MEAT & LIVESTOCK
AUSTRALIA

on farm

Proceedings of the Foundation Meeting of the Annual Ryegrass Toxicity National Coordination and Advisory Team

Foundation Meeting
Urrbrae House, Adelaide

Project number ARGT.002

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Animal Health and Welfare

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1. EXECUTIVE SUMMARY

1.1. Introduction

Research to better understand and minimise the impact of annual ryegrass toxicity has been the subject of investments by MLA and AWI for more than 25 years and by the GRDC and RIRDC for nearly 10 years. GRDC alone has invested several million dollars in ARGT research. While a huge amount of information has been collected and considerable progress has been made in managing ARGT and related issues, a number of important livestock toxicity, food safety and trade issues remain.

Following the Page review commissioned in late 2003 by MLA, the affected research and development corporations (MLA, AWI, GRDC and RIRDC) have agreed to take a joint approach to ARGT and related issues, and have identified the importance of whole-of-industry stakeholder consultation and communication. Focused interaction with stakeholders will allow a better understanding of the issues and the development and initiation of coordinated joint and complementary approaches to ARGT management. The vehicle through which stakeholders may be heard is the ARGT National Coordination and Advisory Team (NatCAT).

The ARGT NatCAT reports to and makes recommendations to the National ARGT Management Group (senior managers within MLA, AWI, GRDC and RIRDC/AFIA) who will ultimately decide what investments or other actions will be taken.

The ARGT NatCAT has been formed to provide information and recommendations concerning issues considered important by the Management Group, including (but not limited to) the following:

- Assessment of the ongoing impact of corynetoxins on livestock, grain and fodder production and trade.
- Development of recommendations for the ARGT Management Group describing strategies that will mitigate this impact.
- Identification of gaps and deficiencies in current knowledge.
- Ranking of the priorities of ARGT research.
- Recommendations on the implementation of research outcomes to ensure rapid and effective adoption by affected parties.
- Assessment of the benefits in ARGT mitigation provided by adoption of research outcomes.
- Recommendations to the ARGT Management Group as to who is best able to undertake priority research programs.
- Critical evaluation of new and ongoing research proposals and recommendations for support or amendment.

In addition, the ARGT NatCAT is encouraged to bring new and emerging significant issues to the attention of the Management Group.

The inaugural meeting of the ARGT NatCAT was held at Urrbrae House on the campus of the University of Adelaide on 31st March 2004 and was attended by 13 participants (representing MLA, AWI, GRDC, RIRDC, AFIA, ARGT Action Committee, WADA, SARDI, University of Adelaide and CSIRO) with apologies from the Commonwealth Department of Agriculture, Fisheries and Forestry (DAFF).

1.2. Background Information

Three reports comprehensively describe ARGT and its potential impacts on agriculture and food safety:

1) **Report of the SCARM Working Group to consider issues associated with Annual Ryegrass Toxicity (ARGT) (February 2000)**

2) **ARGT Workshop, El Caballo Blanco, WA (November 2002)**

3) **Annual Ryegrass Toxicity. Review of Current Management Options and Research Needs (MLA, January 2004)**

These reports provide detailed information on the history and significance of ARGT to livestock, fodder and grain production. The health and welfare of livestock as well as the safety and trade implications of food produced in ARGT endemic areas are discussed. Priorities for actions that could mitigate these impacts are summarised under the following headings:

- The level and distribution of corynetoxins in agricultural commodities
- The factors affecting the levels of corynetoxin
- The bioavailability of corynetoxins in agricultural commodities
- Toxicology of corynetoxin
- Safe level of corynetoxins in food for human consumption
- Phytosanitation
- Farm control strategies
- Managing animal health issues

1.3. ARGT Impact, Management Practices, Needs & Priorities

While there is evidence of the presence of CTs in a number of grass species in most states of Australia, the most significant occurrence of CTs and ARGT is in ryegrass in Western Australia with substantially smaller areas of South Australia affected.

Since the first recorded outbreak of ARGT in sheep in Gnowangerup in 1968, the number of holdings reporting ARGT in WA has increased inexorably and the area affected continues to expand. Currently more than 10 million hectares of agricultural land in WA is affected with cumulative sheep deaths exceeding 500,000. Outbreaks of ARGT in sheep are characterised by their unpredictability and high mortality. However, there are other impacts that are not as evident and include profound psychological distress on owners, subclinical production losses, reduced stock carrying capacity on ARGT affected holdings, as well as the costs of (seemingly futile) control measures. High amongst the priorities for sheep farmers is ensuring the best possible adoption of the range of control measures currently available to minimise the immediate threats of ARGT. Supporting this priority is a strong need to develop an effective means of ARGT prediction. Longer term benefits will be gained from the development of a vaccine that protects sheep from the effects of CT consumption combined with improved and more widespread application of biocontrol agents that replace or reduce CT affected annual ryegrass.

Historically cattle have been less affected by ARGT but as feedlot and dairy enterprises expand and rely on increasing quantities of purchased feedstuffs, there will be a need to ensure freedom from adverse exposure to CTs. There is also an increased movement of cattle production into the wheatbelt where the

impact of ARGT will be similar to that experienced by sheep producers.

The highest priority for grain and fodder production is food safety, ensuring produce is free of unacceptable levels of CT or *R toxicus* contamination. There are no CT standards in place at present for grain or fodder. Exported fodder is currently the subject of a voluntary code of practice that defines the upper limit of acceptable *R toxicus* levels (<1 bacterial gall/kg), but soon there will be a mandatory standard prescribed by AQIS under the Export Control ACT.

A list of priority areas for research support are summarised in ATTACHMENT 1.

1.4. Research Proposals

Two research proposals were presented at the inaugural ARGT NatCAT and concerned the development of a vaccine to protect sheep from the adverse effects of CT consumption and means of improving adoption of ARGT mitigation measures.

Development of a commercially acceptable, anti-corynetoxin vaccine to prevent annual ryegrass toxicity in livestock.

Although ARGT is a dominant animal health problem in WA and some 12 million sheep are potentially at risk, the commercial attractiveness to a potential manufacturer and marketer of a vaccine for such a restricted animal population is far from clear. Before considering a proposal to develop an ARGT vaccine, AWI commissioned a commercial assessment of the business opportunity and a summary was presented to the ARGT NatCAT by Dr David Leyonhjelm of Baron Strategic Services.

The commercial assessment considered the market potential; factors influencing vaccine adoption rate; the likely use pattern of the vaccine; the product life cycle; the current state of the vaccine's development; criteria defining the product's characteristics; vaccine advantages and disadvantages; direct and indirect competitors; manufacturing and packaging considerations including the cost of production; the costs of development and registration; and finally the projected price. Based on a number of assumptions arising from these considerations, various extreme sales as well as profit and loss scenarios were explored. It was concluded that a vaccine against ARGT could be financially viable and that there was a high likelihood of finding a commercial partner. However, the chances of success would be increased if a number of fundamental characteristics of the vaccine were better defined (dose regimen, antigen load, duration of immunity etc). Because the cost of the proposed vaccine is highly dependent on the price and availability of tunicamycin, it was further recommended that consideration be given to an alternative vaccine.

A summary of work completed already on the development of a vaccine against ARGT was presented. Pen trials have shown high levels of protection in vaccinates against challenge with either tunicamycin or CTs (in the form of milled grain screenings dosed by ruminal intubation). It was acknowledged that only small numbers of sheep have been investigated, however, the preliminary evidence is very encouraging.

A number of alternative approaches to vaccine design were described, including a non-immunogenic phage displayed CT mimotope linked to a synthetic peptide.

Given a favourable commercial assessment, a decision will now be made as to what form of vaccine research program is most likely to provide the greatest benefits to sheep farmers in the ARGT endemic area.

Coordinated approach to minimising the impact of annual ryegrass toxicity (ARGT) in agriculture

This proposal was prepared by the WADA ARGT Solutions Team and presented by Linda Leonard. The proposal recognised that tackling ARGT is a long-term endeavour but provides a solid and ambitious program focused on short-term objectives that can be achieved within the first 3 years and will provide

guidance and direction for the next longer-term phase. The objectives of phase 1 include:

1) To develop, using current knowledge, improved farm systems packages to combat ARGT and to ensure widespread adoption by use of an effective extension campaign.

2) To determine the potential of the nematode-resistant ryegrass Safeguard to reduce ARGT across a range of environments within WA and to determine how it may best be applied into farming systems.

3) To develop evidence-based recommendations for the use of twist fungus and to increase the uptake of twist fungus as a bio-control agent of ARGT.

4) To ascertain the benchmark against which progress in improving ARGT control can be measured and to develop better knowledge on the prediction of ARGT risk.

5) To develop and utilise to full effect active communication between and collaboration with key stakeholders (including research organisations).

It was noted that it will be critical to the successful achievement of the objectives to ensure that such a broad programme of work has sufficient dedicated resources. Substantial expertise in the biological control of ARGT resides in South Australia and it will be necessary to ensure solid links are established. All members of the ARGT NatCAT were invited to further review the project proposal and provide comments to both Linda Leonard and the funding RDC (MLA).

Other Research Activities

While not discussed in depth, a range of additional research activities are in progress or planned and include:

- the continuation of toxicology studies by CSIRO to determine the lowest “no adverse effect level” (NOAEL) of CTs;

- a proposal by CSIRO to validate an analytical method to determine the presence of CT residues in edible animal tissues;

- ongoing evaluation and further development by WADA of biocontrol for the ARGT causal organism

1.5. Concluding Remarks

ARGT is a complex phenomenon having clear cross sectoral significance, and with real or perceived impacts on fodder, grain, meat, animal health and trade. Significant progress has been made in a number of vital areas:

- Quality assurance of fodder including a sampling and testing code of practice, with AQIS mandated demonstration of freedom from CT contamination imminent.

- CT occurrence in grain and effective measures to reduce contamination.

- Initiation and conduct of a toxicology program to define a NOEL or NOAEL of the CTs

- Development of biocontrol methods with potential to have a huge impact on ARGT occurrence.

The impact of ARGT is best managed by reducing if not eliminating the presence of *R toxicus* in annual ryegrass and this objective will always remain of fundamental importance. However, it is accepted that eradication is not realistic (at least in the short term) and measures to reduce the likelihood of adverse

effects on livestock, food and trade must be optimised and adoption increased, as reflected by the priorities outlined in ATTACHMENT 1.

Support for three new projects that address a number of these priorities is actively under review while proposals for a fourth priority are sought:

1) **Coordinated approach to minimising the impact of annual ryegrass toxicity (ARGT) in agriculture (WADA).** MLA seeks comments on the draft proposal from members of the ARGT NatCAT with an objective of having a final proposal developed by WADA for consideration and possible approval of support from MLA by mid year.

2) **Development of a commercially acceptable, anti-corynetoxin vaccine to prevent annual ryegrass toxicity in livestock (CSIRO).** AWI remains committed to support of a research proposal that best defines a potential vaccine candidate attractive to a commercial partner.

3) **Meat residue method development (CSIRO).** MLA is assessing the needs and appropriate timing for the development of a validated analytical method for CTs in edible tissues of sheep. Ongoing discussions with CSIRO are planned.

4) **Alternative Safe Grass**. The need to identify or develop an alternative safe grass to support livestock production in WA was emphasised repeatedly during the meeting and remains an important priority. Proposals outlining the benefits, value and research plan for the development of a tetraploid, nematode-resistant ARG are invited by MLA.

Finally, it is important that appropriate attention is focused on the following matters:

- DAFF must be encouraged to play a leadership and proactive role in contingency planning.
- The way in which the ARGT NatCAT interacts with AusToxNet needs to be explored and appropriate links established.
- As high priority research programs are initiated, the potential contribution of basic science investigations need to be reviewed, prioritised and supported.

Commensurate with the breadth and significance of issues and impacts associated with ARGT the inaugural meeting of the NatCAT was densely packed with presentations and information and invaluable discussion. A diversity of special skills, expertise and experience remain a vital and powerful source of advice to the RDCs, ensuring high quality essential projects are designed and supported, ultimately increasing the likelihood of improved management of ARGT. It is planned that the ARGT NatCAT will continue to play this pivotal advisory role. Further meetings of the ARGT NatCAT may be convened as significant project milestones are completed or as new issues emerge.

The contributions of all participants of the inaugural ARGT NatCAT are recognised and greatly appreciated and continuing support highly valued.

2. ATTACHMENTS

Attachment 1: ARGT Priorities

GRDC
Food safety CT assays etc (complete) Application of assay
NOAEL (in progress)
National survey – *R toxicus*, completed *Anguina* spp – to be discussed
Improved farm management practices Decreased CT Decreased *R toxicus* On-farm grain cleaning Identification of current grain production and handling practices associated with decreased contamination
Sampling strategies for grain to determine levels of *R toxicus* and CT.
HACCP plan for wheat Implementation plan Ryegrass receivals' standards
Disposal of *R toxicus* or CT contaminated grain and screenings.
NIRS test for CT in grain (ie need a rapid, reliable, practical test)
Contingency planning? – DAFF?
Nontoxigenic *Rathayibacter* spp

AFIA
Improved ARGT tests Faster Less cost
Reliable and cost effective bale identification
Export standard reassessment
On farm QA
Assessment of OH&S implications of CT exposure

SHEEP/CATTLE
Assessment of subclinical effects Wool Fertility
Alternative safe grass For example: Safeguard; tetraploid approach to reducing herbicide resistance in ARG, other grasses
Effective biocontrol (Twist fungus, Safeguard, non toxigenic Rathayibacter etc)
Effective means of annual ryegrass control (eg integrated weed management)
Better informed farmers re current control strategies (leading to increased adoption of best practices)
Alternative uses or methods of disposal for CT contaminated feed
Vaccine
Effective treatment
Better prediction of ARGT risk
CT assay for meat
Science based food safety standards

Attachment 2: Participants

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APOLOGIES

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Attachment 3: Proceedings Of The Inaugural Argt Natcat Meeting

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ARGT Advisory Team - Inaugural meeting Adelaide, March 2004

Dr Peter Rolfe

Meat and Livestock Australia

ARGT Advisory Team : background

- **Long term investments by various agencies**
- **Toxicity still an industry issue**
- **Complex range of effects and there may be competing interests**
- **What is the solution?**
  - **Better adoption of current solutions?**
  - **New solutions/more investment?**
  - **Better coordination of investment – "whole of industry" approach?**
  - **Extent of investment?**

ARGT Advisory Team : background

- **Actions**
  - **Situation statement – Page review**
  - **RDC's agreement to "joint" approach**
  - **Identified need for "whole of industry" stakeholder consultation and advice**
  - **Develop and initiate joint and complementary approaches**

ARGT Advisory Team : terms of reference

The National ARGT Coordination and Advisory Team reports to and makes recommendations to the National ARGT Management Group

ARGT Advisory Team : terms of reference

- **Assess the impact of corynetoxins on livestock, grain and fodder production and trade.**
- **Develop recommendations for the ARGT Management Group describing strategies that will minimise this impact.**
- **Identify gaps and deficiencies in current knowledge**

ARGT Advisory Team : terms of reference

- **Determine the priorities of ARGT research and the implementation of its findings**
- **Recommend to the ARGT Management Group who is best able to undertake priority research programs**
- **Critically review research proposals and make recommendations for support or change**

Agenda 1: Objectives of the ARGT NatCAT 6

AWI PERSPECTIVE

- The animal health budget of AWI has many demands
- Considerations in determining AWI support include whether there is market failure, need for genuine R&D or extension, roles of Departments of Agriculture and others versus AWI

Agenda 2: AWI Perspective 7

AWI PERSPECTIVE (cont)

- AWI considers that ARGT is important and is committed to the support of projects that meet AWI standards and criteria and subject to AWI Board approval
- Investments in ARGT will be in consultation and collaboration with MLA, GRDC and other bodies as appropriate.

Agenda 2: AWI Perspective 8

GRDC Perspective

- ARGT is a cross sectoral issue, affecting fodder, grain and meat.
- Trade impacts of ARGT first arose with fodder exports to Japan in 1996, but grain exports are also potentially vulnerable
- DAFF must play a leadership role in the design and implementation of a proactive strategy

Agenda 3: GRDC Perspective 9

GRDC Perspective (cont)

- Research priorities were outlined by the SCARM report (2000)
- AusToxNet, formed by the SCARM natural toxins WG, is intended to coordinate communication and consultation.
- Already, GRDC has invested more than $5 million in ARGT research, reflecting the importance of this natural toxin to the grain industry

Agenda 3: GRDC Perspective 10

SCARM Working Group on Natural Toxins
Report on Managing the food safety & trade risks associated with NATURAL TOXINS in Agricultural and Fisheries Products. July 2000

MAIN FINDINGS

- Natural toxins represent a moderate risk to food safety and a moderate to high risk to trade
- Australia needs to enhance its preparedness to deal with a food safety or trade incident arising from natural toxin contamination of agricultural or fisheries products
- This requires a substantial increase in funding for research, monitoring and surveillance, information management and coordination.

Agenda 3: GRDC Perspective 11

SCARM Working Group on Natural Toxins (cont)

MANAGEMENT OF NATURAL TOXINS

Requires:

- Cooperation of industry, government and other relevant parties
- A technical capacity to demonstrate products meet safety standards and guidelines
- Risk-based approach
- Early identification and coordinated response to natural toxins threats
- Coordinated strategic response to minimize impact on human health and trade
- Priority be given to management of natural toxins shown by risk analysis to present highest risk to human health and trade

Focus on:

- Minimizing contamination at source
- Industry-based quality assurance programs

Agenda 3: GRDC Perspective 12

SCARM Working Group on Natural Toxins (cont)

The framework employed for examining the range of research currently being undertaken and the gaps in that research effort comprises the following:

- The level and distribution of corynetoxins (CTs) in agricultural commodities;
- The factors affecting the levels of CTs;
- The bioavailability of CTs in agricultural commodities;
- The toxicology of the CTs;
- A safe level of CTs in food for human consumption;
- Phytosanitation;
- Farm control strategies; and
- Managing animal health issues.

Agenda 3: GRDC Perspective 13

AusToxNet

THE AUSTRALIAN NATURAL TOXINS MANAGEMENT NETWORK

The origins and role of AusToxNet

- Growing concern with natural toxin contamination of important commodities.
- The Standing Committee on Agriculture and Resource Management (SCARM) established a working group
- The SCARM Natural Toxins Working Group recommended *inter alia* formation of AusToxNet.
- AusToxNet was established by a resolution of SCARM

Agenda 3: GRDC Perspective 14

AusToxNet

Purpose
- Provide a mechanism for:
- communication
- consultation
- coordination
- between industry sectors and government agencies

Structure
- Core group
- Co-opted members as appropriate

TERMS OF REFERENCE
- to encourage and facilitate sharing, among the organizations represented, of national and international information on natural toxin issues, particularly on emerging developments that are potentially significant to food safety and/or trade;
- to facilitate a nationally coordinated approach in the event of a natural toxin emergency;
- to provide integrated advice through the Australian Government to the Codex Alimentarius Commission (Codex) on priorities for evaluation of natural toxins and on proposed standards, codes of practice etc being elaborated by Codex;
- to provide advice, through AFFA, to Animal Health Australia (AHA) and Plant Health Australia (PHA) on natural toxin issues;

Agenda 3: GRDC Perspective 15

AusToxNet

AusToxNet could also undertake:
- *to review, and provide advice to industry and government on, the relative risks to human and animal health and trade represented by current and emerging natural toxin/commodity combinations;*
- *to oversee the development and/or implementation of management plans for specific natural toxin problems of national significance; and*
- *to develop appropriate national guidelines and/or regulations for the routine and emergency management of natural toxins for both domestic and export purposes.*

Agenda 3: GRDC Perspective 16

AFIA PERSPECTIVE

- Total fodder production per annum in Australia is estimated at between 7 and 9 million tonnes.
- Of this currently there is about 650,000 tonnes of fodder exported. About 550,000 tonnes is exported into Japan. The remaining tonnage is exported into South Korea, Taiwan and the Middle East.
- The fodder exported is predominantly oaten hay. There are also smaller quantities of wheaten, triticale and lucerne hay exported.
- The fodder exported is predominantly used in the dairy industry with smaller quantities being used in the beef, horse and camel industries.

Agenda 4: RIRDC/AFIA Perspective 17

AFIA PERSPECTIVE (cont)

- In the Japanese dairy and beef industries, all animals are penned therefore requiring all fodder to be fed ie. there is minimal grazing of fodder crops. Whatever is put in front of the animal is what they have to eat.
- The 1996 ARGT incident in Japan where 9 dairy cows died as a result of ARGT poisoning was a major problem for the export fodder industry with the cessation of exports for several months. It took negotiations between Japanese Ministry of Agriculture and Australia's DPIE to allow the reopening of the trade.
- A critical part of these negotiations was the development of an ARGT detection procedure. This procedure was developed through consultation between SARDI, AgWA, major fodder exporters and other associated bodies.
- As a result all remaining fodder exported for the season sourced from South Australia and Western Australia had to be tested under the agreed procedure.
- Contrary to the belief of Japanese Ministry of Agriculture, the ARGT testing of export fodder to Japan is not compulsory but rather done on a voluntary basis.

Agenda 4: RIRDC/AFIA Perspective 18

AFIA PERSPECTIVE (cont)

- The fodder industry in Australia has been unsuccessful in being able to orchestrate the collection of a compulsory research and development levy. This has resulted in very limited funds being available for ongoing research and development within the industry. RIRDC has and still remains the major funder of research and development projects within the fodder industry.
- Some 3 years ago, a voluntary levy of $0.50 per tonne was successfully introduced for all fodder exported. This today is still well supported and via RIRDC 1 for 1 funding, supplies the bulk of funds available for fodder industry research and development. However this levy in total only creates a pool for industry research and development of about $ 650,000 per annum. This is not a large sum of money.

Agenda 4: RIRDC/AFIA Perspective 19

AFIA PERSPECTIVE (cont)

- Significant research and development within the fodder industry has happened over the years, however as a result of only small $ value of available industry funds for research and development a lot of the research and development has been undertaken by private companies and therefore not taken up by the whole industry for some time.
- Japan is very health and safety conscious with regards to agricultural products. This is even more reinforced with the like of BSE and the implication of this into the human chain. If the export fodder industry wants to continue to have a profitable industry, then it is of paramount importance that we do not supply fodder into a market place that:
  a) Might have a human health implication
  or
  b) Negatively effect the productivity of the dairy or beef industry compared to alternative products available in the market place.

Agenda 4: RIRDC/AFIA Perspective 20

RIRDC

- Little funding available
- RIRDC has funded two significant projects:
  1. Sampling protocol for export fodder
  2. ELISA for toxin
- No current projects
- RIRDC 5 year plan is under development, biosecurity is an important priority and should include ARGT.

Agenda 4: RIRDC/AFIA Perspective 21

ANNUAL RYEGRASS TOXICITY

Report to MLA

Stephen Page
Advanced Veterinary Therapeutics

Agenda 5: ARGT Report to MLA 2004 22

Process of assessment

- Consultations with stakeholders
  - 32 interviews
- Review of published and unpublished literature
  - > 350 documents
- Further discussion with research groups
  - Follow up discussions, especially with WADA, SARDI, UAdel, CSIRO

Agenda 5: ARGT Report to MLA 2004 23

OBSERVATIONS

ON THE ONE HAND:	YET ON THE OTHER:
Much data	ARGT persists & grows
Actual problem moderate	Potential problem monumental
CT: high toxicity *in vitro*	CT: lower toxicity *ex vitro*
CT: high mortality in sheep	CT: high level of variability
CT: high parenteral toxicity	CT: lesser toxicity *per os*

Agenda 5: ARGT Report to MLA 2004 24

ASSESSMENT (i)

- Need better understanding of nature of apparent mismatches in potential and actual toxicity
- First principle of clinical toxicology: separate toxicant and site of action (ie no toxicant, no harm)

Agenda 5: ARGT Report to MLA 2004 25

ASSESSMENT (ii)

- Benefits from broad inter-disciplinary interactions eg mycotoxicologists
- Complex problem needing clear priorities and commitment at all levels (from researcher to funder, from farmer to government) to discover and deliver solutions

Agenda 5: ARGT Report to MLA 2004 26

RECOMMENDATIONS

1. COORDINATION & MANAGEMENT
2. ENHANCING ADOPTION OF CURRENT SOLUTIONS
3. FURTHER RESEARCH
• Confirmation and implementation of research priorities. • Vaccination against ARGT • Adsorption of CTs in rumen • Basic research programme
4. FOOD SAFETY

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ARGT WORKSHOP November 2002 - Summary of Outcomes

Jeremy Allen WADA

Agenda 6: ARGT Workshop 2002 28

Meeting participants

- All invited
- 80 delegates
- Farmers (via ARGT Action Committee)
- Rural industry associations (WAFF, PGA, Sheep Council)
- Fodder industry
- Institutions (WADA, CSIRO, UWA, Murdoch University)
- Funding bodies (MLA)

Agenda 6: ARGT Workshop 2002 29

Meeting format

- Invited papers - 13
- 6 interstate and 6 local speakers
- 2 forums
  - Identifying main intervention points
  - Research needs
- Summary session

A very information packed and intense day

Agenda 6: ARGT Workshop 2002 30

Outcomes

- Increased awareness by DAWA and rural industry associations of the problems this disease causes farmers
- Formation of an ARGT Solutions group by DAWA to develop the concept and proposal for an industry and DAWA funded project to research and promote minimisation strategies

Agenda 6: ARGT Workshop 2002 31

Outcomes

- No response from MLA
- Noise made at the MLA AGM
- Stephen Page commissioned to do review of ARGT for MLA
- MLA interest in DAWA proposal and this meeting today

The untiring efforts of the ARGT Action Committee and Barrie Bywater in championing the ARGT problem

Agenda 6: ARGT Workshop 2002 32

Major factors recognised

- The many factors that contribute to ARGT are very complex and interact in complex ways
- The reduced carrying capacity for livestock caused by reduction in ryegrass and widespread spraytopping has been greatly underestimated

Major factors recognised

- Effective biological control agents that would enable continued use of ryegrass would be desirable
- A better predictive tool for the risk of ARGT is required to enable better use of pastures

Major factors recognised

- Need for a corynetoxin assay in meat to be able to assure consumers there is no risk
- Emotionally and financially stressful for farmers

Intervention points

- Ryegrass in crops
  - integrated weed management
  - cultivate versus chemicals
- Ryegrass in pastures
  - replacement grass (not legume)
  - cattle feed
  - Safeguard
- Ryegrass in general
  - effective biocontrol agents

Agenda 6: ARGT Workshop 2002 36

Twist fungus

- Farmer dissatisfaction
  - period it takes to work
  - can't see it
  - extension material makes it sound simple - it isn't
  - need more help in paddock selection
  - effect of spraytopping and fungicides
  - need to see some results that it is actually doing something

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Intervention points

- Livestock
  - prevention - a vaccine
  - treatment - an antidote

Agenda 6: ARGT Workshop 2002 38

Prioritised research recommendations

- A vaccine
  - prevent/minimise stock losses
  - enable continued use of annual ryegrass
- Safeguard
  - is it suitable for WA?
  - to what extent will it be competitive in crops
  - another suitable nematode-resistant ryegrass
- Replacement grass for ryegrass

Agenda 6: ARGT Workshop 2002 39

Prioritised research recommendations

- Twist fungus
  - affect of fungicides and spraytopping
  - develop better procedures for establishment and persistence
- Other biocontrol options
  - non-toxigenic *Rathayibacter* spp.
  - mutant bacteriophage that doesn't induce toxin production
  - inactivated bacteriophage competitor

Agenda 6: ARGT Workshop 2002 40

Prioritised research recommendations

- Corynetoxin assay for meat
- More work on integrated weed management and its adoption
- Develop effective treatment for animals with ARGT
- Develop alternative uses or methods of disposal for contaminated feed and offal

Agenda 6: ARGT Workshop 2002 41

Prioritised research recommendations

- Determine what production affects subclinical ARGT causes
  - reduced lambing percentages
  - reduced growth rates, particularly in feedlots
- Basic research
  - ecology of the nematode and the bacterium, identify the genome in Rathayibacter toxicus responsible for toxin production, correlation between herbicide resistance and bacterial colonisation, etc.

Agenda 6: ARGT Workshop 2002 42

GRDC PRIORITIES

FACTORS INFLUENCING GRDC'S INVESTMENTS

The six most important hazards in the grain industry:

1. Plant Toxins
2. Mycotoxins
3. Microbiological
4. Chemical residues
5. GMOs (Perceived)
6. Physical contamination

Natural toxins of significance to the grains industry

i. Mycotoxins
ii. Pyrrolizidine alkaloids (PA's)
iii. Corynetoxins / ARGT
iv. Phomopsins
v. Ergots

Agenda 7: GRDC Priorities 43

GRDC PRIORITIES

SCARM Report PRIORITIES FOR RESEARCH & DEVELOPMENT
January 2000

1. ***Food Safety***

- There is the highest priority for information on the safety of our agricultural produce and food.
- As a prerequisite, this will require the development or improvement of basic tools such as corynetoxin assays, radiolabelled toxins, and improved methods for corynetoxin production, isolation and concentration.

2. ***Establish a safe/acceptable level of dietary intake.***

- determine the quantitative level of corynetoxins in food commodities.
- determine the levels, distribution and bioavailability of corynetoxins in grains, meat, milk and canola oil, as well as to generate NOEL data suitable for determining a safe, maximum intake for humans.
- The study of in vivo biological effects of corynetoxins on fertility, immuno-competence, peripheral circulation etc. also fall into this category since they underpin NOEL data.

Agenda 7: GRDC Priorities 44

GRDC PRIORITIES

SCARM Report PRIORITIES FOR RESEARCH & DEVELOPMENT
January 2000

3. ***National distribution of C. toxicus***
- Priority should also be applied to define the distribution of C. toxicus nationally and for on-going monitoring of the distribution, leading to better management of infected areas.
- A lower priority should be given to plotting and monitoring the national distribution of Anguina species that could act as vectors for the bacterium.

4. ***Improved farm management practices***
- It is a priority to continue the development of new farm management practices to reduce the incidence of ARGT and the risk of contamination by the bacterium and nematodes. Work in this priority category includes the development of quality standards for fodder contamination resulting in minimal adverse effects on production in livestock.
- The effectiveness of recommended farm management practices should be monitored by measuring not only the incidence of ARGT in livestock but more importantly their effect on levels of corynetoxin contamination of livestock products and their impact on food safety.

5. ***Prevention of ARGT and corynetoxin contamination***
- It is important to develop methods of reducing unacceptable levels and bioavailability of corynetoxins in products such as grain, meat, milk, and canola oil.
- Examples of key research outcomes would include animal treatments such as vaccination and the use of a corynetoxin-binding antidote in livestock, and biological control methods such as twist fungus and nematode resistant ryegrass in the field.

Agenda 7: GRDC Priorities 45

GRDC PRIORITIES

SCARM Report PRIORITIES FOR RESEARCH & DEVELOPMENT
January 2000

Interim recommendations on R&D priorities - 2002

Recommendations of the survey report	STATUS
Use of on-farm grain cleaning equipment should be encouraged. Cleaning grain on farm will result in a substantial reduction in levels of contamination of grain that leaves the farm.	ACTION REQUIRED – an encompassing communication package might be considered
Consideration should be given to the introduction of a ryegrass seed receival standard, at least in areas where *R. toxicus* contamination has been identified as a high risk, to encourage cleaning.	ACTION REQUIRED – discussed as part of the SCARM Working Group and this needs to be completed
More research is required to determine what agronomic practices are currently being used that contribute to a reduction in the level of *R. toxicus* contamination of grain.	Encompassed as part of current project DAW699

Agenda 7: GRDC Priorities 46

GRDC PRIORITIES

SCARM Report PRIORITIES FOR RESEARCH & DEVELOPMENT
January 2000

Interim recommendations on R&D priorities – 2002 (cont)

Recommendations of the survey report	STATUS
Extra resources should be allocated to the herbicide resistance (HR) programs to ensure management strategies developed for managing HR weeds also reduce contamination levels of either the bacterium or its associated toxins.	Encompassed as part of current project DAW699
Encourage dissemination of the twist fungus in areas where *R. toxicus* contamination has been identified as a high risk, and encourage research on the development of additional biological control strategies of *R. toxicus*.	Encompassed as part of current project DAW699
More research is required to evaluate sampling strategies to determine levels of *R. toxicus* and corynetoxin contamination in grain.	ACTION REQUIRED – AQIS and bulk handlers should be encouraged to investigate

Agenda 7: GRDC Priorities 47

GRDC PRIORITIES

SCARM Report PRIORITIES FOR RESEARCH & DEVELOPMENT
January 2000

Interim recommendations on R&D priorities – 2002 (cont)

Recommendations of the survey report	STATUS
The hay industry's field sampling protocol could be adapted to grain crops if it becomes necessary to identify paddocks with high levels of *R. toxicus* prior to harvest.	ACTION REQUIRED – – discussed as part of the SCARM Working Group and this needs to be completed
A simple, rapid, cheap and accurate assay for the corynetoxins in all grains needs to be developed, and studies undertaken to demonstrate what sort of relationship exists between the number of bacterial galls/kg and the corynetoxins concentration in grain samples.	Encompassed as part of current project CSU9
No observable adverse effect levels for the corynetoxins in livestock and humans need to be determined.	Encompassed as part of current project CSU10
Investigate how to dispose of screenings or whole grain samples contaminated with *R. toxicus*	ACTION REQUIRED

Agenda 7: GRDC Priorities 48

FODDER INDUSTRY

ARGT IMPACT, CURRENT MANAGEMENT PRACTICES, FUTURE NEEDS

- The export fodder industry cannot allow any ARGT infected fodder to be directly implicated in negative performance in Japan without it seriously jeopardising the future of the industry.
- With the market becoming increasingly safety conscious, particularly with the likes of BSE incidents occurring, it becomes even more relevant than in the 1996 ARGT incidents in Japan.
- Today the export fodder industry has a sampling/testing code of practise that some 12-18 months ago was scrutinised and modified, in consultation with relevant academic authorities including AgWA and SARDI, by AQIS.
- In the foreseeable future, AQIS will hopefully gain international approval to include export fodder as a prescribed product under the existing Export Control Act. Once this happens, it will be compulsory for all export fodder to be tested for ARGT prior to approval for export being issued by AQIS.

Agenda 8: AFIA Impacts 49

FODDER INDUSTRY: ARGT IMPACT, CURRENT MANAGEMENT PRACTICES, FUTURE NEEDS

- The important components of the sampling/testing procedure are:

a) Sampling procedure outlining frequency, technique and size of sample to be taken
b) Testing procedure
c) Identified trail from the point of sampling through to the container that the fodder is exported in.

- Since the 1996 ARGT incident a high percentage of fodder exported has been sampled and tested for the presence of ARGT bacterium. The system appears to be working well, however, industry is aware that not all fodder for export has been sampled and tested for the presence of ARGT, hence the request for AQIS to become involved.

Agenda 8: AFIA Impacts 50

FODDER INDUSTRY: ARGT IMPACT, CURRENT MANAGEMENT PRACTICES, FUTURE NEEDS

Two areas of current research that the fodder industry is involved in (albeit at a progress rate subject to availability of research and development funds) are:

1. Reliable/cost effective form of bale identification

- Currently bale tags that can be attached to strings on the bales are used to identify individual/groups of bales.
  There are a few weaknesses in this process eg not all bales are tagged at the time of sampling from a representative lot; therefore it relies on accurate communication and honesty for the system to work well.
  All bales are individually tagged at a later stage in the transport process often.
  It is hoped that we can develop a form of bale identification that can be applied to the bale either at the time of bailing or at the time of sampling, to all bales within the line.
  This identification form would need to be able to be 'read' easily and reliably at all stages in the transportation/processing operation and be cost effective.

2. Reduction in soaking time involved in the ELIZA assay, used for the detection ARGT bacterium.

- Reduce the time required for the testing of samples. Currently the testing procedure requires core samples to be soaked for a minimum of 17 hours. Often it is up to 48 hours between completion of bailing until owner of fodder knows the ARGT status of the fodder. This can expose the fodder to external weather damage, which has a detrimental effect on the quality and therefore subsequent dollar value of the product.
  It is hoped that by treating the core sample for testing – eg by grinding, heating the water (soaking agent), addition of detergent or other appropriate chemical – that the time requirement for soaking can be significantly reduced without significantly compromising the overall reliability of the testing procedure.
  This work is being undertaken by AgWA and funded by a group of fodder exporters from Western Australia.

Agenda 8: AFIA Impacts 51

FODDER INDUSTRY: ARGT IMPACT, CURRENT MANAGEMENT PRACTICES, FUTURE NEEDS

Management practises that are currently undertaken within the fodder industry to improve the situation include situations aimed at 'isolating' fodder likely to have ARGT bacterium present, and crop management practises to reduce the likely incident of ARGT.

1. Where ARGT history is supportive of a certain location within a paddock having a higher incidence of ARGT, the paddock is segregated into definable sections and the fodder from the different sections identified, sampled and tested separately. This could for example be the perimeter of the paddock, any section of the paddock associated with a non arable component or areas of paddock that are more conducive to the presence of ARG.
2. Increased seeding rates aiming to supply increased competition to ARG within the crop.
3. Promote the concept that crop rotation can have a major beneficial effect on helping eliminate ARG in the paddock. Eg wheat, barley, oilseed, legume, oaten hay, summer crops etc.
4. Use of green ryegrass testing procedure to help identify areas of high/low ARGT bacterium presence, prior to the cutting of the crop.
5. Spray topping of the residual stubble post cutting so as to ensure ryegrass does not regenerate and set seed.
6. Promote the use of twist fungus
7. Convey on to grower's significant amount of test costs after a presence of ARGT bacterium is confirmed, to ensure the grower has a financial incentive to reduce ARGT bacterium presence. (Once ARGT bacterium is detected, the fodder can only be exported if the fodder under significantly higher sampling frequency is shown not to have ARGT bacterium present. The cost of this often ends up of the order of $25 per tonne of fodder.)

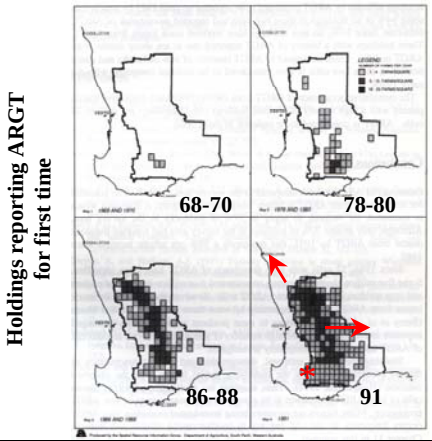
Agenda 8: AFIA Impacts 52

ARGT IMPACT SHEEP PRODUCTION

Jeremy Allen WADA

Agenda 9: Sheep Impacts 53

Spread of ARGT - WA



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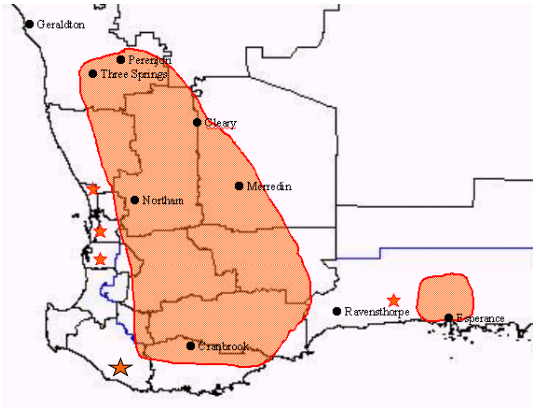
ARGT - current distribution



Agenda 9: Sheep Impacts

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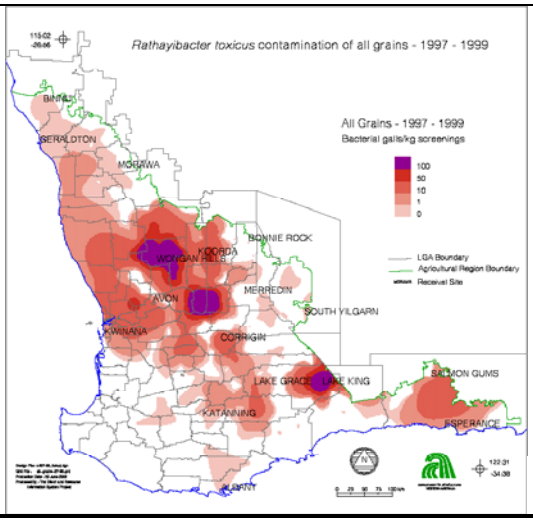
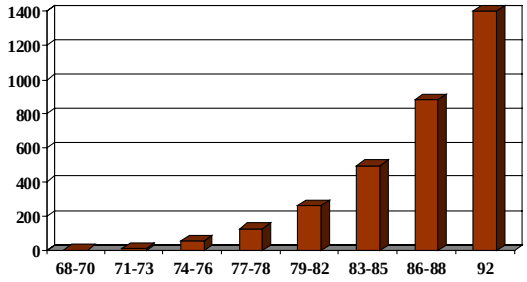


***R toxicus* in grain - W.A.**

56

Spread of ARGT - WA

Cumulative number of holdings reporting ARGT



Agenda 9: Sheep Impacts 57

Sheep losses from ARGT - WA

- **By 1994 over 200,000 sheep had died from ARGT**
- **Estimated average of 20,000-30,000 sheep and 230 cattle dying each year**
- **1991 - 88,168 sheep died**
- **2000 a very bad year as well**
- **2003 was a very good year**

Agenda 9: Sheep Impacts 58

Sheep production in the ARGT area

- ARGT occurs over an area of 10 million ha in WA
- Approximately 55% of the State's flock is in this area
- Losses from deaths, costs of control, unavailability of toxic pasture, reduced carrying capacity
- Emotionally depressing disease
- Subclinical losses?

Agenda 9: Sheep Impacts 59

Subclinical losses due to ARGT

- Reduced wool production - 10% reduced staple length, 7% reduced fibre diameter, 22% reduced wool volume over 11 weeks
- Reduced growth rate ??
- Reduced lambing percentages ??
- Carry over affects to subsequent years ??

Agenda 9: Sheep Impacts 60

Risks in feedlotting

- Contaminated hay
- Contaminated grain

Agenda 9: Sheep Impacts 61

Current management practices

- Reduce ryegrass
- Spraytopping to stop toxin production
- Regular observation of livestock during the risk period
- Twist fungus
- Testing of purchased hay

Agenda 9: Sheep Impacts 62

Future needs

- Alternative safe grass
- Effective biocontrol agents
- Effective means of controlling ryegrass
- Better informed on current control strategies
- Vaccine
- Effective treatment
- Better prediction of the risk of ARGT

Agenda 9: Sheep Impacts 63

ARGT IMPACT CATTLE PRODUCTION

Jeremy Allen WADA

Agenda 10: Cattle Impacts 64

Current trends

- More cattle moving into the wheatbelt
- Grazing and feedlot
- The dairy area is remote from the main ARGT area - but isolated cases of ARGT have occurred on the coastal strip, including this year
- Cases on the coastal strip have so far involved beef cattle, horses and one of dry cows

Agenda 10: Cattle Impacts 65

Concern areas

- Lake Grace - Lake King area; cattle moving into this area
- Esperance - ARGT is just getting going in this area, and there are a lot of cattle in this area

Impact, management practices

- As for sheep
- In feedlots they must be careful to purchase only hay that has been tested and never use seconds grain

Future needs

- As for sheep - vaccine**

ARGT Vaccine Commercial Assessment

David Leyonhjelm
Baron Strategic Services
31 March 2004

Objectives

- Assess business opportunity
- Find a way to make it commercial

Market Potential

	WA	SA
Sheep population	23 million	13 million
Sheep in infected area	12 million	3 million*
Sheep in endemic area	9 million	2 million*

* Estimate based on SA government livestock officer feedback.

Adoption Rate

- Perceived threat of disease
- Awareness of vaccine
- Perceived effectiveness of vaccine
- Ease of use of vaccine
- Cost of vaccine
- Acceptability of alternatives

Product Use Pattern

- Annual or intermittent
- All or some sheep
- Wethers, ewes, lambs

Product Life Cycle

- May be very long
- May use vaccine to help eliminate disease

Other Vaccines

Product	Dose volume	Retail per dose
Ovine Johnes Disease (Gudair)	1 ml	$1.80
Footrot	1 ml	$1.55
Scabby mouth	n/a	19c
Erysipelothrix	1 ml	33c
6 in 1 plus moxidectin (Eweguard)	2-3 ml	63c
6 in 1 plus moxidectin (Weanerguard)	2-3 ml	44c
Clostridial 6 in 1	1 or 2 ml	18c
Clostridial 6 in 1 plus Se	1 or 2 ml	20c
Clostridial 6 in 1 plus B12	1 or 2 ml	36c
Ovastim (fecundity stimulant)	2 ml	$1.00

State Of Development

- Experimental vaccine
- Pen challenge
- IP protection
- Multiple unknowns

Product Definition

- Injectable
- Oil adjuvant
- Plastic packs
- Requires refrigeration
- Initial two doses just prior to risk period
- One booster prior to risk period each year
- Season-long protection
- Registered for sheep
- Dose volume 1 or 2 ml

Features & Benefits

Feature	Benefit
Vaccinated animals are not susceptible to death or illness due to ARGT	Cessation of mortalities and disease due to ARGT. Contaminated pasture can be safely grazed Less need to purchase supplementary or replacement fodder
Vaccinated animals are not subject to sub-clinical production and reproduction effects of ARGT	Productivity increase
Vaccinated animals may be able to consume hay that has been rejected for export due to ARGT contamination	Lower feed costs Improvement in market for hay
Vaccinated animals do not carry residual toxin	Assurance of meat safety

Product Disadvantages

- Site reactions
- OH&S
- Dose volume
- Administration regime
- Handling & storage
- Less convenient
- Expense

Competitors

- Direct
  - None
- Indirect
  - Remove stock
  - Avoid pasture
  - Prevent seed set
  - Controlled burning
  - Twist fungus
  - Safeguard seed
  - Non-toxic *Rathayibacter*

Presentation & Packaging

- Single purpose vaccine
- Multi antigen later (?)
- Plastic packs
  - 200 dose

Distribution

- Rural merchandise
- WA Dept of Ag
- Veterinary practices

Promotion

- Increase awareness of ARGT inc sub-clinical and productivity effects
- Achieve awareness of vaccine availability
- Ensure vaccine benefits are known and understood.
- Advise where vaccine may be purchased

Commercialising The Vaccine
Steps Required

- Finalise/optimise formulation
  - Adjuvant
  - Conjugation method
  - Protein
  - Antigen load & dose volume

Finalise Admin Regime

- Initial dose regime
- Duration of immunity
- Previously vaccinated animals
- Maternal antibodies

Other

- Shelf life
- Confirm raw material sources
- Optimise production
- Efficacy data
- Safety data
- Regulatory dossier

Costs Of Development

Pen trials	150,000
Dose regime	
Maternal Abs	
Immunological memory	
Challenge	
Ab assays	5,000
Field trials	
Efficacy x3	75,000
Concurrent use	-
Reproductive safety	80,000
Repeat treatment	30,000
WHP (residues)	-
Dossier	10,000
Stability	15,000
Total	365,000

No allowance for cost of modifying the current experimental vaccine.

Costs Of Production
Tunicamycin

Company	Location	Price
A.G. Scientific (via Total Lab Systems)	USA	US$1900/g
Fermentek	Israel	US$1000/g
Serva Electrophoresis	Germany	
US Biological	USA	

Costs Of Production
Production Overheads

- Depends on batch size and plant utilisation
  - $15-20/vial typical
  - Up to $40/vial

Costs Of Production
Summary

	Expected $ per vial (200 dose)	Expected $ per dose	Min $ per dose	Max $ per dose
Tunicamycin	110.00	0.55	0.55	1.05
Other materials inc packaging	4.00	0.02	0.02	0.02
Production costs	30.00	0.15	0.08	0.20
Total	144.00	0.72	0.65	1.27

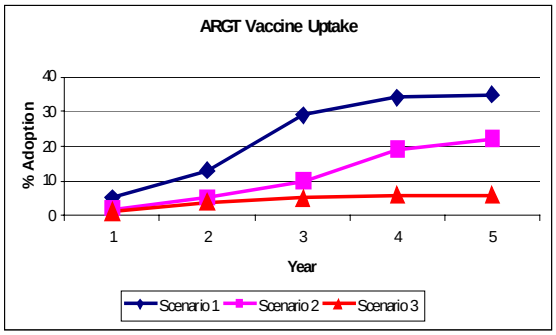
Projected Price

Expected	$ per vial (200 dose)	$ per dose	$ per vial (200 dose)	$ per dose
COGS	$ 144	$ 0.72	$ 144	$ 0.72
Gross margin	40%	40%	60%	60%
Ex manufacturer price	$ 240	$ 1.20	$ 360	$ 1.80
Distribution margin	15%	15%	15%	15%
Retail price	$ 282	$ 1.41	$ 424	$ 2.12

Projected Price
Maximum & Minimum

Maximum				
COGS	$ 254	$ 1.27	$ 254	$ 1.27
Gross margin	40%	40%	60%	60%
Ex manufacturer price	$ 423	$ 2.12	$ 635	$ 3.18
Distribution margin	15%	15%	15%	15%
Retail price	$ 498	$ 2.49	$ 747	$ 3.74
Minimum				
COGS	$ 129	$ 0.65	$ 129	$ 0.65
Gross margin	40%	40%	60%	60%
Ex manufacturer price	$ 215	$ 1.08	$ 323	$ 1.61
Distribution margin	15%	15%	15%	15%
Retail price	$ 253	$ 1.26	$ 379	$ 1.90

Adoption Rate



Projected Sales

Revaccination rate			90%	80%	80%	70%
Doses sold (000)	Scenario 1	1,500	3,075	6,360	4,980	3,870
	Scenario 2	600	1,170	2,100	3,900	2,895
	Scenario 3	300	1,035	780	900	630
Sales Revenue (000)		Year 1	Year 2	Year 3	Year 4	Year 5
Price/dose	$ 1.20					
	Scenario 1	$1,800	$3,690	$7,632	$5,976	$4,644
	Scenario 2	$720	$1,404	$2,520	$4,680	$3,474
	Scenario 3	$360	$1,242	$936	$1,080	$756
Price/dose	$ 1.80					
	Scenario 1	$2,700	$5,535	$11,448	$8,964	$6,966
	Scenario 2	$1,080	$2,106	$3,780	$7,020	$5,211
	Scenario 3	$540	$1,863	$1,404	$1,620	$1,134

Profit And Loss

Marketing		$400	$300	$200	$100	$100
Technical Support		$100	$100	$100	$100	$100
Marketing Contribution						
Price/dose	$ 1.20					
	Scenario 1	$1,300	$3,290	$7,332	$5,776	$4,444
	Scenario 2	$220	$1,004	$2,220	$4,480	$3,274
	Scenario 3	-$140	$842	$636	$880	$656
Price/dose	$ 1.80					
	Scenario 1	$1,120	$3,152	$3,071	$8,764	$6,766
	Scenario 2	$580	$1,706	$3,480	$6,820	$5,011
	Scenario 3	$40	$1,463	$1,104	$1,420	$934

NPV, Payback

- NPV strongly positive for all scenarios.
- Payback for scenarios 1 and 2 is favourable at both high and low margins.
- Scenario 3 is favourable under the higher margin.

Potential Partners

• **Fort Dodge**	Penrith, NSW
• **CSL (Pfizer)**	Parkville, Vic
• **Intervet**	Bendigo, Vic
• **Schering-Plough**	Upper Hutt, NZ
• **Agvax**	Upper Hutt, NZ
• **Bioproperties**	Glenorie, NSW
• **Allied Biotechnology**	Kings Park, NSW
• **Zenith Technology**	Dunedin & Auckland, NZ
• **Biotech Australia**	Roseville, NSW
• **Peptech**	North Ryde, NSW
• **Progen**	Darra, Qld
• **Numico Research**	Oakden, SA
• **Eimeria**	Werribee, Vic
• **Tick Fever Research Centre (DPI)**	Wacol, Qld

Level Of Interest

- Pfizer +++++
- Intervet +++++
- Schering Plough ++++
- Fort Dodge +++

Information Gaps

Information Gap	Means of resolution
How many farmers will use the vaccine at the projected price	Market research
Will all animals receive the vaccine, or will stockowners use it selectively	Market research
Are Twist fungus and/or Safeguard likely to be employed as well as, or instead of the vaccine	Market research
Will the vaccine be used every year or less frequently	Market research and experience
Will sheep that are vaccinated one year be revaccinated the following year	Market research and experience
Is tunicamycin available in the quantities required	Inquiry and negotiation
Will the conjugate be stable under commercial production conditions	Pilot production
Will the vaccine prevent death and disease from ARGT in sheep under field conditions	Field trials
Can an acceptable administration regime be developed.	Pen trials

Risks & Threats

- Vaccine performance
- Vaccine convenience
- Adverse reactions
- Vaccine production
- Tunicamycin availability
- Vaccine price
- Life cycle
- Twist fungus
- Safeguard
- Non-toxic *Rathayibacter*

Opportunities

- Cattle
- Horses
- Flood Plain Staggers
- Add to Clostridials

Conclusions

- Financially viable
- Product definition needs work
- High potential for commercial partner
- For maximum ARGT prevention, substantial price reduction needed

Recommendations

- CSIRO define product further
- Invite commercial participation
- Consider research into recombinant tunicamycin replacement

Annual Ryegrass Toxicity

Steve Colgate CSIRO

Some Questions

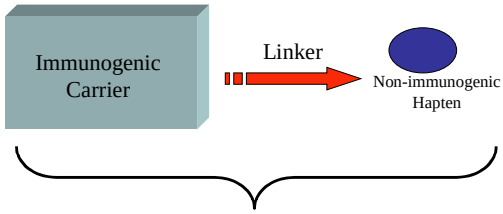
- What is the true cost of acute poisoning?
- What are the sub-clinical productivity losses and the associated “hidden” costs?
- How (when) will animal welfare issues impact on farm management?
- What implications are there for Human food safety?

Potential Benefits of a Vaccine

- Prevent clinical disease in animals
  - Reduce stock losses (income and farmer morale issues)
  - Reduce impact of animal welfare issues
  - Reduce ARGT-related management imposts
- Prevent/decrease productivity losses (wool, reproduction) due to sub-clinical exposure
- Potential to clear accumulated CTs from animal tissue
  - Reduce potential for secondary poisoning or trade-related issues

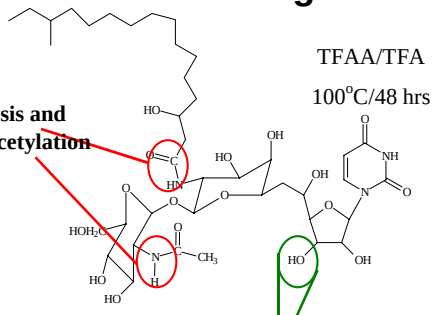
Corynetoxins are not Naturally Immunogenic *Vaccines for Small Molecules*

General approach

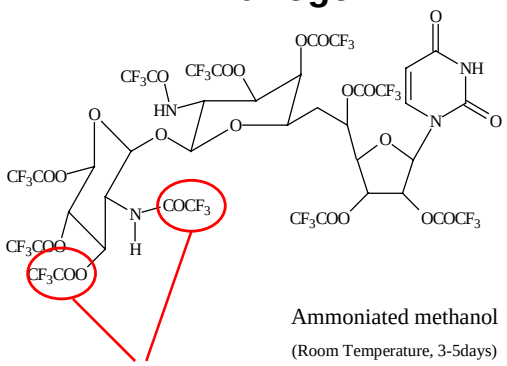


Immunogenic Conjugate

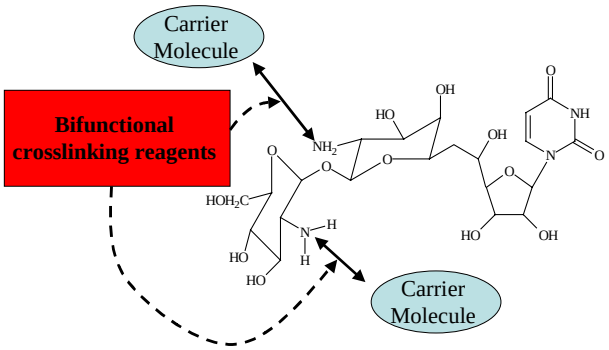
Synthesis of Hapten and Immunogen



Synthesis of Hapten and Immunogen



Synthesis of Hapten and Immunogen



Agenda 12: Vaccine R&D 108

Vaccine Development ... General Protocol

- Formulate *hapten – carrier* conjugate with an adjuvant (CSIRO-patented "Triple Adjuvant")
- Primary vaccination
- Booster vaccination after 2-8 weeks
- Monitor antibody production
- Reboost as necessary
- Challenge experiments

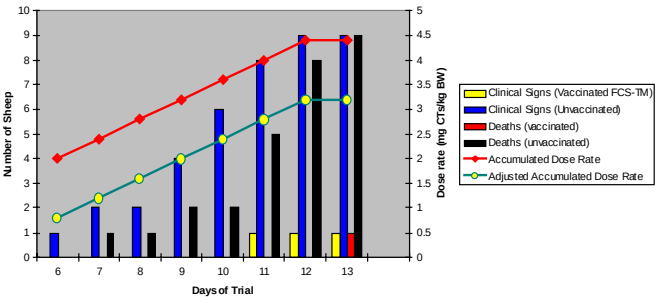
Agenda 12: Vaccine R&D 109

Vaccine Development
Pen Trials
Oral Dosing

- Milled grain screenings estimated at 83 ug CTs/gm (ppm)
- All sheep were dosed (ruminal intubation) with water slurries of 170g milled screenings/sheep/day (i.e.,14 mg of CTs per sheep/day or about 0.4 mg CTs/kg BW/day (acute LD_{50} is 1-3 mg/kg BW)
- Dosing continued daily (for up to 11 days)

Agenda 12: Vaccine R&D 110

Vaccine Development
Pen Trials... FCS-TM Vaccine
Oral Dosing



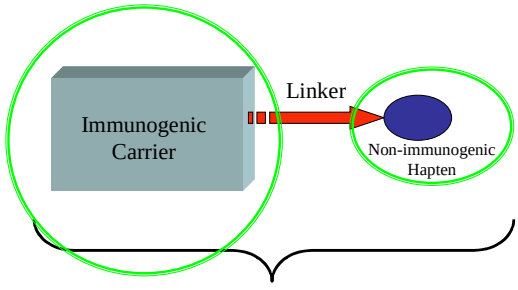
Agenda 12: Vaccine R&D 111

Further Development
FCS-TM Vaccine

- Immunization schedule
  - How many boosters?
  - Re-immunisation?
- Shelf life of vaccine
- Field trials
- Cost reduction
  - Hapten production
    - Improved synthetic procedures
  - Australian-based tunicamycin production
- Commercial development
  - Synthesis and formulation
  - Registration

Agenda 12: Vaccine R&D 112

New Research
Improved vaccine ...efficacy, acceptability and cost



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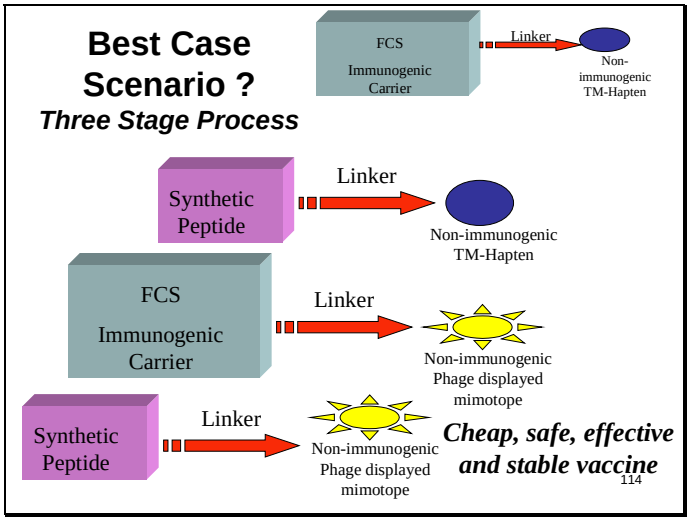

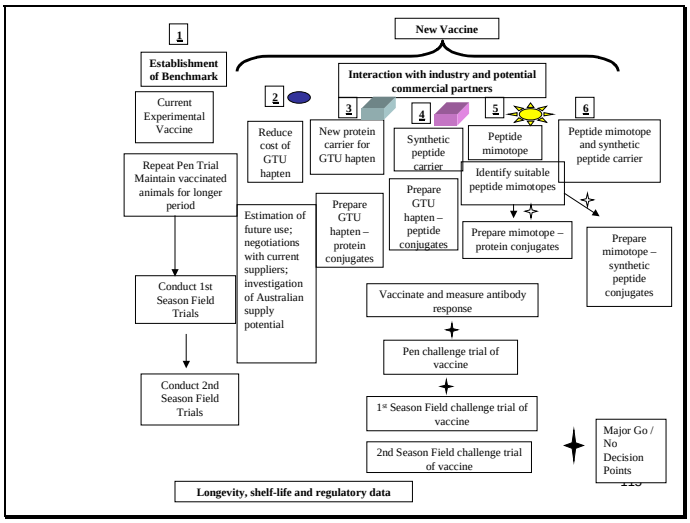

Summary

- A vaccine does exist that protects sheep against oral exposure to corynetoxins present in milled grain screenings
- Further R&D is required to prove the field efficacy and the commercial viability of the current vaccine
- New R&D is being progressed to improve the properties and the commercial acceptability of the vaccine

Basic Food Safety-related Questions

- What is the maximum tolerated intake (daily or weekly)?
  - Toxicology studies ..... NOEL
    - » clinical effect (including ill-health, neurological competence, behaviour)
    - » pathology
    - » biochemistry
    - » pregnancy/reproduction
- What is level of human exposure?
  - Levels of contamination in grains, meat and dairy?
    - » analytical methods of detection and quantitation
    - » toxicodynamic/kinetic studies
    - » bioavailability resulting from primary or secondary exposure

Agenda 12: Food Safety 117

Summary

- Determination of a NOEL for some toxicity indices is well advanced
- NOELs for other indices of toxicity are slowly advancing
- Detection methodology for grains is well advanced
- Adaptation to meat and dairy is required
- Future development to “real-time” assays is progressing very slowly
- A need for scientific confirmation of distribution and clearance times
- Research to determine biomarkers of exposure is progressing slowly

Agenda 12: Food Safety 118

Current GRDC investments

GRDC project	Status 2004
Development of a rapid, sensitive and reliable quantitative ELISA for screening Australian wheat and barley for ARGT-causing corynetoxins *CSU5 -*	Completed
Survey levels of diseased ryegrass in Australian grain *DAS272, DAW570 and CSU4.*	Completed
Implementation of CT assay and relating levels of CT and ARGT bacterium in wheat and barley *CSU9*	Completed
Determination of a No Observable Effect Level (NOEL) for corynetoxins *CSU10*	Current
Evaluation and further development of biocontrol for the ARGT causal organism *DAW699*	Current

Agenda 13: Current GRDC Investment 119

Current GRDC investments

MANAGEMENT PLANS including a HACCP-based analysis for CTs in wheat

- CTs in grain and fodder were used by AFFA working with an industry technical group as a case study to:
- establish a generic risk management framework for natural toxins
- sent to industry organizations for application to through-chain management of high risk natural toxins

HACCP Plan for Wheat

- the HACCP plan included a series of hurdles
- the hurdles are cumulative measures that may be taken to reduce the presence of causative agents of ARGT
  - ryegrass
  - nematode
  - bacteria
  - toxin

Logic flow diagrams show the critical decision points in the process:

- Logic flow diagram 1 shows selection, risk categorization and management of paddocks
- Logic flow diagram 2 shows pre-harvest inspection; and
- Logic flow diagram 3 shows grading of wheat from high-risk paddocks

Agenda 13: Current GRDC Investment 120

AFIA CURRENT RESEARCH PROPOSALS

- All research projects contemplated by the fodder industry are severely limited by this availability of research and development funds; therefore research and development proposed projects are thought of in this context.
- The more complex research and development associated with concepts like eliminating ARGT will need to be funded by bodies that have more funds available.
- Two areas that I believe would be of benefit are:

A. Promote quality assurance at the farm gate. The fodder export industry has established a fairly strong quality and assurance package as a result of the ARGT situation. The next step in this process may be to push this back to the farm gate and this become a part of a farm becoming quality assured with respect to ARGT for all products produced on the property.

B. Establishing the human safe levels eg what are the health implications of a person handling hundreds of ARGT samples.

- In conclusion, I would like to say that all industries must accept that all of the Japanese customers that the export fodder industry deal with are fully aware of ARGT and its presence in Australian agriculture. It would be very naive to adopt an attitude that because it is not a current issue in particular sectors of the agriculture industry, it will not become a significant issue. Do not turn a blind eye because you think the issue of ARGT is not relevant or too hard.

Agenda 14: Current AFIA Research 121

Coordinated approach to minimising the impact of annual ryegrass toxicity (ARGT) in agriculture

Application Prepared by ARGT Solutions Team:

Jeremy Allen, *Veterinary toxicology, biocontrol*
Perry Dolling, *Pasture Research Officer*
Mark Dolling, *Wool Program Manager*
Alex Douglas, *Grains Industry Research*
Stephen Gherardi, *Sheep Industries*
Linda Leonard, *Central Agricultural Region*
Greg Shea, *Grain Biosecurity*
Don Telfer, *Northern Agricultural Region*
Sandy White, *Southern Agricultural Region*

Agenda 15: Increasing Research Adoption 122

Presentation outline

- Whose perspective
- The approach
- What is going to be done
- When -Long term and interim Targets
- Who is involved
- Short term goals
- How will it be done
- Impact - Project contribution to change
- Budget
- Conclusion

Agenda 15: Increasing Research Adoption 123

Collective Action

Whose perspective?

What do researchers and farmers know Stock loss due to ARGT Visual symptoms of diseases The problem of ryegrass resistance *Implications: continuous learning/ sharing*	**What do farmers know more than researchers** History of disease incidence Local agroclimatic patterns *Implications: documentation/assessment*
What do researchers know more than farmers Pathogenicity of diseases Host organisms Latent infection *Implications: training and extension*	**What don't farmers and researchers know** Viable options, competition Adaptability of component technologies Projections on disease incidence *Implications: basic and applied research*

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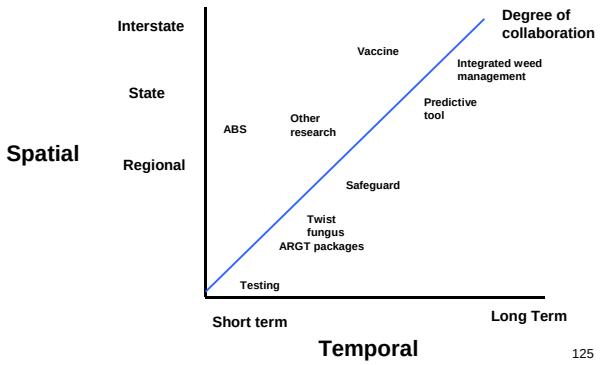
Our Approach



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What do we intend to do

- **using current knowledge develop improved farm systems packages**
- **establish the impact of Safeguard in the field in various environments**
- **investigate factors that influence the establishment and persistence of the twist fungus**
- **collect new intelligence on the losses from ARGT**
- **better coordination between all ARGT associated research**

Agenda 15: Increasing Research Adoption 126

Targets

By the December 2010 there will be minimal numbers of livestock at risk from corynetoxins in Western Australia

Increase sales of Twist Fungus and Safeguard by 20% over the area to be treated.

Amount of Safeguard pasture sown	Amount of Twist fungus applied
Amount of Safeguard sales	Amount of Twist fungus sales
Livestock deaths	

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Who

•Multidisciplinary reference group to provide advice and promote discussion in developing and promoting proven systems for managing ARGT	***Department of Agriculture, Landholders form ARGT Action Committee, the Sheep Research Council and elsewhere, NatCat***
•Coordinator	***Manage promote coordinate***
•Technical officer	***Technical support***

Support from regionally based Farming Systems Development Officers

Agenda 15: Increasing Research Adoption 128

Short Term Goals

Packages will be in place that will provide farmers with the tools to assess and reduce ARGT risk

How

- **Build a picture of information systems to help promote good management**
- **Issues to clarify include**
- **What type of information people need**
- **What forms of information are valued**
- **Important issues and topics**
- **How to ensure accessibility of information and improvements into the future**

Agenda 15: Increasing Research Adoption 129

Project contribution to practice change

- **Farming systems options will be developed to enhance adoption capacity**
- **A range of new information products and services developed and improved through time**
- **Gaps in information will be identified**
- **Coordinate and transfer of information from researchers to Farming Systems teams to landholders**

Agenda 15: Increasing Research Adoption 130

Short Term Goals

To have an understanding of the potential for Safeguard to reduce ARGT and how it may fit into the farming system

How

- **Develop baseline information**
- **Develop relationships with supplier to establish demand**
- **Testing in a range of environments medium rain fall zone (average rainfall 400mm per year) and low rainfall zone, (300mm per year)**
- **Complementary work to establish crop competition**

Agenda 15: Increasing Research Adoption 131

Project contribution to practice change

- Landholders will be able to recognise the flowering time of ryegrass
- Large scale demonstrations
- Known limitations of Safeguard
- A susceptible nematode resistant ryegrass
- Motivation for growers to plant Safeguard
- Better understanding and ability to break the nematode cycle

Short Term Goals

To have suitable recommendations for twist fungus and improvement in the prevention of ARGT across different environments

How

- Study factors influencing the establishment and persistence of twist fungus in the field as demonstrations - soil type, pH, moisture, use of fungicides and spray topping
- Conduct demonstrations north of the Great Eastern Highway
- Collection of ryegrass heads and doing nematode gall counts
- Provide analysis of paddocks which are best suited to twist

Project contribution to practice change

- Greater uptake of the twist fungus due to better advice on how and where to apply it leading to greater establishment and persistence of it
- Provision and adoption of a quick and effective testing service that will help farmers to identify where best to apply the twist fungus
- Greater control of the causative organisms of ARGT through larger areas of the state having effective populations of twist fungus

Short Term Goals

Benchmark data to measure the progress of the project, and provide information used to predict ARGT risk in the future

How

- **Passive and active forms of monitoring**
- **Annual ABS survey**
- **Interactive website**
- **Feedback mechanism to landholder**

Agenda 15: Increasing Research Adoption 135

Project contribution to practice change

- **Availability of a simple to use reporting mechanism in which landholders can remain anonymous**
- **Better knowledge on the occurrence and economic affects of the disease**
- **Identification of possible new avenues of research**
- **Collection of information on the epidemiology of ARGT that may form the basis for the development of a predictive tool for the occurrence of ARGT**

Agenda 15: Increasing Research Adoption 136

Short Term Goals

Achieve communication between key stakeholders over the life of the project

How

- **Regular communication with relevant groups**
- **Seek out champions and promote case studies**
- **Gather information on understanding and practices**
- **Build on technical knowledge**
- **Collate data**
- **Develop shared language consulting with experts, checking with farmers**

Agenda 15: Increasing Research Adoption 137

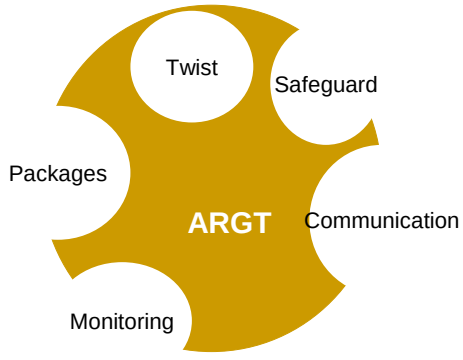
Project contribution to practice change

- **Agreed group actions**
- **Access to information and resources**
- **Partnerships**

Budget

Date	Employment $	Operating $	Total $
04/05	136,078	91,000	227,078
05/06	150,369	66,000	216,369
06/07	159,778	66,000	225,778

Attribution for Impact



POSSIBLE NEW RESEARCH ACTIVITIES

Jeremy Allen WADA

Decisions

- Prevent disease developing, or treat the disease, in animals - Option 1

OR

- Remove the causative organisms so there is no disease to develop or treat in animals - Option 2
- Option 2 is preferable - hay and grain industries, residues in meat

Option 2 possibilities

- Safeguard
  - biodynamics, development of herbicide resistance, crop competitiveness
    - NOT FUNDED
  - strategies - short term vs long term planting
- Alternative grass or nematode-resistant ryegrass for annual ryegrass
  - if Safeguard not suitable

Option 2 possibilities

- Tetraploid ryegrass
  - Use to break or dilute herbicide resistance
  - Move nematode-resistance into successful tetraploid ryegrass
    - NOT FUNDED
- Biocontrol agents
  - Twist fungus
  - Non-toxigenic *Rathayibacter* spp.
  - Others

Biological control

- Twist fungus
  - interaction between fungus and causative organisms in the field. Is there a fungus prevalence level above which ARGT doesn't occur?
  - comparison of paddocks in which twist fungus is either successfully established or does not establish
  - additional work on the effects of fungicides and spraytopping

Biological control

- Non-toxigenic *Rathayibacter* spp.
  - These are exotic bacteria
  - Previously shown that these bacteria can displace *R toxicus* in ryegrass infested with *Anguina funesta*
  - Currently undergoing evaluations to see if they cause any deleterious effects on non-target plant species
    - FUNDING ENDING

Biological control

- Others
  - mutant or inactivated bacteriophage
  - genetically modified R toxicus - adhesiveness(?) or toxin production
  - non-adhesive nematodes

Option 1 possibilities

- Vaccine
- Treatment
  - big pharmacological advances since the 1980's
  - activated charcoal, bentonite
    - cumulative toxin
    - only 5% ingested is absorbed
    - lends itself to PhD or Masters studies

Option 1 possibilities

- Feed additives or pretreatments - successful outcome would provide a means of feeding contaminated feeds and offal
  - lignin (lucerne), activated charcoal, clays, specialised resins, glucomannans
  - other alkalis (Ca and NH4 hydroxides), formaldehyde, ammonia, sodium bisulphite
    - such a small quantity of corynetoxins needs to be absorbed for toxicity
    - lends itself to PhD or Masters studies

Option 1 possibilities

- Manipulation of rumen microflora
  - find organisms that detoxify corynetoxins and put the genes into rumen microflora
    - *Alternaria alternata* (fungus); transforms tunicamycin to far less toxic metabolites
    - *Sphingobacterium multivorum*; detoxifies tunicamycin and corynetoxins
- Use of silage

Agenda 16: Possible Research Activities 150

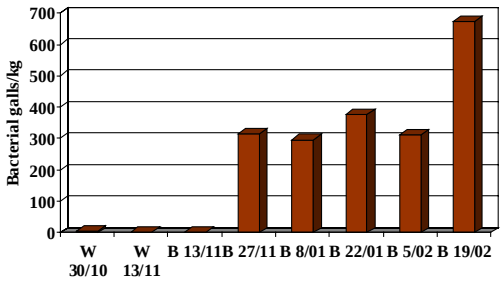
Additional, important research areas

- Subclinical effects
  - poor growth rates
  - reduced lambing percentages
  - carry over effect to subsequent years
    - are they real?
    - quantify them

Agenda 16: Possible Research Activities 151

Additional, important research areas

- Hay industry - do we need to change the sampling protocol?



Agenda 16: Possible Research Activities 152