

**REPORT OF ADVERSE
EXPERIENCES
2004 CALENDAR YEAR
PESTICIDES**

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EXECUTIVE SUMMARY

This is the first Annual Report of Adverse Experiences for Pesticides prepared by the APVMA.

The APVMA implemented the *Adverse Experience Reporting Program for agricultural chemicals* (AERP Ag), a new post-market surveillance program for agricultural chemicals, in December 2003. The AERP Ag uses scientifically-based risk assessment processes to evaluate adverse experience reports received from members of the public, farmers and other chemical users, agronomists, bystanders, health workers (including doctors, nurses, alternative medicine specialists etc), state and territory authorities and product registrants. Based on these risk assessments, risk management strategies (or *corrective actions*) may be required to ensure that products on the market remain safe, effective, are of acceptable quality and are used in the best possible way, and that instructions and warnings on labels are appropriate.

The purpose of the AERP Ag is to provide the APVMA with feedback about the performance of agricultural chemical products in the field to:

- ensure that registration decisions being made by the APVMA are appropriate and effective, and
- promote and maintain public confidence in the APVMA and the National Registration Scheme.

The AERP Ag complements the national post-market pharmacovigilance program for veterinary medicines (the AERP Vet), which has been in operation since 1995.

This Annual Report contains a summary of all adverse experience reports assessed, evaluated and classified by the APVMA during the 2004 Calendar Year under the AERP Ag. A similar Report is also available on the APVMA website for the AERP Vet.

Although the AERP Ag is a very new program and it has received a relatively small number of reports so far when compared to the AERP Vet a number of activities have been undertaken to promote the program within the wider community.

Activities undertaken

There has been a focus on promoting the AERP Ag to various community, farming and pesticide working groups throughout 2004. Activities undertaken to raise awareness of the program include:

- giving presentations to Australian Ground Sprayers Association and the ChemCert National Conference; and
- contributing to the Wildlife Health in Australia Newsletter, 1(2).

Various corrective actions have also been taken and these are listed separately in this report under the relevant active constituent listings.

1. INTRODUCTION

1.1 Program Outline

The APVMA is the independent Australian Government Statutory Authority responsible for the assessment and registration (marketing authorisation) of pesticides and veterinary medicines prior to sale, and their regulation up to and including the point of retail sale. 'Pesticides' include agricultural and many household chemicals such as insecticides, herbicides and fungicides; water treatment products including swimming pool and spa products; products for treating algae and mould; products for preventing rot and infestation in marine structures and other similar products. 'Veterinary medicines' include all veterinary chemical products such as vaccines, antibiotics, worming treatments, flea and tick washes and other parasiticides for both domestic and production animals. Under the National Registration Scheme, the APVMA evaluates and registers agricultural and veterinary chemicals and manages quality assurance programs that monitor the safety and performance of registered products.

The Adverse Experience Reporting Program for agricultural chemicals (AERP Ag) is a post-registration quality assurance program established by the APVMA to facilitate responsible management of agricultural chemicals throughout their lifecycle. The program provides a means for identifying corrective actions necessary to assure the continued safety, quality and effectiveness of registered agricultural chemicals. Recording and investigating reports of adverse experiences is an important step in detecting unusual or rare conditions that were not evident in clinical or field trials and as a result, could not be assessed during the product registration process. The AERP Ag helps to ensure that products on the market:

- remain safe, effective and of acceptable quality,
- are used in the best possible way, and
- that instructions and warnings on the label are appropriate.

1.2 What is an adverse experience?

"An adverse experience is an unintended or unexpected effect (deleterious) on plants, plant products, animals, human beings or the environment, including injury, sensitivity reactions or lack of efficacy associated with the use of an agricultural chemical product when used according to label directions."

The following definitions outline what constitutes "serious", "minor" and "urgent" adverse experiences.

Definition of a serious adverse experience:

"A serious adverse experience is one that involves:

- *widespread and significant crop and plant damage (eg crop death, severe stunting or significant yield loss),*
- *life-threatening or other significant effects in a human, including death,*
- *farm, domestic and native animal deaths, or*
- *significant environmental damage, including fish kills and water quality issues.*

Definition of a minor adverse experience:

"A minor adverse experience is one that involves:

- *crop and plant damage that is not widespread or significant (eg minor wilting or yellowing of crops, minor yield loss),*
- *human health effects that require medical attention, but are not life-threatening,*
- *injury to domestic and native animals that require veterinary attention, or*
- *minor environmental damage."*

A number of agricultural chemicals have known side effects when used as directed and it is useful to maintain a record of this so that the true incidence of these side effects can be assessed. Therefore it is important that all adverse experiences are reported.

1.3 Who can report an adverse experience?

Anyone – voluntary reporting is encouraged from members of the public, farmers and other chemical users, agronomists, bystanders, health workers (including doctors, nurses, alternative medicine specialists etc), and state and territory authorities.

Section 161 of the *Agvet Codes* requires registrants to provide the APVMA with any ‘new information’ that they become aware of. This ‘new information’ includes adverse experience information relating to human health issues, harm to animals, damage to plants, property or the environment and lack of efficacy when the products are used according to label directions.

The ‘registrant’ component of the AERP *Ag* is one method that product registrants can meet certain legislative obligations of section 161 of the *Agvet Codes*.

1.4 Reporting an adverse experience

Adverse experiences with agricultural chemicals may be reported using the Adverse Experience Reporting Form for agricultural chemicals available from the APVMA or on the APVMA website at http://www.apvma.gov.au/qa/aerp_ag.shtml.

1.5 Benefits of the AERP *Ag*

The AERP *Ag* provide numerous benefits to a wide range of stakeholders:

Benefits to the community

- Ensures the safety and efficacy of registered products in the marketplace.
- Provides confidence in the regulatory system.

Benefits to states

- Provide an integrated approach between national and state programs.
- Provides a format for communication of issues that cross over jurisdictional boundaries.

Benefits to farmers

- Provides up-to-date safety information on registered products.
- Ensures that the latest safety information is available on product labels.

- Provides information on modifications needed to work practices to ensure safe use of chemicals.
- Identifies and acts on emerging issues quickly.

1.6 Evaluation of adverse experience reports

Reports received by the APVMA are assessed to determine whether the adverse experience is related to the use of or exposure to the product or not. The APVMA may rely on advice from other commonwealth government agencies (such as the Department of Health and Ageing), and relevant state or territory agencies (such as the relevant Department of Agriculture) when assessing adverse experience reports. The APVMA will also take into account any published material available from similar reports as well as any relevant scientific literature published worldwide.

The conclusions drawn by the APVMA during investigation and evaluation of each adverse experience report will be provided to the reporting person. This will include an explanation of whether the APVMA considers that the observed adverse effects (including health symptoms) were related to the use of or exposure to the product. The APVMA will explain what these conclusions are and what corrective action, if any, will be taken in response to the information.

1.7 Classification of adverse experience reports

Once the relationship between the use of the product and the reported effect has been assessed after investigation of the incident it is expressed in terms of:

Probable

For inclusion in the category 'probable' all of the following minimum criteria should be met:

- there should be a reasonable association between the use of the product and onset and duration of the reported adverse experience,
- the description of the effect should be consistent with or at least plausible given the known mode of action, toxicology and metabolism of the product, and
- there should be no other equally plausible explanation (or contributing factors) for the clinical signs.

When any of the above criteria cannot be satisfied (due to lack of sufficient information or conflicting data) then the association cannot be assessed as 'probable'.

Probable/Off-label

As per the classification of 'probable' and where there is obvious evidence of off-label use (including use in crops/plants/situations not listed on the product label, excessive rates etc).

Possible

For inclusion in the category 'possible' association of the adverse experience with use of the product is one of other possible and equally plausible explanations (or contributing factors) for the described adverse experience.

Possible/Off-label

As per the classification ‘possible’ and where there is obvious evidence of off-label use (including use in crops/plants/situations not listed on the product label, excessive rates etc).

Unlikely

Where sufficient information exists to establish that the described adverse experience was not likely to have been associated with use of the product(s), or other more plausible explanations exist, the assessment should be categorised as ‘unlikely’.

Unknown

All adverse experiences where reliable data is either unavailable or is insufficient to make an assessment should be categorised as ‘unknown’.

1.8 Corrective action determination

There are many factors that need to be considered when determining whether corrective action is required and if so, what corrective action is needed to mitigate the issue. The APVMA takes into account a broad range of issues and options when deciding what, if any corrective action is required.

For each registered agricultural chemical, and more broadly for each active constituent, the APVMA conducts a trend analysis of all adverse experience reports received. All reports that have been classified as ‘probable’ or ‘possible’ are compared to the total number of doses sold within the relevant financial year and a ‘reporting incidence’ is calculated (ie the number of adverse experience reports per number of doses sold). A control limit or “warning line” for reporting incidence figures, which indicate that further action may be required is one or more per 10,000 doses sold. If the reporting incidence is greater than one per 10,000 in two out of three consecutive years or an exceptional incidence of three or more per 10,000 occurs on any one occasion, or a consistent rising trend is seen over five years (irrespective of the reporting incidence) then action may be required.

The APVMA considers other scientific literature and information relating to trend analysis and risk assessment when determining whether corrective action is required. The APVMA also takes into account whether the noted clinical signs are listed in warning statements on the product label, in which case a slightly higher reporting incidence may be acceptable, and considers the severity of clinical signs (ie more severe signs may trigger corrective action at a lower reporting incidence).

1.9 Outcomes of the program

Based on the assessment of adverse experience reports certain risk mitigation strategies or corrective actions may be required. These may include, but are not restricted to, the following:

- registration amendments, such as label changes, changes to the method of manufacture or product's physical or chemical design, changes to container design, changes to production line processes, or suspension and/or cancellation of registration and approval
- referral for action, such as compliance action, including product and batch recalls, referral to state authorities for action, or nomination of products or active constituents for formal chemical review by the APVMA, (note that once the recommendation for review has been made by the AERP the review program will conduct consultation and scoping prior to determining whether a review is necessary or not); and
- education and publicity, such as providing scientific papers or articles on issues identified for relevant journals, magazines or newspapers.

The conclusions drawn by the APVMA during investigation and evaluation of each adverse experience report will be provided to the reporting person. This will include an explanation of whether the APVMA considers that the observed adverse effects (including health symptoms) were related to the use of or exposure to the product. The APVMA will explain what these conclusions are and what corrective action, if any, will be taken in response to the information.

1.10 Report Structure

This report is arranged into the following sections:

- **Section 1** a summary of adverse experience reports other than human health (including crop damage, environmental damage and lack of efficacy) listed by active constituent, and
- **Section 2** a summary of adverse experience reports involving human health.

The information contained in this Annual Report is only a general reference to the type of adverse experience that farmers, health professionals, bystanders, and others have reported either to the APVMA or to product registrants. This information should NOT be used for:

- associating clinical signs with a particular product or active constituent,
- assessing the safety and efficacy of a product or active constituent,
- establishing acceptable frequency of occurrence of an adverse experience, or
- comparing one product or active constituent with another product or active constituent.

1.11 For further information

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2. SECTION 1

2.1 A summary of adverse experience reports involving crop damage, domestic animal harm, environmental damage or lack of efficacy listed by active constituent

The following information is contained in this section:

The active constituent name

- Each active constituent is listed alphabetically, with a summary of the adverse experience reports.
- It is important to note that the number of adverse experience reports and the presenting signs observed may be listed under more than one active constituent if they refer to a product that contains multiple active constituents.

The number of reports

- Only adverse experience reports that were classified by the APVMA as being either 'probable' or 'possible' have been included in these lists. The summary table indicates how many reports were classified as 'probable' and how many were classified as 'possible'.

The presenting signs

- All observed clinical signs for reports that were classified as 'probable' and 'possible' are listed in order of frequency.
- It is important to note in the following summaries of adverse experience reports that in one report a number of different clinical signs may have been observed. Therefore the list of clinical signs observed does not relate directly to the total number of reports received.

Summary of corrective action

- A short narrative is provided on any corrective action taken as a result of assessment of the adverse experience information for each active constituent.

AZINPHOS-METHYL

Number of reports	Probable	Possible
1	0	1

Presenting Signs	Number of reports
Lack of effect	1

On further investigation of this report it was discovered that the field efficacy of this product was shown to be lower than other products for the treatment of fruit spotting bugs on macadamias. As a result of this information a label change was recommended to remove the claim for fruit spotting bugs on macadamias.

HEXAZINONE

Number of reports	Probable	Possible
1	0	1

Presenting Signs	Number of reports
Dead trees	1

Based on the very low number of adverse experience reports for these products when compared to the total number of doses sold no regulatory action was required other than continued ongoing monitoring for any future adverse experience reports. It is noted however, that based on the investigation of this report the local shire council that applied this product reviewed their herbicide application programs in order to identify safer alternative products.

METHIOCARB

Number of reports	Probable	Possible
1	1	0

Presenting Signs	Number of reports
Poisoning (canine)	1

The APVMA published an article in the *Australian Veterinary Journal* (Volume 82, No 11: November 2004) to alert veterinarians on appropriate treatment measures for these products. Further information is available on the Australian Veterinary Association website at <http://www.ava.com.au/infosheets.php?infosheetid=7>.

PROCYMIDONE

Number of reports	Probable	Possible
1	1	0

Presenting Signs	Number of reports
Phytotoxicity	1

On investigation of this report the APVMA identified that fungicides containing procymidone should not be used in Chinese cabbages as there is the potential for 'black dot' to occur.

Additionally, a recent scientific assessment identified that procymidone causes birth defects in laboratory animals and therefore may pose the same risk to humans under some circumstances associated with worker exposure. This has resulted in a revision to the scheduling of procymidone under the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). The revised scheduling means that stricter controls are required for the supply and use of procymidone products. These, in turn, require that new instructions and warnings be put on labels. Please see the APVMA website at <http://www.apvma.gov.au/chemrev/procymidone.shtml> for more information on the review of procymidone.

3. SECTION 2

3.1 A summary of adverse experience reports in humans listed by active constituent

The following information is contained in this section:

The active constituent name

Each active constituent is listed alphabetically, with a summary of the adverse experience reports.

It is important to note that the number of adverse experience reports and the presenting signs observed may be listed under more than one active constituent if they refer to a product that contains multiple active constituents.

The number of reports

Only adverse experience reports that were classified by the APVMA as being either 'probable' or 'possible' have been included in these lists. The summary table indicates how many reports were classified as 'probable' and how many were classified as 'possible'.

The presenting signs

All observed clinical signs for reports that were classified as 'probable' and 'possible' are listed in order of frequency.

It is important to note in the following summaries of adverse experience reports that in one report a number of different clinical signs may have been observed. Therefore the list of clinical signs observed does not relate directly to the total number of reports received.

Summary of corrective action

A short narrative is provided on any corrective action taken as a result of assessment of the adverse experience information for each active constituent.

CHLORPYRIFOS**Human**

Number of reports	Probable	Possible
1	1	0

Presenting Signs	Number of reports
Coughing	1
Respiratory problems	1

Based on the very low number of adverse experience reports for these products when compared to the total number of doses sold no regulatory action was required other than continued ongoing monitoring for any future adverse experience reports.

DI-N-PROPYL ISOCINCHOMERONATE**Human**

Number of reports	Probable	Possible
2	1	1

Presenting Signs	Number of reports
Irritation (skin)	1
Pruritis	1
Blisters	1
Rash	1

Based on the very low number of adverse experience reports for these products when compared to the total number of doses sold no regulatory action was required other than continued ongoing monitoring for any future adverse experience reports.

DIETHYLTOLUAMIDE**Human**

Number of reports	Probable	Possible
2	1	1

Presenting Signs	Number of reports
Irritation (skin)	1
Pruritis	1
Blisters	1
Rash	1

Based on the very low number of adverse experience reports for these products when compared to the total number of doses sold no regulatory action was required other than continued ongoing monitoring for any future adverse experience reports.

MALDISON**Human**

Number of reports	Probable	Possible
1	0	1

Presenting Signs	Number of reports
Multiple health effects	1

Based on the very low number of adverse experience reports for these products when compared to the total number of doses sold no regulatory action was required other than continued ongoing monitoring for any future adverse experience reports.

N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE**Human**

Number of reports	Probable	Possible
1	0	1

Presenting Signs	Number of reports
Irritation (skin)	1
Blisters	1

Based on the very low number of adverse experience reports for these products when compared to the total number of doses sold no regulatory action was required other than continued ongoing monitoring for any future adverse experience reports.

POOL/SPA PRODUCTS BASED ON SILVER OR COPPER AND SILVER ION COMBINATIONS**Human**

Number of reports	Probable	Possible
2	2	0

Presenting Signs	Number of reports
Rash	1
Pneumonia	1
Death	1

The APVMA received two adverse experience reports in late 2003/early 2004 involving separate incidents of pool transmitted disease in spas using a silver ion based, cartridge-type spa sanitiser system. In one incident, 15 people contracted folliculitis after visiting a private spa. The spa was found shortly after to be contaminated with extremely high counts of *Pseudomonas aeruginosa*, the causative agent of the folliculitis. In another incident, a man died from legionellosis following use of a spa shown shortly afterward to contain high numbers of *Legionella pneumophila* bacteria. The relevant State health authority, after conducting a thorough investigation, concluded that the spa was the most likely source of the man's fatal infection.

Please see the APVMA website for more information on actions being taken by the APVMA regarding our concern for public health in relation to pool and spa sanitisers
http://www.apvma.gov.au/qa/poolspa_FAQ_May2005.shtml.

4. GLOSSARY

Analgesic	pain relieving treatment
Anaphylaxis/ anaphylactic	an exaggerated allergic reaction of an animal to a foreign protein or other substances
Anaphylactoid	an anaphylactic-type reaction
Anthelmintic	an agent destructive to worms
Antimicrobial agent	an agent that kills micro-organisms or suppresses their multiplication or growth
Ataxic	unsteady walking action due to muscular incoordination
Colic	a general term for abdominal pain
Cyanotic	blue discolouration of the mucous membranes and other tissues due to a lack of circulating oxygen in the blood
Erythema	abnormal redness of the skin due to local congestion, as in inflammation
Folliculitis	inflammation of the follicles
Hypersalivation	excessive salivation
Hypersensitivity	an excessive reaction to an allergen
Intramammary	within or into the mammary gland
Oedematous	abnormal accumulation of fluid in body cavities and under the skin
Parasiticide	an agent that is destructive to parasites
Parvovirus	viral infection of dogs that is characterised by diarrhoea, dehydration and pyrexia
Pruritus	irritation and itching
Pyrexia	animal suffering from a high fever
Registrant	the commercial party which is responsible for the marketing of the product
Urticaria	vascular reaction of the skin as a result of contact with a chemical or may be immunologically based
Withholding period	the time interval after the withdrawal of a drug from the treatment of an animal before the animal or its products can be used for human food