, including checklists, brainstorming, reported international experience and consultation (OGTR 2013). A weed risk assessment approach is used to identify traits that may contribute to risks from GM plants. In particular, novel traits that may increase the potential of the GMO to spread and persist in the environment or increase the level of potential harm compared with the parental plant(s) are considered in postulating risk scenarios (Keese et al. 2014). In addition, risk scenarios postulated in previous RARMPs prepared for licence applications of the same and similar GMOs are also considered.

156. Substantive risks (i.e. those identified for further assessment) are characterised in terms of the potential seriousness of harm (Consequence assessment) and the likelihood of harm (Likelihood assessment). The level of risk is then estimated from a combination of the Consequence and Likelihood assessments. The level of risk, together with analysis of interactions between potential risks, is used to evaluate these risks to determine if risk treatment measures are required.

Section 2 Risk Identification

157. Postulated risk scenarios are comprised of three components (Figure 3):

i. The source of potential harm (risk source).

ii. A plausible causal linkage to potential harm (causal pathway).

iii. Potential harm to an object of value (people or the environment).

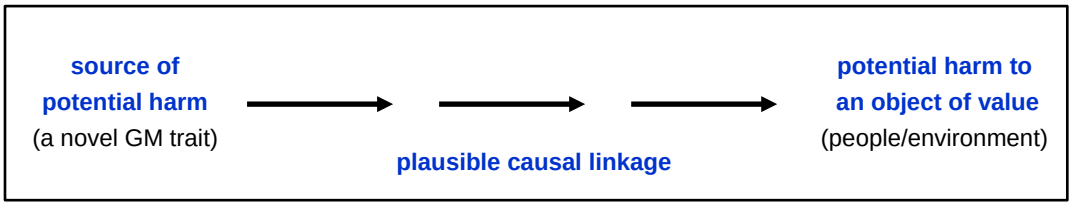

Figure 3 Risk scenario

158. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors:

- the proposed dealings, which may be to conduct experiments, develop, produce, breed, propagate, grow, import, transport or dispose of the GMOs, use the GMOs in the course of manufacture of a thing that is not the GMO, and the possession, supply and use of the GMOs in the course of any of these dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMOs
- characteristics of the parent organism(s)

2.1 Risk source

159. The source of potential harms can be intended novel GM traits associated with one or more introduced genetic elements, or unintended effects/traits arising from the use of gene technology.

160. As discussed in Chapter 1, XF cotton has been modified by the introduction of three genes for tolerance to the herbicides glyphosate, glufosinate and dicamba, respectively. BG3 XF cotton has been modified by the introduction of three insect resistance genes in addition to the same three herbicide tolerance genes.

The introduced genes for herbicide tolerance

161. The *cp4 epsps* gene and *bar* genes, which confer tolerance to the herbicides glyphosate and glufosinate, respectively, have been extensively characterised in a number of commercial cotton RARMPs (DIR 012/2002, DIR 023/2002, DIR 059/2005, DIR 066/2006, DIR 118 (*G. barbadense*) and DIR 124 for *cp4 epsps* and 062/2005 for *bar*). The genes were assessed as posing negligible risk to human or animal health or to the environment by the Regulator, as well as other regulatory agencies in Australia and overseas (see Chapter 1, Sections 5.2, 5.3 and 5.4).

162. No new metabolites are produced by GM plants containing the *cp4epsps* gene when sprayed with glyphosate, as the encoded protein is insensitive to glyphosate. The proteins encoded by the *cp4 epsps* and *bar* genes are highly substrate specific and are thus highly unlikely to interact with

one another when expressed in the same plant. The potential toxicity of herbicide metabolites is considered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) in its assessment of a new use pattern for particular herbicides over the top of a new GM crop.

163. In addition, FSANZ has approved the use of material derived from a number of GM crops, including cotton, containing the *cp4 epsps* or *bar* genes and their proteins. GM canola expressing both the *cp4epsps* and *bar* genes has been approved for commercial release in Australia under DIR 138.

164. Therefore, these individual genes will not be considered further as potential sources of risk. Nor will the combination of the three herbicide tolerance genes be considered with respect to toxicity or allergenicity. The CP4 EPSPS, PAT and DMO proteins expressed in the GM cotton are all highly substrate specific and participate in independent metabolic pathways. Thus it is unlikely that overall plant metabolism would be affected, or toxic novel compounds produced, as a result of the stacking of these three genes by conventional crossing of GM parents (J-BCH 2015). Risk scenario 2 will, however, consider the three herbicide tolerance genes in combination with respect to potential for weediness.

165. The *dmo* gene, which encodes the DMO protein and thus confers dicamba herbicide tolerance, has not been assessed previously for commercial release in Australia. This introduced gene is considered further as a potential source of risk.

The introduced genes for insect resistance

166. The *cry1Ac*, *cry2Ab*, *vip3Aa* insect resistance genes and the proteins for which they encode have been assessed, individually and in combination, in a number of commercial cotton licence RARMPs (see Sections 5.2 and 5.3 in Chapter 1). The RARMP for DIR 124 also considered the potential for interaction (e.g. synergistic or antagonistic) between these proteins that may lead to increased harm. That RARMP concluded that the genes and their proteins pose negligible risk to human health or the environment. There are no credible reports of adverse effects of these proteins on human or environmental health. Therefore, these genes will not be considered further as potential sources of risk for this application.

Selectable marker genes

167. The GM cottons also contain three selectable marker genes that confer antibiotic resistance (*npt II*, *aph4* and *aad*) and a reporter gene (*uidA*). These genes and their products have already been extensively characterised and have been assessed as posing negligible risk to human or animal health or to the environment by the Regulator, as well as other regulatory agencies in Australia and overseas. Further information about these genes can be found in the document *Marker genes in GM plants* available from the Risk Assessment References page on the OGTR website. As the genes have not been found to pose a substantive risk to either people or the environment, their potential effects will not be further considered for this application.

The regulatory sequences

168. The introduced genes are controlled by introduced regulatory sequences. These are derived from plants, bacteria and plant viruses (see Chapter 1, Table 2). Regulatory sequences are naturally present in plants and the introduced elements are expected to operate in similar ways to endogenous elements. The regulatory sequences are DNA that is not expressed as a protein and dietary DNA has no toxicity (Society of Toxicology 2003). As discussed in Chapter 1 and in previous RARMPs, these sequences have been widely used in other GMOs, including the parental GM lines that are grown commercially, without reports of adverse effects. Hence, risks from these regulatory sequences will not be further assessed for this application.

Unintended effects

169. The genetic modifications have the potential to cause unintended effects in several ways, including altered expression of endogenous genes by random insertion of introduced DNA in the genome, increased metabolic burden due to expression of the proteins encoded by the introduced genes, novel traits arising out of interactions with non-target proteins and secondary effects arising from altered substrate or product levels in biochemical pathways. However, the range of unintended effects produced by genetic modification is not likely to be greater than that from accepted traditional breeding techniques. These types of effects also occur spontaneously and in plants generated by conventional breeding (Bradford et al. 2005; Ladics et al. 2015; Schnell et al. 2015). In general, the crossing of plants, each of which will possess a range of innate traits, does not lead to the generation of progeny that have health or environmental effects significantly different from the parents (Weber et al. 2012; Steiner et al. 2013). Therefore, unintended effects resulting from the process of genetic modification will not be considered further in this application.

2.2 Causal pathway

170. The following factors are taken into account when postulating plausible causal pathways to potential harm:

- routes of exposure to the GMOs, the introduced gene(s) and gene product(s)
- potential effects of the introduced gene(s) and gene product(s) on the properties of the organism
- potential exposure to the introduced gene(s) and gene product(s) from other sources in the environment
- the environment at the site(s) of release
- agronomic management practices for the GMOs
- spread and persistence of the GM plants (e.g. reproductive characteristics, dispersal pathways and establishment potential)
- tolerance to abiotic conditions (e.g. climate, soil and rainfall patterns)
- tolerance to biotic stressors (e.g. pest, pathogens and weeds)
- tolerance to cultivation management practices
- gene transfer to sexually compatible organism
- gene transfer by horizontal gene transfer (HGT)
- unauthorised activities

171. Although all of these factors are taken into account, some have been considered in previous RARMPs or are not expected to give rise to substantive risks (see sections 2.2.1 to 2.2.5 below).

2.2.1 Tolerance to abiotic factors

172. The geographic range of non-GM cotton in Australia is limited by a number of abiotic factors including climate and soil compatibility, as well as water and nutrient availability (OGTR 2016). The introduced genes are unlikely to make the GM cotton plants more tolerant to abiotic stresses that are naturally encountered in the environment and are therefore unlikely to alter the potential distribution of the GM cotton plants. Also, as discussed in Chapter 1 (Section 6.2.3), there was no significant difference between the GM cottons and non-GM cotton varieties in their responses to a number of abiotic factors. Therefore, tolerance to abiotic stresses will not be assessed further.

2.2.2 Gene transfer to sexually compatible relatives

173. As discussed in Chapter 1, Section 4.3, *G. hirsutum* is sexually compatible with all GM and non-GM *G. hirsutum* varieties, as well as *G. barbadense*. Therefore, some cross-hybridisation with these plants is inevitable. Gene transfer to Australian native cotton species is not expected due to genetic incompatibility.

174. Some feral cotton does occur outside cultivation in northern Australia, including in nature reserves. However, these plants are not routinely subjected to control measures such as the use of herbicide or cultivation. Records of feral cotton presence do not indicate a marked change in the number of records or the pattern of occurrence (Australia's Virtual Herbarium accessed May 2016) since the previous comprehensive review in DIR 124 (OGTR 2014). If gene transfer from the GM cottons to feral cotton were to occur, the presence of herbicide tolerance genes in these feral cottons would not be expected to provide a selective advantage in the absence of herbicide application. Therefore, only gene transfer to cultivated *G. hirsutum* and *G. barbadense* will be considered further.

175. It should be noted that XF and BG3 XF cottons were generated by conventional crossing between two (XF) or four (BG3 XF) GM lines, so the introduced genes are located in different regions of the plant genome and may segregate independently of one another. Therefore, after any initial outcrossing of XF and BG3 XF cottons to other cotton, subsequent generations of cotton volunteer plants may contain all the genes from XF or BG3 XF cottons, genes from one of the GM parental cottons, genes from combinations of some of the parental lines of BG3 XF, or none of the genes from the GM lines. The resulting cottons will have equivalent or less insecticidal efficacy and herbicide tolerance than a GM cotton volunteer plant with all genes, so the assessment for weediness as a result of gene transfer of the introduced genes to other cottons is not affected. Therefore, segregation of the inserted genes will not be considered further.

2.2.3 Gene transfer by HGT

176. The potential for horizontal gene transfer (HGT) and any possible adverse outcomes has been reviewed in the literature (Keese 2008) and has been assessed in many previous RARMPs. HGT was most recently considered in detail in the RARMP for DIR 108. No risk greater than negligible was identified due to the rarity of these events and because the gene sequences (or sequences which are homologous to those in the current application) are already present in the environment and available for transfer via demonstrated natural mechanisms. Therefore, HGT will not be assessed further.

2.2.4 Unauthorised activities

177. Previous RARMPs have considered the potential for unauthorised activities to lead to an adverse outcome. The Act provides for substantial penalties for non-compliance and unauthorised dealings with GMOs. The Act also requires the Regulator to have regard to the suitability of the applicant to hold a licence prior to the issuing of a licence. These legislative provisions are considered sufficient to minimise risks from unauthorised activities, and no risk greater than negligible was identified in previous RARMPs. Therefore unauthorised activities will not be considered further.

2.3 Potential harm

178. Potential harms from GM plants include:

- harm to the health of people or desirable organisms, including toxicity/allergenicity
- reduced biodiversity through harm to other organisms or ecosystems
- reduced establishment of desirable plants, including having an advantage in comparison to related plants
- reduced yield of desirable vegetation
- reduced products or services from the land use
- restricted movement of people, animals, vehicles, machinery and/or water

- reduced quality of the biotic environment (e.g. providing food or shelter for pests or pathogens) or abiotic environment (e.g. negative effects on fire regimes, nutrient levels, soil salinity, soil stability or soil water table)

179. These harms are based on those used to assess risk from weeds (Standards Australia Ltd et al. 2006). Judgements of what is considered harm depend on the management objectives of the land into which the GM plant is expected to spread and persist. A plant species may have different weed risk potential in different land uses such as dryland cropping or nature conservation.

2.3.1 Production of a substance toxic or allergenic to people or toxic to other organisms

180. Toxicity is the adverse effect(s) of exposure to a dose of a substance as a result of direct cellular or tissue injury, or through the inhibition of normal physiological processes (Felsot 2000).

181. Allergenicity is the potential of a substance to elicit an immunological reaction following its ingestion, dermal contact or inhalation, which may lead to tissue inflammation and organ dysfunction (Arts et al. 2006).

182. Expression of the introduced genes involved in insect resistance or herbicide tolerance could result in production of novel toxic or allergenic compounds, or alter the production of endogenous compounds of cotton that are toxic or allergenic.

Endogenous cotton toxins

183. Cotton (*G. hirsutum* and *G. barbadense*) tissue, particularly the seeds, can be toxic if ingested in excessive quantities because of the presence of endogenous anti-nutritional and toxic factors including gossypol and cyclopropenoid fatty acids (including dihydrosterculic, sterculic and malvalic acids).

184. The presence of gossypol and cyclopropenoid fatty acids in cottonseed limits its use as a protein supplement in animal feed. Ruminants are less affected by these components because they are detoxified by digestion in the rumen (Blasi & Drouillard 2002). However, its use as stockfeed is limited to a relatively small proportion of the diet (Blasi & Drouillard 2002).

185. The presence of the introduced genes is not expected to directly affect the levels of endogenous toxins. This is supported by data provided by the applicant (Chapter 1, section 6.2.3) showing that gossypol levels in seed from the GM cottons lie within the recorded range for the parental cottons. Furthermore, there are established management practices to control the preparation and use of cottonseed products as feed for livestock, including poultry. Therefore, endogenous cotton toxins will not be considered further.

2.4 Postulated risk scenarios

186. Three risk scenarios were postulated and screened to identify any substantive risks. These scenarios are summarised in Table 8 and examined in detail in Sections 2.4.1 – 2.4.3. Postulation of risk scenarios considers impacts of the GM cotton or its products on people undertaking the dealings, as well as impacts on people and the environment exposed to the GM cotton or its products, as the result of the commercial use or the spread and persistence of plant material, including pollen.

187. In the context of the activities proposed by the applicant and considering both the short and long term, none of the three risk scenarios gave rise to any substantive risks that could be greater than negligible.

Table 8: Summary of risk scenarios from dealings with the GM cottons

Risk scenario	Risk source	Causal pathway	Potential harm	Substantive risk?	Reason
1	Introduced herbicide tolerance gene (*dmo*)	Commercial cultivation of GM cottons expressing the *dmo* gene ⬇ Exposure of humans and other desirable organisms by ingestion of, or contact with, GM cotton plant material or products, or inhalation of GM cotton pollen	Increased toxicity or allergenicity for humans and increased toxicity to other desirable organisms	No	• There is limited exposure of humans to the expressed protein. • The DMO protein has no demonstrated toxicity or allergenicity for humans. • Consumption of cotton by livestock is limited. • Low toxicity of DMO protein to other organisms. • Genes and proteins homologous to the *dmo* gene and DMO protein are widespread in the environment.
2	Introduced herbicide tolerance genes	Commercial cultivation of GM cotton expressing herbicide tolerance genes in GM plants ⬇ Dispersal of cottonseed to nature reserves, roadsides, drains or intensive use areas ⬇ Establishment of volunteer GM cotton plants in nature reserves, roadside areas or intensive use areas ⬇ Reduced effectiveness of weed management measures to control the volunteer GM cotton plants	Reduced establishment or yield of desirable agricultural crops OR Reduced utility of roadsides, drains, channels and intensive use areas OR Reduced establishment of desirable native vegetation OR Increased reservoir for pests or pathogens	No	• Glyphosate and glufosinate are not generally used to control volunteer cotton plants. Dicamba is neither used nor registered for direct control of volunteer cotton in Australia. • GM cotton containing the herbicide tolerance genes will have no advantage over other plants in areas where the herbicides are not applied. • The presence of the herbicide tolerance genes in the GM cotton plants will not affect the use of cultivation methods to control volunteers. • As cotton is unlikely to spread and persist in the environment, it will not provide a reservoir for pests or pathogens.
3	Introduced herbicide tolerance genes	Transfer of herbicide tolerance genes to other herbicide tolerant GM cotton plants by pollen flow ⬇ Establishment of volunteer GM cotton plants ⬇ Reduced effectiveness of weed management measures to control the hybrid plants	Reduced establishment or yield of desirable agricultural crops OR Reduced utility of roadsides, drains, channels and intensive use areas OR Reduced establishment of desirable native vegetation OR Increased reservoir for pathogens	No	• Stacking of genes with non-GM cotton or other GM cottons will not broaden the range of herbicide tolerance beyond that of the GM cotton in this application. • The stacking of the herbicide tolerance genes in the GM cotton plants will not affect the use of cultivation methods to control volunteers. • GM cotton containing the herbicide tolerance genes will have no advantage over other plants in areas where the herbicides are not applied. • As cotton is unlikely to spread and persist in the environment, it will not provide a reservoir for pests or pathogens.

2.4.1 Risk scenario 1

Risk Source	Introduced herbicide tolerance gene (*dmo*)
Causal pathway	Commercial cultivation of GM cottons expressing the *dmo* gene ⬇ Exposure of humans and other desirable organisms by ingestion of, or contact with, GM cotton plant material or products, or inhalation of GM cotton pollen
Potential harm	Increased toxicity or allergenicity for humans and increased toxicity to other desirable organisms

Risk source

188. The source of potential harm for this postulated risk scenario is the introduced *dmo* gene for herbicide tolerance to dicamba.

Causal pathway

189. The herbicide tolerance gene *dmo* is expressed in all parts of the GM cotton plant including leaf, stem, root, pollen and seed, at all developmental stages. People may be exposed to the GM cotton or its products through contact, consumption, or inhalation of pollen. However, the introduced genes and expressed proteins are not present in cotton products such as cottonseed oil, fibres and linters. Therefore, the majority of people that will be exposed to the introduced gene and its product will be workers involved in breeding, cultivating, harvesting, transporting and processing the GM cotton. The public, who consume cottonseed oil and cottonseed linters, or have contact with cotton fabrics, are not exposed to the introduced gene and its products.

190. Expression of the herbicide tolerance gene in cultivated GM cotton plants, or in volunteer GM cottons, may expose other organisms including livestock to the GM plant material through contact or ingestion. Apart from presence in all parts of the GM cotton plants including cottonseed and leaves, the DMO protein may also occur at low levels in the soil from plant material left after harvesting.

191. Livestock would be exposed to the expressed protein when consuming the GM cotton as forage, whole seed or seed meal, or through limited grazing of stubble. However, the amount of cotton plant material (both GM and non-GM) that is consumed by livestock is, by necessity, limited due to presence of endogenous toxins such as gossypol. Other organisms, including other mammals, birds, soil microbes and non-insect invertebrates are also expected to be exposed to cotton material in agricultural areas under cotton cultivation. These organisms may be exposed to the introduced insecticidal proteins through contact, ingestion or indirectly by feeding on herbivores that have ingested the GM cotton.

192. Cotton volunteers are commonly found along roadsides neighbouring cultivation sites and some transport routes, which may provide a pathway for exposure. However, there appears to be limited ability for cotton to establish persistent populations at these locations, so extended exposure to the GM cotton will occur mostly in the agricultural context.

Potential harm

193. Potentially, people exposed to the proteins expressed by the introduced genes may show increased toxic reactions or increased allergenicity. From consideration of the causal pathway, these are primarily people involved in cultivating or processing the GM cotton, or using GM cotton meal as animal feed.

194. The introduced herbicide tolerance gene was isolated from the bacterium *S. maltophilia*, which is widespread and prevalent in the environment (Chapter 1, Section 5.4.1). Information provided as part of this application indicates that the DMO protein is not likely to be toxic to humans or animals or allergenic to humans, as outlined in Chapter 1, Section 5.5.2.

195. When FSANZ assessed the safety of human food derived from linters and cottonseed oil from all the parental GM lines, including MON 88701, they concluded that food derived from MON 88701 cotton is as safe for human consumption as food derived from conventional cotton (FSANZ 2013). This assessment is applicable to foods derived from GM cotton lines produced by conventional breeding of this line.

196. FSANZ has examined dicamba herbicide residue data from MON 88701 cottonseed in the US, including the metabolites produced when dicamba is applied to the GM plants expressing the *dmo* gene (DSCA, DCGA, 5-hydroxydicamba). They concluded that the risk to public health and safety from exposure to dicamba metabolites is negligible in the absence of significant exposure to the parent herbicide or metabolites (FSANZ 2013).

197. The other metabolite of dicamba applied to the MON 88701 cotton plants is formaldehyde. This metabolite is likely to be present at levels within the expected range for other agricultural commodities.

198. In addition, the USDA-APHIS Final Environmental Impact Statement (FEIS) for MON 88701 concluded that the release of MON 88701 cotton is 'not expected to change the existing composition of soil microflora in cropping systems' (USDA-APHIS 2014).

Conclusion

199. Risk scenario 1 is not identified as a substantive risk, due to extremely limited exposure and the lack of toxicity or allergenicity of the DMO protein to humans or other desirable organisms. Therefore, this risk could not be considered greater than negligible and does not warrant further detailed assessment.

2.4.2 Risk scenario 2

Risk Source	Introduced herbicide tolerance genes
Causal pathway	Commercial cultivation of GM cotton expressing the herbicide tolerance genes in GM plants ⬇ Dispersal of cottonseed to nature reserves, roadsides, drains or intensive use areas ⬇ Establishment of volunteer GM cotton plants in nature reserves, roadside areas or intensive use areas ⬇ Reduced effectiveness of weed management measures to control the volunteer GM cotton plants
Potential harm	Reduced establishment or yield of desirable agricultural crops OR Reduced utility of roadsides, drains, channels and intensive use areas OR Reduced establishment of desirable native vegetation OR Increased reservoir for pests or pathogens

Risk source

200. The source of potential harm for this postulated risk scenario is the introduced genes that encode the proteins for herbicide tolerance to glyphosate, glufosinate and dicamba herbicides.

Causal pathway

201. If volunteer cotton plants establish in cotton fields after cultivation of a cotton crop, the presence of the genes for herbicide tolerance could reduce the ability to control volunteer cotton plants.

202. Volunteers will occur in cotton fields and also where bales or modules are placed. In addition, volunteers may be found along roads between farms and processing facilities as well as in irrigation channels and drains where cotton trash may accumulate. In southern Australia, most volunteer

seedlings that emerge over winter are likely to be killed by frosts. However, seedlings that emerge later can establish and grow at all these locations.

203. A limited amount of cottonseed is used for ruminant stockfeed. Cottonseed may be spread to intensive use areas such as dairies or cattleyards, where volunteer cotton plants may establish and some cottonseed may pass through digestion intact and able to germinate (as discussed in the RARMP for DIR 120).

204. Cottonseed may be spread by wind and by water, as well as by transport, so there is potential for spread into native vegetation reserves.

205. However, cottonseed is not likely to be spread by wind over long distances, so unless nature reserves are close to production areas spread into these areas by wind is unlikely.

206. Spread of cottonseed by water can occur during flooding. However, management practices (Good Management Practice of the cotton industry) includes retaining irrigation water runoff and some stormwater runoff, so this would reduce the dispersal of seed by water. Cottonseed is also unlikely to be viable after water-borne transport (OGTR 2016).

207. Volunteer cotton with the herbicide tolerance genes would have a fitness advantage in areas where glyphosate, glufosinate or dicamba are used to control weeds. If these herbicides were the primary means of control for volunteer cotton, expression of the herbicide resistance gene in volunteer cotton plants would reduce the effectiveness of control and enhance the chance of survival and establishment of volunteer cotton with the herbicide tolerance genes.

208. However, as noted in Chapter 1, Section 4.2.3, glyphosate and glufosinate herbicides are not generally used to control established cotton and are not registered for control of mature cotton volunteer plants. Although dicamba is registered for pre-plant weed control in cotton, it is not currently registered for control of volunteer cotton (CottonInfo 2015). Also, as mentioned in Chapter 1, Section 5.4, the dicamba tolerant cotton lines show the same susceptibility to other herbicides as non-GM cotton plants. Thus other herbicides (aside from glyphosate and glufosinate) could be used as part of weed management practices to control volunteer cotton plants. Bromoxynil, carfentrazone and a combination of paraquat and diquat have been shown to be effective (CRDC 2013b), but there are no herbicides registered for seedlings beyond nine nodes of growth (CottonInfo 2015). Mechanical removal is the preferred option for older plants.

209. IWM, which involves a range of methods to control weeds in cotton crops, including controlling volunteer cotton, is recommended as best practice for weed control in cotton cropping in Australia (CRDC 2013b; CottonInfo 2015).

210. Cotton volunteers may occur in roadside areas, however, survival of volunteers is likely be controlled by slashing or herbicide application (Eastick 2002) or lack of available moisture (Addison et al. 2007). Herbicides other than those to which the GM cotton is tolerant would have to be used in this situation. In intensive use areas such as cattle yards, grazing and trampling by cattle will also assist in controlling cotton volunteers (Eastick 2002; Eastick & Hearnden 2006). To date no self-sustaining feral populations have been established in such areas.

211. In areas outside cultivation, cotton plants are unlikely to outcompete other plant species. Commercial cotton is cultivated under highly controlled conditions to ensure adequate moisture, nutrition and reduced competition from other plants species. Cottonseed expressing the introduced herbicide tolerance genes would only have an advantage over other plants in areas where glyphosate, glufosinate or dicamba are used. Areas such as nature reserves are not sprayed with herbicides, so any advantage from the genes would be lost.

Potential harm

212. If volunteer cotton plants cannot be destroyed efficiently, they could potentially reduce the establishment of subsequent crops in the field. However, as noted, these herbicides are not used for control of cotton volunteers. The efficacy of cultivation for cotton volunteer control will not be affected by the presence of the introduced herbicide tolerance genes in GM cotton.

213. In non-cropping areas on farm, such as drains and irrigation channels, volunteer cotton control is similar to that recommended for fallow cropping areas – residual herbicide and/or cultivation or hand chipping.

214. As the presence of the introduced herbicide tolerance genes in the GM cotton plants will not assist the spread and persistence of GM cotton in any of these situations, it is highly unlikely that there will be an increased weedy populations. Thus, it is also highly unlikely that there would be an increased reservoir of pests or pathogens due to the presence of the introduced herbicide tolerance genes.

Conclusion

215. Risk scenario 2 is not identified as a substantive risk, as glyphosate, glufosinate and dicamba are not used commonly to control volunteer cotton. Nor are they used in native vegetation areas to control other weeds, thus there would be no advantage for the GM cotton plants in these areas. As such, the presence of the herbicide tolerance genes in cotton would not affect currently used methods of volunteer control.

216. In addition, other means, both specific methods and natural abiotic factors, are available to control any volunteer GM cotton plants, depending on their location. It is also highly unlikely that there would be an increased risk of weediness or an increased reservoir for pests and pathogens under this scenario.

217. Therefore, this risk could not be considered greater than negligible and does not warrant further detailed assessment.

2.4.3 Risk scenario 3

Risk Source	Introduced herbicide tolerance genes
Causal pathway	Transfer of herbicide tolerance genes to other herbicide tolerant GM cotton plants by pollen flow ⬇ Establishment of volunteer GM cotton plants ⬇ Reduced effectiveness of weed management measures to control the hybrid plants
Potential harm	Reduced establishment or yield of desirable agricultural crops OR Reduced utility of roadsides, drains, channels and intensive use areas OR Reduced establishment of desirable native vegetation OR Increased reservoir for pests or pathogens

Risk source

218. The source of potential harm for this postulated risk scenario is the introduced herbicide tolerance genes.

Causal pathway

219. The GM *G. hirsutum* cottons proposed for release are sexually compatible with other *G. hirsutum* cultivars and with *G. barbadense*, including both GM and non-GM lines of both species, but not indigenous cotton species (Chapter 1, Section 4.3, this Chapter, Section 2.2.3). Therefore, the introduced herbicide tolerance genes could be transferred to other GM herbicide tolerant cotton plants by pollen flow.

220. The applicant proposes the BG3 XF and XF cottons would be cultivated on a commercial scale in all Australian cotton-producing areas. Outcrossing could occur when the GM cotton proposed for release and other cotton crops are grown in close proximity, with synchronous flowering times.

221. Most commercial cotton currently grown in Australia (approximately 87 %) is BGII RRF cotton. Although not yet widely grown, smaller scale plantings of BG3 RRF accounted for approximately six per cent of cotton plantings in Australia in 2015/16 (data supplied by applicant). Limited areas of Liberty Link® (glufosinate tolerant) cotton are also grown and Widestrike™ insect resistant cotton has been approved for commercial release, although none has been planted commercially. *G. barbadense* is also grown commercially in Australia, however the majority of cotton planted in Australia is *G. hirsutum*.

222. Gene transfer to non-GM cotton could occur, however the resulting progeny would not have an increased range of herbicide tolerance compared to the GM parent and as such would pose no harm that has not already been considered for the GM parental cottons.

223. RRF cotton is a parent for XF and BG3 XF cotton. If these cottons were to cross with RRF, the resulting progeny would not have an increased range of herbicide tolerance as the *cp4 epsps* genes in both parents are the same. Thus there is no increased risk to spread and persistence for progeny of this cross than is present for the parental cottons.

224. Liberty Link® cotton contains the *bar* gene which confers tolerance to glufosinate herbicide. This is the same gene as that in XF and BG3 XF cottons. Therefore, in the event of hybrids being produced, no new herbicide tolerance traits will be generated. However, as this is a different event, there could be two copies of the *bar* gene so there may be an additive effect, such that the hybrids could tolerate higher rates of herbicide application for glufosinate.

225. Currently two GM cottons (GlyTol® and GlyTol TwinLink Plus®) are being evaluated for commercial release under DIR 143. These cottons have either glyphosate tolerance (GlyTol®) or glyphosate and glufosinate tolerance, in combination with three insect resistance genes (GlyTol TwinLink Plus®). Both contain the *2mepsps* gene for glyphosate tolerance and GlyTol TwinLink Plus® cotton also contains the *bar* gene for glufosinate tolerance. The *2mepsps* gene in the GlyTol® and GlyTol TwinLink Plus® cottons currently under evaluation for DIR 143 is the only herbicide tolerance gene currently approved or under assessment that is not included in the current release. If these cottons were approved for commercial production, the XF or BG3 XF cotton plants could cross with them. This could result in progeny with the *2mepsps* gene for glyphosate tolerance and in the case of GlyTol TwinLink Plus®, an extra copy of the *bar* gene for glufosinate tolerance, in addition to the herbicide tolerance genes in XF and BG3 XF cottons.

226. As the *2mepsps* gene acts in a very similar manner to *cp4 epsps*, by reducing the affinity for glyphosate binding in GM cotton plants, no metabolites are produced through the action of this gene that are different from the pathways seen with the *cp4 epsps* gene in the current application. Therefore, in the event of hybrids being produced, no new herbicide tolerance traits will be generated, although there could be additive effects so that the hybrids could tolerate higher rates of herbicide application for glyphosate or glufosinate.

227. With gene transfer to either non-GM cotton or to another GM cotton, resulting in stacking with the *2mepsps* gene and/or with another copy of the *bar* gene, there are no changes to the

spectrum of herbicide tolerance (i.e. no tolerance to different herbicide classes or modes of action). Neither herbicide is commonly used to control volunteer cotton and alternative control measures would not be affected by the level of tolerance to glyphosate or glufosinate. Thus, the survival and invasiveness of such GM lines in cropping areas, non-cropping areas of agricultural land, roadsides or other intensive use areas are likely to be limited in the same ways as those discussed for Risk Scenario 2.

Potential Harm

228. No plausible path exists by which spread and persistence of cotton would increase in agricultural areas, roadsides or nature reserves under the current scenario. Thus it is highly unlikely that the establishment of crops, utility of roadside areas or high intensity use areas would be negatively affected. It is also highly unlikely that establishment of native vegetation would be adversely affected under this scenario. As no plausible path by which survival and invasiveness would increase exists in the current scenario, it is also highly unlikely that there would be an increased reservoir for pests and pathogens under the current scenario.

Conclusion

229. Risk scenario 3 is not identified as a substantive risk, because even if there is gene transfer to other GM or to non-GM *G. hirsutum* or *G. barbadense*, there is no advantage to such plants outside cultivation.

230. For the same reasons as those discussed in Scenario 2, it is highly unlikely that these plants would be more weedy in agricultural areas, roadsides, high intensity use areas or in nature reserves. In these areas there are natural limitations on survival, or the non-herbicidal control measures may be used.

231. Therefore, this risk could not be considered greater than negligible and does not warrant further detailed assessment.

Section 3 Uncertainty

232. Uncertainty is an intrinsic part of risk and is present in all aspects of risk analysis[2].

233. There are several types of uncertainty in risk analysis (Bammer & Smithson 2008; Clark & Brinkley 2001; Hayes 2004). These include:

- uncertainty about facts:
  - knowledge – data gaps, errors, small sample size, use of surrogate data
  - variability – inherent fluctuations or differences over time, space or group, associated with diversity and heterogeneity
- uncertainty about ideas:
  - description – expression of ideas with symbols, language or models can be subject to vagueness, ambiguity, context dependence, indeterminacy or under-specificity
  - perception – processing and interpreting risk is shaped by our mental processes and social/cultural circumstances, which vary between individuals and over time.

234. Uncertainty is addressed by approaches such as balance of evidence, conservative assumptions, and applying risk management measures that reduce the potential for risk scenarios

[2] A more detailed discussion is contained in the Regulator's *Risk Analysis Framework* available from the OGTR website or via Free call 1800 181 030.

involving uncertainty to lead to harm. If there is residual uncertainty that is important to estimating the level of risk the Regulator will take this uncertainty into account in making decisions.

235. As mentioned in Chapter 1 (Section 6.1), the RARMP for DIR 120 identified information that may be required to assess an application for a large scale or commercial release of BG3 XF and XF cottons, or to justify a reduction in containment conditions. These have been addressed in the relevant sections in Chapter 1 and in risk scenarios in Chapter 2.

236. Uncertainty can also arise from a lack of experience with the GMO itself. The level of uncertainty is low for the parental cottons BGII and RRF cotton, given several years' experience growing these GMOs in Australia and internationally. None of these releases have resulted in concerns for human health, safety or the environment. The BG3 XF GM cotton also contains the Vip3Aa protein. BG3 and BG3 RRF cottons producing Vip3Aa have been approved for commercial release in Australia, but have had only limited release. Approximately 20,000 ha of BG3 RRF was planted in season 2015/16 (CSD 2016). The *dmo* gene in BG3 XF and XF cottons has not been approved for commercial release in Australia in any crop. Therefore, for the current application there is uncertainty with respect to the following:

- Lack of experience growing cotton with the *dmo* gene, encoding the DMO protein for dicamba tolerance. There is limited commercial experience with this trait worldwide. Approval for commercial release of soybean containing the *dmo* gene has been granted in the US in 2015 and approval for GM corn containing genes for glufosinate and dicamba tolerance also granted in the US in March 2016 (USDA-APHIS 2016). While Bollgard II® Xtend Flex is listed for planting in the US, the current application, if approved will probably be the first for commercial cultivation of this GM cotton. It should also be noted that although the GM crops containing the *dmo* gene for dicamba tolerance have been granted nonregulated status in the US, the US EPA is yet to approve the in-crop use of any dicamba formulation and recently extended the consultation period for consideration of registering dicamba for use in GM soybean.
- There is a lack of experience with commercial cotton growing in Northern Australia. Wide scale planting of cotton in northern Australia appears to be unlikely in the short term. The RARMP for DIR 124 addressed this question with the conclusion that newer GM cottons were unlikely to behave differently in this respect than non-GM and other GM cottons. Additionally, as mentioned in Chapter 2, Section 2.2, there has been no indication since that RARMP that there has been a change in the presence of weedy cottons in northern Australia. Nonetheless, there is only a short and limited history of commercial cotton production in Northern regions of Australia.

237. Overall, the level of uncertainty in this risk assessment is considered low and does not impact on the overall estimate of risk.

238. Post release review will be used to address uncertainty regarding future changes to knowledge about the GMO (Chapter 3, Section 4). This is typically used for commercial releases of GMOs, which generally do not have limited duration.

Section 4 Risk evaluation

239. Risk is evaluated against the objective of protecting the health and safety of people and the environment to determine the level of concern and, subsequently, the need for controls to mitigate or reduce risk. Risk evaluation may also aid consideration of whether the proposed dealings should be authorised, need further assessment, or require collection of additional information.

240. Factors used to determine which risks need treatment may include:

- risk criteria
- level of risk

- uncertainty associated with risk characterisation
- interactions between substantive risks

241. Three risk scenarios were postulated whereby the proposed dealings might give rise to harm to people or the environment. The level of risk for each scenario was considered negligible in relation to both the seriousness and likelihood of harm, in the context of the control measures proposed by the applicant, and considering both the short and long term. The principal reasons for these conclusions are summarised in Table 12.

242. The Risk Analysis Framework, which guides the risk assessment and risk management process, defines negligible risks as insubstantial with no present need to invoke actions for their mitigation (OGTR 2013). Therefore, no controls are required to treat these negligible risks. Therefore, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment.[3]

[3] As none of the proposed dealings are considered to pose a significant risk to people or the environment, section 52(2)(d)(ii) of the Act mandates a minimum period of 30 days for consultation on the RARMP. However, the Regulator has allowed up to 8 weeks for the receipt of submissions from prescribed experts, agencies and authorities and the public

Chapter 3 Risk management plan

Section 1 Background

243. Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management addresses risks evaluated as requiring treatment, evaluates controls and limits proposed by the applicant, and considers general risk management measures. The risk management plan informs the Regulator's decision-making process and is given effect through imposed licence conditions.

244. Under section 56 of the Act, the Regulator must not issue a licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in a way that protects the health and safety of people and the environment.

245. All licences are subject to three conditions prescribed in the Act. Section 63 of the Act requires that each licence holder inform relevant people of their obligations under the licence. The other statutory conditions allow the Regulator to maintain oversight of licensed dealings. Section 64 requires the licence holder to provide access to premises to OGTR inspectors and section 65 requires the licence holder to report any information about risks or unintended effects of the dealing to the Regulator on becoming aware of them. Matters related to the ongoing suitability of the licence holder must be reported to the Regulator.

246. The licence is also subject to any conditions imposed by the Regulator. Examples of the matters to which conditions may relate are listed in section 62 of the Act. Licence conditions can be imposed to limit and control the scope of the dealings and to manage risk to people or the environment. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under section 152 of the Act.

Section 2 Risk treatment measures for substantive risks

247. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed release of Xtend Flex™ and Bollgard® 3 Xtend Flex™ cottons. These risk scenarios were considered in the context of the large scale of the proposed release and the receiving environment. The risk evaluation concluded that no controls are required to treat these negligible risks.

Section 3 Section 3 General risk management

248. All DIR licences issued by the Regulator contain a number of conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- identification of the persons or classes of persons covered by the licence reporting structures
- a requirement that the applicant allows access to specified sites for purpose of monitoring or auditing

3.1 Applicant suitability

249. In making a decision whether or not to issue a licence, the Regulator must have regard to the suitability of the applicant to hold a licence. Under section 58 of the Act, matters that the Regulator must take into account include:

- any relevant convictions of the applicant (both individuals and the body corporate)
- any revocation or suspension of a relevant licence or permit held by the applicant under a law of the Commonwealth, a State or a foreign country

- the capacity of the applicant to meet the conditions of the licence

250. The licence includes a requirement for the licence holder to inform the Regulator of any circumstances that would affect their suitability.

251. In addition, any applicant organisation must have access to a properly constituted Institutional Biosafety Committee and be an accredited organisation under the Act.

3.2 Testing methodology

252. Monsanto is required to provide a method to the Regulator for the reliable detection of the presence of the GMOs and the presence of introduced genetic materials in a recipient organism. This instrument is required prior to conducting any dealings with the GMOs.

3.3 Identification of the persons or classes of persons covered by the licence

253. Any person, including the licence holder, may conduct any permitted dealing with the GMOs.

3.4 Reporting requirements

254. The licence obliges the licence holder to immediately report any of the following to the Regulator:

- any additional information regarding risks to the health and safety of people or the environment associated with the dealings
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the release

255. The licence holder is obliged to submit an Annual Report containing any information required by the licence.

256. There are also provisions that enable the Regulator to obtain information from the licence holder relating to the progress of the commercial release (see Section 4, below).

3.5 Monitoring for Compliance

257. The Act stipulates, as a condition of every licence, that a person who is authorised by the licence to deal with a GMO, and who is required to comply with a condition of the licence, must allow the Regulator, or a person authorised by the Regulator, to enter premises where a dealing is being undertaken, for the purpose of monitoring or auditing the dealing.

258. In cases of non-compliance with licence conditions, the Regulator may instigate an investigation to determine the nature and extent of non-compliance. The Act provides for criminal sanctions of large fines and/or imprisonment for failing to abide by the legislation, conditions of the licence or directions from the Regulator, especially where significant damage to the health and safety of people or the environment could result.

Section 4 Post release review

259. Regulation 10 requires the Regulator to consider the short and the long term when assessing risks. The Regulator takes account of the likelihood and impact of an adverse outcome over the foreseeable future, and does not disregard a risk on the basis that an adverse outcome might only occur in the longer term. However, as with any predictive process, accuracy is often greater in the shorter rather than longer term.

260. For the current application for a DIR licence, the Regulator has incorporated a requirement in the licence for ongoing oversight to provide feedback on the findings of the RARMP and ensure the

outcomes remain valid for future findings or changes in circumstances. This ongoing oversight will be achieved through post release review (PRR) activities. The three components of PRR are:

- adverse effects reporting system (Section 4.1)
- requirement to monitor specific indicators of harm (Section 4.2)
- review of the RARMP (Section 4.3).

261. The outcomes of these PRR activities may result in no change to the licence or could result in the variation, cancellation or suspension of the licence.

4.1 Adverse effects reporting system

262. Any member of the public can report adverse experiences/effects resulting from an intentional release of a GMO to the OGTR through the Free-call number (1800 181 030), fax (02 6271 4202), mail (MDP 54 – GPO Box 9848, Canberra ACT 2601) or via email to the OGTR inbox (ogtr@health.gov.au). Reports can be made at any time on any DIR licence. Credible information would form the basis of further investigation and may be used to inform a review of a RARMP (see Section 4.3 below) as well as the risk assessment of future applications involving similar GMO(s).

4.2 Requirement to monitor specific indicators of harm

263. Collection of additional specific information on an intentional release provides a mechanism for 'closing the loop' in the risk analysis process and for verifying findings of the RARMP, by monitoring the specific indicators of harm that have been identified in the risk assessment.

264. The term 'specific indicators of harm' does not mean that it is expected that harm would necessarily occur if a licence was issued. Instead, it refers to measurement endpoints which are expected to change should the authorised dealings result in harm. The licence holder is required to monitor these specific indicators of harm as mandated by the licence.

265. The triggers for this component of PRR may include risk estimates greater than negligible or significant uncertainty in the risk assessment.

266. The characterisation of the risk scenarios discussed in Chapter 2 did not identify any risks greater than negligible. Therefore, they were not considered substantive risks that warrant further detailed assessment. Uncertainty is considered to be low. No specific indicators of harm have been identified in this RARMP for application DIR 145. However, specific indicators of harm may also be identified during later stages, e.g. following the consideration of comments received on the consultation version of the RARMP, or if a licence were issued, through either of the other components of PRR.

267. Conditions have been included in the licence to allow the Regulator to request further information from the licence holder about any matter to do with the progress of the release, including research to verify predictions of the risk assessment.

4.3 Review of the RARMP

268. The third component of PRR is the review of RARMPs after a commercial/general release licence is issued. Such a review would be take into account any relevant new information, including any changes in the context of the release, to determine if the findings of the RARMP remained current. The timing of the review would be determined on a case-by-case basis and may be triggered by findings from either of the other components of PRR or be undertaken after the authorised dealings have been conducted for some time. If the review findings justified either an increase or decrease in the initial risk estimate(s), or identified new risks to people or to the environment that require management, this could lead to changes to the risk management plan and licence conditions.

Section 5 Conclusions of the RARMP

269. The risk assessment concludes that this proposed commercial release of GM cotton poses negligible risks to the health and safety of people or the environment as a result of gene technology, and that these negligible risks do not require specific risk treatment measures.

270. However, general licence conditions have been imposed to ensure that there is ongoing oversight of the release.

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Appendix A Summary of submissions from prescribed experts, agencies and authorities

The Regulator received a number of submissions from prescribed experts, agencies and authorities on matters considered relevant to the preparation of the RARMP. All issues included in submissions relating to risks to the health and safety of people and the environment were considered. The issues raised and how they are addressed in the consultation RARMP, are summarised below.

Submission	Summary of issues raised	Consideration in RARMP	Comment
1.	Does not support the proposed "field trial" of genetically modified (GM) cotton in this local government area. The city does not produce cotton but perceive both environmental and economic risks that could damage various communities in Australia.	-	This application is for a commercial release of GM cotton. If the application is approved, the GM cotton may be sold to farmers who may grow it anywhere in Australia. The Act requires the Regulator to identify and manage risks to human health and safety and the environment posed by or as a result of gene technology. Economic risks lie outside the matters to which the Regulator may have regard when deciding whether or not to issue a licence.
	States that the fact that the application is for cotton which could tolerate the application of three herbicides 'provides very little comfort'. Notes media articles highlighting the difficulties of treating roadside vegetation that is now immune to easy chemical treatment. It is suggested that this excessive vegetation is often from a GM product. Most roadsides and railway easements now have fugitive crops growing with little or no treatment from the relevant authorities.	Chapter 1, Sections 4.2, 5.2; Chapter 2, Section 2.2	In Australia, the occurrence of roadside cotton is likely to be dependent upon spillage during harvest and transport, and not to constitute self-sustaining populations. The GM cotton is not expected to be any more invasive or persistent than non-GM cotton. The potential for GM cotton to establish in roadsides is addressed in risk scenarios 2 and 3 in Chapter 2 of the RARMP. It is considered that feral GM cottons can be controlled by non-chemical weed management strategies or by herbicides other than glyphosate, glufosinate and dicamba.
	Supports the view that Australia should be seen as being "green and pure" for the health and market advantages that can provide. Thus do not support the growing, storage and transport of GM crops within Australia that is in direct opposition to this marketing strategy. Not convinced that the release of GM products without significant direct benefits to public health should be permitted.	-	Marketing and trade issues, including segregation and coexistence regimes, are outside the matters to which the Regulator may have regard when deciding whether or not to issue a licence. These issues are the responsibility of the State and Territory governments. State or Territory governments can declare areas to be GM-free for marketing purposes. Similarly, consideration of potential benefits of a release is outside the scope of the Act.
2.	Notes role in these matters only extends to issues relating	-	Noted.

Submission	Summary of issues raised	Consideration in RARMP	Comment
	to Land Protection and Stock-route Management Act 2002 at the moment and from July 2016, the Bio Security Act 2015.		
	Raises questions/concerns re long term outcomes.	-	
	- does conferring insect resistance and herbicide tolerance give opportunity for weeds and insects to undergo selection?	Chapter 1, Section 6.2.5	Any pest control measure – by use of chemical insecticides and herbicides or through use of GM plants - has the potential to influence selection in insect and weed populations if resistance management strategies are not in place. The efficacy of insecticidal products and appropriate resistance management strategies are regulated by APVMA.
	- if so what strategies are in place?	Chapter 1, Section 6.2.3	Growers using the GM cottons are required to sign a technology User Agreement (TUA) and the applicant has stated that a Technical Manual which contains technical information about the GM crop and requirements for growing the crop is being developed for Bollgard°3 cotton Discussion of Integrated Weed Management which is designed to limit the development of herbicide resistance in weed populations, is included in Chapter 1. Herbicide resistance issues also come under the regulatory oversight of the APVMA.
	- what are implications for public health if selection occurs?	-	Questions about implications for public health in the event of selection for resistant weeds or insects are beyond the scope of this RARMP. Issues of herbicide use and resistance management plans are under the regulatory oversight of the APVMA.
3.	Does not have the scientific expertise to comment.	-	Noted
4.	Noted that the two cottons have been assessed as part of a limited and controlled licence RARMP (DIR 120). Also three of four GM parental lines have been assessed previously for commercial release in a number of DIRs. Conclusions of these RARMPs should be broadly applicable to DIR 145. The following areas should be considered in the RARMP:	-	Noted
	- The presence of multiple genes for insect resistance, with respect to possible non-target insecticidal effects.	Chapter 1, Section 6.2.3; Chapter 2, Section 2.1	Many studies have been conducted to examine potential cross-reactivity, synergies or additive effects with multiple insect resistance genes in GM plants. The genes included in the current release are the same as those in DIR 120 and DIR 124 and effects on non-target insect were assessed in those RARMPs. This information is summarised in the RARMP.
	- The presence of multiple	Chapter	The RARMP discusses the control of volunteer cotton

Submission	Summary of issues raised	Consideration in RARMP	Comment
	genes for herbicide tolerance with respect to control of GM cotton plants by other herbicides or cultural methods.	1,Section 6.2.3, Chapter 2 Section 2.3 (Risk Scenarios 2 and 3)	and the control of weeds. Also discussed is the use of integrated weed management in cotton generally, including its use in crops with herbicide tolerant genes.
	- Comparison to conventional breeding for insect resistance and herbicide tolerance	Chapter 2, Section 2.1	The range of unintended effects produced by genetic modification is not likely to be greater than that from accepted traditional breeding techniques. The potential for unintended effects due to both conventional breeding and genetic modification are discussed in Chapter 2, Section 2.1.
	- Summarise findings of previous RARMPs with respect to potential breeding with indigenous *Gossypium* spp.	Chapter 1, Section 4.3; Chapter 2, Section 2.2.3	*G. hirsutum* is extremely unlikely to hybridise with native Australian cottons, due to genetic incompatibility. Earlier RARMPs comprehensively examined literature in this area, and the findings have been summarised in the current RARMP. No new information has been found that is inconsistent with the conclusions from previous RARMPs.
	- Cotton in northern Australia has been considered in previous RARMPs (066/2006 and 091), but this issue needs revisiting with respect to the role of *Helicoverpa* pests in influencing the survival of weedy cottons in the absence of and discussion of theories around this.	Chapter 1, Section 4.2.5	More recent RARMPs (DIR 120 and DIR124) have re-examined the likelihood of spread and persistence of cotton in northern Australia. These RARMPs have concluded that there are a number of factors that are important in limiting spread and persistence and that Lepidopteran herbivory is not the key factor in limiting cotton survival in these areas. The current RARMP summarises the information from DIR 120 and DIR 124, including relevant information from earlier RARMPs.
5.	Agrees with the issues identified by the office for consideration in the RARMP and no new issues were identified for consideration.	-	Noted

Appendix B Summary of advice from prescribed experts, agencies and authorities on the consultation RARMP

The Regulator received a number of submissions from prescribed experts, agencies and authorities on the consultation RARMP. All issues raised in submissions that related to risks to the health and safety of people and the environment were considered in the context of the currently available scientific evidence and were used in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence. Advice received is summarised below.

Submission	Summary of issues raised	Consideration in RARMP	Comment
1	No comment	-	Noted
2	Concerns about cotton becoming a pest plant. States that cotton is easily spread and it is not uncommon to find cotton in adjoining paddocks. Concerns about limiting control measures to physical removal as cotton is resistant to herbicides Has GM cotton also been modified to prevent self-propagating outside controlled conditions	Chapter 1, Section 6.2.3; Chapter 2, Risk Scenario 2 and Risk Scenario 3 - -	Cotton does not thrive outside a cultivated area in which water, nutrients and soil condition are carefully managed. Although some cotton plants may grow in areas where seed is spread, they generally compete poorly with other plants, particularly in areas which are not managed for agricultural production. This is addressed in Chapters 1 and 2 of the RARMP. Best practice for the cotton industry recommends integrated weed management systems that rely on a number of methods, including physical removal. In addition, the herbicides to which these GM cottons are tolerant are either not registered by the APVMA for use to control volunteer cotton or not commonly used for this purpose. Other herbicides are available to control volunteer cotton plants. The GM cottons have not been modified to prevent self-propagating outside controlled conditions, but the inserted genes do not give it any advantage outside cultivation compared to non-GM cotton.
3	Supports the application based on the RARMP conclusion of negligible risks to people and the environment. Understands there are a range of licence conditions to ensure ongoing oversight of the release Notes that food from the GM cottons has been approved by FSANZ.	-	Noted
4	Notes that FSANZ has assessed the food made from GM parental cotton lines and approved them to be safe for human consumption. This	-	Noted

Submission	Summary of issues raised	Consideration in RARMP	Comment
	approval covers food from lines produced by conventional breeding from such GM lines. No further comment.		
5	No comments	-	Noted
6	Supports the conclusion that DIR 145 poses negligible risk of harm to human health and safety and the environment.	-	Noted
7	Satisfied with the conclusions of the consultation Risk Assessment and Risk Management Plan, no additional comments.	-	Noted
8	Agrees with the overall conclusions of the RARMP The risk assessment identifies all plausible risk scenarios Suggests clarifying the implication of recent references relating to the spectrum of toxicity of Cry proteins by making reference to previous assessments of Cry proteins	- - Chapter 1, Section 5.3.1	Noted Noted This information has been clarified including information regarding insect populations in non-GM, Bollgard® II and Bollgard® 3 cottons.

Appendix C Summary of submissions from the public on the consultation RARMP

The Regulator received seven submissions from the public on the consultation RARMP. The issues raised in this submission are summarised in the table below. All issues that related to risks to the health and safety of people and the environment were considered in the context of currently available scientific evidence in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence.

Submission	Summary of issues raised	Consideration in RARMP	Comment
1	Objects to licence application with a number of concerns (summarised below)		
	- Genetic engineering of plants for herbicide tolerance is unnatural. - Disapproves of controlling nature.	-	This statement refers to matters that are outside the scope of the assessment conducted by the Regulator.
	- Approvals are not made within context of natural and human needs thus cannot assure safety.	Chapter 2	The Gene Technology Act 2000 requires the Gene Technology Regulator to prepare a risk assessment for licence applications, which takes into account risks to the health and safety of people or risks to the environment. Therefore, the Regulator's assessment must be framed in terms of risks associated with the release.
	- Disagree with profit-driven agriculture and resultant loss of human cultures, loss of biodiversity, climate change and social alienation. - GM cotton accelerates the expansion of monoculture agriculture due to herbicide tolerance and thus poses a greater risk to human health and the environment	-	The commercial motives of biotechnology companies, social and cultural issues are outside the scope of responsibility of the Regulator.
	- Heavier herbicide application is related to GM herbicide tolerant crops. Both practices are unnatural and destroy natural ecosystems.	-	Issues relating to herbicide use are outside the scope of the Regulator's assessments. The APVMA has regulatory responsibility for agricultural chemicals, including herbicides, in Australia. The APVMA considers risks to human health, animals and the environment in assessing agricultural chemicals for registration and in setting maximum application rates. The APVMA will not register a chemical product unless satisfied that its approved use would not be likely to have an effect that is harmful to people or the environment. Pesticide application is standard practice for control of weeds and insect pests in all agricultural systems. The National Academy of Science's 2010 report, *Impact of Genetically*

Submission	Summary of issues raised	Consideration in RARMP	Comment
			Engineered Crops on Farm Sustainability in the United States, said that "Generally, GE (GMO) crops have had fewer adverse effects on the environment than non-GE crops produced conventionally."
2	Supports approval, noting that cotton growers rely on using less pesticide to produce a cleaner product to sell to international markets.	-	Marketing and trade issues are outside the matters to which the Regulator may have regard when deciding whether or not to issue a licence. These matters fall under the jurisdiction of individual States and Territories.
	Cotton is not a food product	Chapter 1	Some food products are derived from cotton. However, issues related to food safety are outside the scope of the RARMP and are regulated by FSANZ.
3	States that GM cotton "certainly is a danger to human health and the environment"	Chapter 2	The Gene Technology Act 2000 requires the Regulator to prepare a risk assessment for licence applications, which takes into account risks to the health and safety of people or risks to the environment. The risk assessment conducted for this application assessed a number of general and specific risks to human health and the environment for the GM cottons and concludes that the potential risks are negligible. The RARMP considered the risks associated with gene flow to other cotton and determined that there was negligible risk to human health and safety and the environment from this release.
	"As organic consumers and growers, we object to this application". GM cotton "poses huge economic costs to surrounding non-GM farms trying to keep their own crops pure."	-	Marketing and trade issues, including segregation and coexistence regimes, are outside the matters to which the Regulator may have regard when deciding whether or not to issue a licence. These issues are the responsibility of the State and Territory governments. State or Territory governments can declare areas to be GM-free for marketing purposes.
	"The heavy use of glyphosate and other herbicides mentioned in this application should not be condoned or reinforced." Use of undiluted glyphosate to eradicate banana plants by Banana Freckle eradicators in NT has killed livestock and made people sick.	-	Issues relating to herbicide use are outside the scope of the Regulator's assessments. The APVMA has regulatory responsibility for agricultural chemicals, including herbicides, in Australia. The APVMA considers risks to human health, animals and the environment in assessing agricultural chemicals for registration and in setting maximum application rates. Further information on the safety assessment of glyphosate is available on the APVMA website.

Submission	Summary of issues raised	Consideration in RARMP	Comment
			APVMA and FSANZ have shared responsibilities in setting maximum residue limits (MRLs) for agricultural chemicals in food. At the time the MRLs are set, a dietary exposure evaluation is undertaken to ensure that the levels do not pose an undue hazard to human health. The FSANZ website has an information page regarding herbicides in GM foods. The APVMA considers risks to human health, animals and the environment in assessing agricultural chemicals for registration and in setting maximum application rates.
	"Monsanto is being encouraged by agribusinesses too lazy to care for their food crops in more traditional ways not dependent on chemicals."	-	The commercial motives of biotechnology companies are outside the scope of responsibility of the Regulator.
	"The food that is feeding the world comes from organic, small-scale and subsistence permaculture or polyculture farming using already highly resistant heritage seeds and corms. It also protects the environment and becomes essential habitat for threatened species and beneficial insects"	-	The Act requires the Regulator to identify and manage risks to human health and safety and the environment posed by or as a result of gene technology. The Regulator conducts a comparative risk assessment, whereby the effect of the genetic modification in the GM plant is assessed for its potential to cause harm as compared to the unmodified parent organism. The Regulator's assessment concluded that this release poses negligible risk to the environment. Consideration of the relative merits of different farming production methods is outside the scope of assessments conducted by the Regulator.
	"It is the blatant disregard of how chemical abuse kills our beneficial insects and honey bees that lowers the resilience of the environment and serious negatively impacts on human health."	Chapter 1, Section 6.2.3; Chapter 2, Section 2.1	Pesticide application is standard practice for control of weeds and insect pests in all agricultural systems. The potential for the introduced insecticidal proteins to be toxic to beneficial insects, including bees, was considered in Chapters 1 and 2 of the RARMP; the potential for harm was assessed as negligible.
4	Requests refusal of licence for DIR 145 due to a number of concerns summarised below.		
	The failure of Bt crops internationally is evident.	-	Issues relating to efficacy of insecticides are outside the scope of the Regulator's assessments. The efficacy of insecticidal products and appropriate resistance management strategies are regulated by APVMA. More information can be found on the APVMA website.
	Modification of GM plants makes them more susceptible to attack by non-target pests. New insect pests have emerged as a result of introducing Bt crops and will require increased pesticide use.		
	Bt crops are not effective or sustainable and the technology has had a deleterious effect on crops.	-	In Australia, the use of Bt cotton has been accompanied by resistance management strategies.

Submission	Summary of issues raised	Consideration in RARMP	Comment
		Chapter 1, 4.1.1	The number of insecticide sprays has been reduced in Australian cotton crops since the introduction of GM insect resistant cotton (CottonInfo 2015). Pesticide application is standard practice for control of weeds and insect pests in all agricultural systems. Broadly speaking, there has been a reduction in the amount of insecticides used in the US since the introduction of GM crops (*Impact of Genetically Engineered Crops on Farm Sustainability in the United States*).
	"Please protect the health of Australian's and refuse this application."	-	The Regulator is required to assess GMO applications in accordance with the Gene Technology Act 2000, the object of which is to protect the health and safety of people and the environment. For each licence application, the Regulator must prepare a risk assessment and risk management plan (RARMP) prior to making a decision whether or not to issue a licence. The RARMP concludes that the commercial release of this GM cotton poses negligible risks to the health and safety of people and the environment.
	Effects of industrial agriculture in creating insect pests through monoculture, use of chemical fertilisers, insect resistance to pesticide use, removal of beneficial insects and disruption of pest-predator balance.	-	Consideration of the relative merits of different farming production methods is outside the scope of assessments conducted by the Regulator. The use of agricultural chemicals including insecticides is regulated by the APVMA.
5	Requests refusal of licence for DIR 145 due to a number of concerns summarised below.	-	
	"…it is obvious from your Questions & Answers document that OGTR, FSANZ and APVMA have already conferred and decided to approve these Genetically manipulated (GM) cotton seed varieties for general commercial sale throughout Australia."	-	While the Regulator must consider risks to human health and safety and the environment relating to dealings with GMOs, other agencies have responsibility for regulating GMOs or genetically modified products as part of a broader or different mandate. Accordingly, the Regulator must consult Commonwealth regulatory agencies prescribed in the Regulations (including FSANZ and APVMA) on all licence applications for dealings involving the intentional release of GMOs to the environment.
	Raises concerns about use and toxicity of synthetic chemicals and combinations of more than one herbicide on GM cotton. Release of Xtend Flex cotton would facilitate the use of three chemical herbicides.	-	Issues relating to herbicide use are outside the scope of the Regulator's assessments. The APVMA has regulatory responsibility for agricultural chemicals, including herbicides, in Australia, including application of herbicides on GM cotton.

Submission	Summary of issues raised	Consideration in RARMP	Comment
	Increasing development of glyphosate resistance in weeds.	Chapter 1, Section 4.1.2	Herbicide resistance issues come under the regulatory oversight of the APVMA. Relevant discussion is included in Section 4.1.2 in Chapter 1 of the RARMP.
	Potential for insects to develop resistance to the Bt toxins.	-	Issues relating to insecticide use are outside the scope of the Regulator's assessments. The efficacy of insecticidal products and appropriate resistance management strategies are regulated by APVMA. In Australia, the use of Bt cotton has been accompanied by resistance management strategies. More information can be found on the APVMA website.
		Chapter 1, Section 4.1.1	The Australian cotton industry has recommendations for use of Integrated Pest Management (IPM) methods in cotton crops to reduce resistance development, which are discussed in Chapter 1 of the RARMP.
	Recommends that the OGTR requires removal of antibiotic resistance genes from GM organisms as a precautionary measure in the interests of public health and safety.	Chapter 2, Section 2.1	The antibiotic resistance genes have been extensively characterised and been assessed as posing negligible risks to human health and safety. The potential for these genes to pose risks (e.g. through reduction of therapeutic efficiency of antibiotics, or an increase in bacterial antibiotic resistance) is addressed in the document Marker genes in GM plants available from the Risk Assessment References page on the OGTR website.
	Recommends more specific reporting of the quantity, area, number of growers and seeding rate of GM cotton grown under the licence. Suggests that information provided under previous licences was incorrect.	Chapter 4	Under licence conditions the licence holder is required to provide an Annual report containing a range of information, including information about the scale of GMO planting (as mentioned by the submitter). Note that giving false or misleading information in connection with an application made to the Regulator is an offence under the Act and is punishable by imprisonment or substantial fines.
6	Requests refusal of licence for DIR 145 due to a number of concerns summarised below. Concerns about the safety of GM cotton products.	Chapter 1, Section 5.4.2; Chapter 2, Risk scenarios 1 and 3.	The risk assessment for these GM cottons includes consideration of the impacts of the GM plant and its products on people through potential increase in toxicity or allergenicity. The RARMP concludes that the commercial release of this GM cotton poses negligible risks to the health and safety of people and the environment. FSANZ has approved food from the GM cottons. More information about their assessments is available from the FSANZ website.

Submission	Summary of issues raised	Consideration in RARMP	Comment
	Raises concerns about testing of GM plants and products: "…it is obvious that industry testing falls well short of what is expected to guarantee health & environmental safety in the immediate and longer term."		
	"There has been no controlled trials of the combinatorial, dosage or dietary effects on children, pregnant and breastfeeding mothers, the elderly, sick or immuno-compromised."	-	FSANZ has regulatory responsibility for food safety assessments in Australia. Human trials are not part of the information required by FSANZ for the safety assessment of a GM food.
	No labelling of GM products, consumer choice issues	-	Product labelling is outside the matters to which the Regulator may have regard when deciding whether or not to issue a licence, as are matters related to marketing or consumer preferences Labelling of food, including GM foods, is the responsibility of FSANZ. Labelling of GM status is legally required for GM foods that contain novel DNA or protein or have altered characteristics.
	Reference to 'money bombing' by Monsanto to oppose GM labelling in the United States	-	The commercial motives of biotechnology companies are outside the scope of responsibility of the Regulator.
	Concerned about the build-up of weed and pest resistance	Chapter 1, Section 4.1.2	Herbicide resistance issues come under the regulatory oversight of the APVMA. Relevant discussion is included in Section 4.1.2 in Chapter 1 of the RARMP. Issues relating to insecticide use are outside the scope of the Regulator's assessments. The efficacy of insecticidal products and appropriate resistance management strategies are regulated by APVMA. More information can be found on the APVMA website.
		Chapter 1, Section 4.1.1	The Australian cotton industry has recommendations for use of Integrated Pest Management (IPM) methods in cotton crops, which are discussed in Chapter 1 of the RARMP.
	Banning of GM cotton in Burkina Faso	Chapter 1, Sections 5.2.2 and 5.4.5	Scientific information relating to international risk assessments of GM plants is considered during preparation of the RARMP. A list of the countries in which GM cottons are approved for food, feed and cultivation is provided in Chapter 1 of the RARMP. However, decisions in other countries relating to agricultural policy are outside the scope of the Regulator's assessments.
	Banning of glyphosate in Sri Lanka	-	Issues relating to herbicide use are outside the scope of the Regulator's assessments. The APVMA has regulatory responsibility for

Submission	Summary of issues raised	Consideration in RARMP	Comment
			agricultural chemicals, including herbicides, in Australia. The APVMA considers risks to human health, animals and the environment in assessing agricultural chemicals for registration and in setting maximum application rates. Further information on the safety assessment of glyphosate is available on the APVMA website.
7	Concerns raised are identical to those of Submitter 6.	Please refer to comments for Submitter 6.	Please refer to comments for submitter 6.