National Registration Authority
for Agricultural and Veterinary Chemicals

REPORT OF ADVERSE EXPERIENCES 1997 AND 1998

November 1999

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National Registration Authority for Agricultural and Veterinary Chemicals
Adverse Experience Reporting Program

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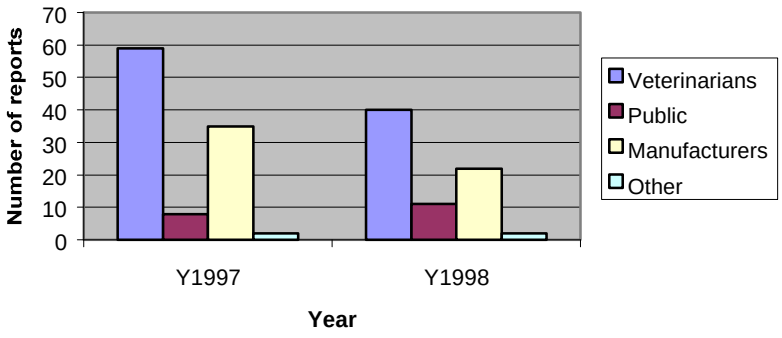
Executive summary

This is the third Annual Report for the National Registration Authority's (NRA) Adverse Experience Reporting Program (AERP) for veterinary chemicals. This report includes voluntary reports received by the NRA during 1997 and 1998.

Since 1995, the AERP has received a total of 448 voluntary reports that have been submitted by private practice veterinarians, the public (animal owners/farmers or other chemical users) or other organisations (eg Department of Agriculture). Some reports were initially sent to the product manufacturers by the reporter for comment and the manufacturer then forwarded a copy on to the NRA.

A total of 104 reports were submitted to the NRA during 1997 and 75 were received in 1998. Of these, 99 were submitted by veterinarians, 19 came from the public, 57 via manufacturers and 4 from other sources (eg Department of Agriculture and Australian Quarantine and Inspection Service). Figure 1 outlines this information graphically for each year.

Figure 1:
Numbers of reports received for 1997 and 1998 according to source



It can be seen that the greatest number of reports were sent in by veterinarians in private practice, followed by reports that came via manufacturers.

Of the suspected adverse experiences in animals, all incidents were classified as one of the following: 'product-related', 'possibly product-related', 'not product-related' or 'caused by not using the product according to label directions'. Reports classified as not product-related have previously not been included, but those reports of interest have been included in this annual report for completeness.

Of the reports involving animal reactions, the number of each species affected is outlined in Table 1.

Table 1:

Species	1997	1998	Total
Cat	12	6	18
Cattle	16	25	41
Dog	27	39	66
Goat	0	1	1
Horse	25	13	38
Rabbit	2	2	4
Sheep	5	2	7

The majority of reports received refer to suspected reactions involving dogs, cattle and horses. This possibly reflects that these species are the most common of the domestic animals kept both privately and commercially.

As a result of reports received during 1997 and 1998 the following regulatory action has been taken:

- Label changes

Twelve products were identified as requiring a change to their labels. Some reports involved allergic responses by factory and farm workers being exposed to a pig feed premix. A label change was recommended after evaluation of this report and other scientific literature. The revised label will carry a warning statement indicating that care must be taken when handling these products as there is the potential for such allergic reactions.
Other reports included sheep drenching products that were often being administered incorrectly. A warning statement has been included on the label of these products to increase user awareness of these potential problems.

- Notification to veterinarians on restrictions on use

Veterinarians are entitled to use products off-label by exercising their professional right to prescribe an appropriate treatment for an animal under their direct care. The AERP received a number of adverse reaction reports involving a flea treatment for cats and dogs being used off-label on rabbits. In these reports, after the rabbits were treated, they developed neurological signs and in most instances died within two days. The registrant has been requested by the NRA to inform the veterinary profession of possible links between the product and adverse reactions in rabbits.

1 INTRODUCTION

1.1 Program Outline

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is the Australian agency responsible for regulating agricultural and veterinary chemicals up to the point of retail sale.

Under the National Registration Scheme, we evaluate and register agricultural and veterinary chemicals and manage quality assurance programs that monitor ongoing safety and performance of registered products.

The NRA's Adverse Experience Reporting Program (AERP) is a quality assurance program that was established in January 1995 to provide a national mechanism for reporting, recording and analysing adverse experiences with veterinary chemical products, with a view to developing better use practices and preventing avoidable side-effects.

An adverse experience is defined as 'an unintended or unexpected effect on animals, human beings or the environment, including injury, toxicity, sensitivity reactions or lack of efficacy associated with the clinical use of a drug'. In general, adverse experiences refer to abnormalities that occur when a drug is administered at an appropriate dose rate for the purpose intended. However, often in veterinary medicine, drugs may be used that are primarily intended for use in man or other species and limited or no information may be available on appropriate dose rates and adverse reactions in other species.

1.2 Reporting/ Evaluation Procedures

Procedures for dealing with adverse experience reports are as follows:

- Adverse experience reports are received by the NRA from veterinarians, farmers, and other users of veterinary chemical products. The NRA forwards each report in the first instance to the product registrant (or manufacturer) for investigation and comment, and their comments are taken into account when assessing the report.

- Registrants are required to report their findings and conclusions from their investigations directly back to the AERP Coordinator.

- Once the registrants' comments are received, the AERP Coordinator then assesses each case closely and gathers as much information as possible by researching the available scientific literature (eg. worldwide veterinary, medical and toxicological databases), examining published information from pharmacovigilance agencies in other countries (eg. the Food and Drug Administration website) and asking for the opinions of other people experienced in the relevant field to arrive at a final conclusion as to whether the incident was related to the product or not. To be classified as product-related, the product must have been used according to label directions.

- The final decision is made by an in-house panel of experienced veterinary clinicians and pharmacologists who consider all the available information relating to the report.

1.3 Classification of Adverse Experiences

On the basis of available information, each reported adverse experience is classified by the NRA as one of the following:

- **Product related:** where the NRA is satisfied that the adverse reaction, whether expected or unexpected, is related to the use of the product. Included in this group are those reactions where it is probable or almost certain that the adverse experience is related to the use of the product;

- **Possibly product related:** where the NRA is not satisfied that the product was responsible for the reaction but the possibility that the product was implicated cannot be excluded;

- **Not product related:** where the NRA is satisfied that the reaction is definitely not related to the use of the product, or there was not enough information to allow classification;

- **Caused by not using the product according to label directions:** where there is clear evidence of over-dosing or incorrect route of administration and other such causes. This category includes reactions reported after off-label use of products by veterinarians exercising their professional right to prescribe an appropriate treatment.

1.4 Report Structure

This report is arranged into the following sections:

1. The first section contains seven tables arranged alphabetically by species. Each table shows the numbers of reports received during 1997 and 1998 for each class of product, the number of animals involved in the reports and the final classification given to the reports by the NRA after careful consideration and investigation. The number of animals involved in each case is divided into the number of animals treated, the number affected and the number that died. A brief discussion of the adverse experiences, by product categories, follows each species table.

2. The second section contains a table and discussion of adverse experience reports received during 1997 and 1998 regarding human reactions.

3. The third section contains a summary table with details of all individual reports of adverse animal reactions and their final classification since publication of the 1996 report. The table lists each animal species in alphabetical order and is divided into sections that show for each of the products identified by active constituent, the number of animals involved, a brief description of each adverse reaction and the NRA classification of the incident.

4. The fourth section provides a summary table of all reports of alleged lack of efficacy received during the 1997 and 1998 reporting periods.

5. The fifth section has a summary table of reported human reactions to veterinary chemicals for 1997 and 1998.

1.5 For further information

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2. ADVERSE EXPERIENCES REPORTED FOR CATS IN 1997 AND 1998

TABLE 1 – CATS

Product Category	No. of Reports Received	No. Treated	No. Affected	No. Died	Product Related	Possibly Product Related	Not Product Related	Caused by not using product according to label directions
Antimicrobials	5	5	5	0	1	4	0	0
Parasiticides	4	5	4	0	3	1	0	0
Vaccines	3	3	3	1	2	0	1	0
Anti-inflammatory agents	2	2	2	0	0	0	1	1
Hormones	2	2	2	0	2	0	0	0
Anaesthetic agents	1	1	1	1	1	0	0	0
Parasympatho-mimetic	1	1	1	1	0	0	0	1

2.1 Antimicrobials

There were five reports received for cats during the 1997/1998 reporting period involving antimicrobials. Three reports concerned the use of the active constituent enrofloxacin. One report related to a reaction observed in a cat after treatment with doxycycline. The fifth report described a reaction that occurred in a cat after the administration of eardrops containing a mixture of antimicrobial, antifungal, anti-caricidal and local anaesthetic agents.

2.1.1 Enrofloxacin

In the three reports concerning the use of enrofloxacin, the cats were treated with an oral liquid formulation. In two of the reports, the cats started salivating excessively immediately after treatment. Enrofloxacin is known to be quite bitter and the label directions clearly state that these types of reactions are only transient and that treatment should be stopped immediately if they occur. In the third report, the cat developed unusual neurological signs while being treated with this product at the recommended dose. On the second day of treatment, the cat started salivating excessively. On the third day, the cat stopped eating and collapsed once or twice. Despite this occurring, the owner continued with the treatment. The following day, the cat was not eating, drinking, defecating or urinating, so the owner stopped treatment. The next day the cat developed an ataxic gait and constantly needed to rest when walking. Signs similar to these have only been recorded previously when cats were significantly overdosed during clinical trials. For this reason, no further action was considered necessary except continued monitoring of this product for any future similar reactions.

2.1.2 Doxycycline

In another report, a cat was treated with a product containing doxycycline to treat an infection that had developed after it had been fighting with another cat. After seven days of treatment, the cat developed swollen eyelids and ears and continually shook its head. It appears that this cat was allergic to this product and these types of reactions are very rare. After the treatment was ceased, the cat recovered uneventfully.

2.1.3 Various

In the final report, a cat was treated with eardrops containing polymyxin B, nitrofurazone, neomycin sulfate, lignocaine and pyrethrins to treat an ear mite infestation. Immediately after the drops were applied to the cat's ears, it began to cry and paw at the ears. The cat was treated twice daily with this medication despite this reaction occurring each time. After two days, the cat's ears became bright red and ulcerations could be seen in the ear canals. The ears were painful to the touch. On presentation to the veterinarian at this time, the cat was panting heavily and the pupils were dilated. From the description of events, it appears that the initial mite infestation was quite serious and probably would have been best treated with irrigation before using eardrops. However, there is a possible temporal relationship between the administration of the eardrops and the clinical signs, so the reaction was classified as possibly product related.

Considering the large number of cats treated with antimicrobials each year, five reports represent a very low incidence of adverse reactions.

2.2 Parasiticides

Four reports were received regarding the use of parasiticides in cats and subsequent suspected adverse reactions during 1997/98. One report involved the use of an oral product containing the active constituent lufenuron used in a flea prevention program. Another report involved an injectable formulation of this active. A third report concerned the external application of a product containing the active constituent imidacloprid, which is used to aid in the prevention of fleas. The fourth report involved the use of an oral broad-spectrum internal parasiticide, containing the active constituents praziquantel and pyrantel embonate.

2.2.1 Lufenuron

In the first report the cat was given an oral liquid product containing lufenuron and the attending veterinarian recorded that the night following treatment, the cat became inappetent, vomited and on admission to the clinic the following day was found to be dehydrated. Blood taken from the cat for laboratory testing revealed a number of biochemical changes, similar reactions have been reported in the literature in a very small number of cats after treatment with this product (1). In the case reported to the NRA, it was not recorded whether this treatment was given with a full meal as directed on the label; therefore this incident is classified as possibly product related.

In the second report, the cat had been treated with the same oral lufenuron formulation described above for some time without ill effect. When the cat was treated with a new injectable form of this product it was reported appear very lethargic soon after the injection

was given and seemed to have pain at the injection site. When the cat was returned to the oral formulation, no further ill effects were observed. Due to the clear cause and effect relationship this incident was classified as product related, possibly an idiosyncratic reaction. As this is an extremely rare occurrence, no further action was considered necessary other than to continue to monitor any future reports of this nature for this product.

2.2.2 Imidacloprid

The third incident involved the use of another flea preventative, which is applied externally and contains the active constituent imidacloprid. According to this report, the cat developed a bald patch on the back of the neck at the site of application. This type of reaction has been reported before with this product in a very small percentage of cases (approximately 0.002% incidence). As this is an extremely rare occurrence, and the adverse effect is not serious no further action was considered necessary other than to continue to monitor any future reports of this nature for this product.

2.2.3 Praziquantel and pyrantel embonate

The last report involved the use of a broad-spectrum internal anthelmintic containing the active constituents praziquantel and pyrantel embonate. Within two hours of treatment, the cat became lethargic, ataxic, hyperaesthetic, its pupils became dilated and it seemed to be in a trance. This type of reaction has been reported previously with an earlier formulation of this product (2, 3). As a result of these earlier reactions, the formulation was modified to reduce the incidence of such possible problems and the label was modified to warn users that these non-fatal, transient effects may occur. The current formulation has a much lower incidence of such reactions.

2.3 Vaccines

Three reports were received during the 1997/98 reporting periods regarding the use of vaccines in cats. Three cats were affected, two of the reports were product-related and one was not product-related.

2.3.1 Feline influenza and panleucopenia vaccine

In one report, a cat was treated with two vaccines – a combined feline influenza virus and panleucopenia virus vaccine and a leukaemia virus vaccine. This cat became quiet and appeared to be sore to touch soon after the vaccination and was aggressive when patted. It also developed a fever the day following the vaccination. Reactions such as this have been reported previously in the veterinary literature and are rare, but unavoidable (2). They occur in a very small percentage of the very large number of cats that are vaccinated yearly.

2.3.2 Feline leukaemia vaccine

Another report involved the formation of a non-painful lump at the site of injection with a feline leukaemia virus vaccine, which developed into a fluid-filled cyst that required surgical removal. This type of reaction has been reported in previous years and is due to a sterile local reaction to the adjuvant in the vaccine. Again, these types of reactions are very rare and occur in only a small percentage of cats vaccinated each year.

The final report involves a cat that was found dead by the owner about one hour after being vaccinated with a similar vaccine. This reaction was determined to be not product-related, as there is no evidence to suggest that the vaccine was responsible in any way. Numerous other cats were vaccinated with the same batch of vaccine and showed no ill effects. No other similar reports have been received.

2.4 Anti-inflammatory agents

Two reports concerning suspected reactions to anti-inflammatory agents in cats were received during 1997/98. Both reports involved off-label use of a product containing the active constituent carprofen. This product is unregistered for use in cats.

2.4.1 Carprofen

In the first report the cat was administered doxycycline (an antimicrobial agent) concurrently and the adverse reaction observed was considered to be due to this agent, not the anti-inflammatory. The cat treated developed swollen eyelids and ears, and continually shook its head about one week into treatment. This reaction was considered to be possibly related to the doxycycline and is likely to have been an allergic reaction.

In the second report, the cat was administered one tablet, containing carprofen, twice daily for three days. The cat became lethargic, anorexic, jaundiced and laboratory tests revealed haemolysis, renal failure and non-regenerative anaemia. One week after treatment ceased the signs resolved. The elimination half-life for this chemical is thought to be forty-eight hours in cats; therefore each dose resulted in a residual build up of the agent in the system. This residual effect could have resulted in a dosage that may have been four to eight times over the recommended dose. This incident was classified as caused by not using the product according to label directions.

2.5 Hormones

Two reports were submitted regarding adverse reactions recorded in cats after being administered hormonal therapies.

2.5.1 Progesterone

The first report involved a cat that was administered a product containing the hormone progesterone by subcutaneous injection. It developed enlargement of the entire mammary chain (teats) six weeks after the injection. Each gland became swollen, and was described as being as large as “half an orange”. They appeared extremely turgid and one nipple had split open. The skin surrounding the teats was reddened.

This type of reaction has been reported previously (4), but it is considered extremely rare and has not been reported before in Australia for this product. The registrant indicated that this case is unusual for the following reasons:

a. This type of reaction, described as feline mammary hypertrophy, can occur in oestrus in normally cycling female cats and in pregnant queens, and has also been seen in neutered male and female cats with no history of progestogen therapy. (4)

b. Usually only a small number of glands are affected after progestogen treatment (4), whereas in this case the entire mammary chain was affected.

c. The swelling responded to medical treatment (diuretics and antibiotics), and no relapse was reported. In previously reported cases, medical treatment was not successful and withdrawal of treatment and surgical removal was necessary with cases of feline mammary hyperplasia such as this.

It was concluded that this reaction was possibly product-related.

In a second report, a cat developed mammary lumps approximately three weeks after discontinuation of a hormonal therapy program. The lumps had to be surgically resected and were submitted for laboratory evaluation. A diagnosis was made by the pathologist of benign mammary growths. The use of progestagens has been known to cause mammary hyperplasia regardless of the neutering state of the cat (4). This type of reaction is a well-documented and recognised side effect that needs to be carefully considered by the veterinarian when deciding on any form of hormonal therapy.

2.6 Anaesthetic agents

Only one report was received regarding an adverse reaction in a cat following the use of anaesthetic agents.

2.6.1 Alphaxalone and alphadolone

This report indicated that after administration of an anaesthetic agent containing the active constituents alphaxalone and alphadolone, the cat stopped breathing immediately, and then its heart stopped shortly after. Despite resuscitation techniques performed by the attending veterinarian, the cat could not be revived.

All general anaesthetics are associated with a certain level of risk. A polyoxyethylated castor oil is the vehicle or carrier substance for the active constituents in this product. This may liberate mast cell histamine in the cat and induce arterial hypotension. Allergic reactions such as hyperaemia of ears and peripheral oedema are commonly seen in cats and an anaphylactic reaction may have been responsible for this death (4). Respiratory failure after use of anaesthetics containing alphaxalone acetate and alphadolone acetate has also been known to result in death.

Again it is important to carefully monitor and record any suspected reactions reported about anaesthetic agents by programs such as the AERP to ensure that any increase in incidence for a particular batch or lot is identified early and appropriate action is taken.

2.7 Parasympathomimetics

One report was received during the 1997/98 reporting period for an off-label use of a human product containing the active constituent bethanechol. A cat was administered this product for treatment of urinary retention. Soon after administration, the cat developed diarrhoea and started vomiting and salivating. The cat died approximately 18 hours after treatment. This treatment is currently being widely used by veterinarians to treat urinary retention. As this is the only report of its kind for this product, no further action is required at this stage other than continued monitoring of any future reports similar to this.

3. ADVERSE EXPERIENCES REPORTED FOR CATTLE IN 1997 AND 1998

TABLE 2 – CATTLE

Product Category	No. of Reports Received	No. Treated	No. Affected	No. Died	Product Related	Possibly Product Related	Not Product Related	Caused by not using product according to label directions
Antimicrobials	18	174	55	22	43	2	10	0
External parasiticides	7	1021+	445+	182	0	0	9	436+
Hormones	4	133	52	6	4	0	48	0
Anti-bloat therapies	4	650+	7	7	6	1	0	0
Anthelmintics	1	42	25	0	0	0	25	0
Vaccines	1	16	2	0	16	0	0	0

3.1 Antimicrobials

The largest number of reports received during 1997/98 for cattle involved antimicrobials. Eighteen reports were received and 174 cattle were treated. Of these, 55 animals were affected, with 22 reported deaths. One report involved the use of a product containing ceftiofur in a bull. Three reports described adverse experiences following treatment with intra-mammary mastitis therapies. Six reports concerned the use of oxytetracycline and eight reports involved the use of procaine penicillin.

3.1.1 Ceftiofur

In one report, a bull was treated with an intramuscular injection of a product containing ceftiofur for treatment of septic arthritis. This product was chosen based on culture and sensitivity testing performed on the joint fluid, which indicated that it would be the most effective treatment. The bull was injected daily for eighteen days. Within fifteen minutes of receiving the eighteenth injection, the bull began having breathing difficulties and then became recumbent after a further fifteen minutes. The animal died approximately one hour post-injection.

The attending veterinarian in this case indicated that during the course of treatment, on hot days, the bull would pant for some time after the injection was given. It was also recorded that this bull required unusually small doses of anaesthetic to achieve sedation, and it was suggested that the animal might have had some kind of underlying cardiovascular abnormality, which may have contributed to the reaction in this incident. It is therefore impossible to determine the exact cause of this animal's death as there are a number of factors involved, so the incident was classified as possibly product related.

3.1.2 Intramammary preparations

3.1.2.1 Cloxacillin

There were three reports involving the use of intramammary treatments for the control of mastitis in dairy cattle. The first two reports referred to the use of dry cow treatments (which are used in cattle when they are dried off, to help prevent mastitis in the following lactation) and the third report concerns the use of a lactating cow treatment.

In the first of these reports, an intramammary dry cow therapy containing cloxacillin was used to treat a herd of 100 cows. In two of the cows, there was persistence of the blue dye in the milk well outside the recommended with holding period. As there is a clear cause and effect relationship between the use of the dry cow treatment and the presence of the dye in the milk, this incident has been classified as product-related.

There are a number of reasons that may have caused persistence of the blue dye, such as:

- cow problems – old cows (both cows were nine years old) and cows with chronic infections have a tendency to pocket intramammary formulation in damaged parts of the udder, potentially slowing the washout of dye with milk;

- cow variability – the excretion of blue dye and antibiotic are not linked and not precisely predictable;

- product problem – the batch contains concentrations of active or non-active constituents that are outside the tolerable range for the product. This batch was checked and found to have tested within specifications.

Taking into account the age of the cows, and that the product tested within specifications, the reason for the persistent blue dye excretion is most likely to be due to cow problems/variability.

The collation of such information by the AERP is important in determining the safety of such treatments in milk-producing animals.

In the second report, thirty cattle were administered an intramammary antimicrobial containing cloxacillin at drying-off. When the cattle calved approximately six weeks later, ten were found to have mastitis. It was concluded that the infection was not product-related for the following reasons:

- investigations into the batch of intramammary product used in this case indicated that it met all specifications required and no other reports of problems with this batch had been reported from this or any other batch;

- the time elapsed between the administration of the product and the detection of infection was six weeks – if the infection had been introduced at the time of treatment, then infection and signs of disease would have occurred much sooner.

3.1.2.2 Neomycin, streptomycin and novobiocin

The third report involved an intramammary therapy used in five cattle to treat clinical mastitis. The product contained the antimicrobial agents neomycin, streptomycin and novobiocin. In the treated cattle, the milk was described by the farmer as unusual in appearance and they returned a positive residue test after the recommended withholding period. A sample of this milk was analysed by a more accurate test and the antibiotic levels in the milk were below the maximum residue levels, which indicates that the previous positive test was unlikely to have been due to this product. There is no physical evidence to indicate that this product caused the abnormal appearance to the milk, but the cause and effect relationship cannot be discounted either. For this reason it has been decided that there may be some link between this abnormal appearance and the product, although other factors such as the mastitis itself are also involved.

3.1.3 Oxytetracycline

Six reports concerning the use of an oxytetracycline-containing product in cattle were submitted in 1997/98. All incidents were considered to have been caused by hypersensitivity reactions to a component of the product.

In the first report, within five minutes of being treated by intramuscular injection, a bull started salivating, developed muscle tremors and incoordination, which led to it becoming recumbent. It then developed severe breathing difficulties and died about eight minutes post-injection.

In another report, a number of cattle were being prepared for transport overseas. In preparation for this the cattle are treated with a number of products including antimicrobial products containing penicillin/streptomycin and oxytetracycline and an antiprotozoal product. Eighteen cattle were treated, and all of them reacted to the injections within two minutes of being treated. They all showed signs of anaphylaxis such as depression, head dropping, intense salivation and severe forehead irritation, which led to self-mutilation. Seven of the cattle died over the following 24 hours. The reactions were clearly hypersensitivity reactions occurring to a component of the antimicrobial product. Investigations are continuing into this incident to determine more precisely the cause of the problems and whether they relate to interaction with excipients of vaccines used previously on the animals.

In another report, the owner treated two bulls with an oxytetracycline product. One bull began shaking its head, salivating and showed signs of distress for about forty minutes following treatment. The second bull was found dead ten minutes after treatment. This was attributed to anaphylactic reactions in both cases.

Another bull was treated for a jaw abscess with a product containing oxytetracycline. The bull had been treated six months previously with the same product and had a reaction. For this reason, it was given only a partial dose (approximately 50% of the recommended dose). Within three minutes of treatment, the bull began excessively shaking its head, swinging its tail, salivating, foaming at the mouth, discharging from the nostrils, its face and anus began to swell and the skin over the body started to wrinkle. This reaction was also classified as product-related and most likely an anaphylactic reaction.

The next report recorded that a bull treated for footrot became weak, sat down, started salivating and developed a nasal discharge about half an hour after treatment. This incident was determined to have been a hypersensitivity reaction to the product.

In the final report, one bull died within five minutes of treatment with signs of anaphylaxis. This was also considered to be an anaphylactic reaction, directly product-related.

Reaction with the oxytetracycline itself, or one of the carriers, such as polyvinylpyrrolidone is suspected as causing these anaphylactic reactions that occur to oxytetracycline-containing products. In most cases the animals have been previously sensitised to the product following earlier injections of the same or similar products, or from use of vaccines (such as Bovine Ephemeral Fever) that may contain traces of polyvinylpyrrolidone in the Quill A adjuvant present in these vaccines. This type of problem has been widely reported and it is now recommended that if there is a chance that the animal may have been previously sensitised, then it should be treated with antihistamines prior to injection.

3.1.4 Procaine penicillin

Eight reports concerned the use of products containing procaine penicillin were received during the reporting period. Seven of the reports were considered to be product related, and one possibly product related.

The first six reports all clearly involved hypersensitivity reactions to the procaine penicillin. All animals treated reacted shortly after being injected and the signs observed varied from staggering, falling down, bloating, snorting blood from the nostrils, agitation, salivation and death. Hypersensitivity reactions of this type, occurring following treatment with penicillin, have been well documented and recorded in the literature. They only occur in a very small percentage of animals treated. Although they are unavoidable, continued reporting and monitoring of these reactions is necessary to identify any increase in frequency of reactions to specific product batches, which may indicate a defect with that batch.

3.1.5 Procaine penicillin and benzathine penicillin combined

A product containing both procaine penicillin and benzathine penicillin was used to treat one animal for footrot. It was discovered dead the next day. The post mortem showed signs consistent with an anaphylactic reaction, although it is impossible to say for certain due to the length of time between treatment and the post mortem being conducted. Thus it was decided that this case was possibly product-related.

3.1.6 Procaine penicillin and dihydrostreptomycin combined

The final report concerned the use of a combination of procaine penicillin and dihydrostreptomycin. Four animals were treated – one bull and three heifers. One heifer exhibited signs of anaphylaxis and died ten minutes after treatment. The bull also reacted within five minutes of the injection, but recovered uneventfully. Another heifer showed signs of anaphylaxis and was treated and survived. All reactions were product related.

3.2 External parasiticides

Seven reports were received for this product category. Over one thousand cattle were treated, more than 445 were affected and 182 cattle died. However, none of the incidents were considered to be product related.

3.2.1 Chlorfenvinphos

In the first two reports, cattle were treated with a product containing the active constituent chlorfenvinphos for management of buffalo fly. In both cases, the animals received approximately five times the dose recommended on the label. All animals affected showed signs of organo-phosphate poisoning.

3.2.2 Cypermethrin and chlorfenvinphos combined

In another report, the farmer dipped 240 cattle in a plunge dip containing the active constituents cypermethrin and chlorfenvinphos. Nine calves drowned and were discovered later in the afternoon floating on top of the dip. Independent analysis of the dip indicated that the dip concentration was within normal limits. The drowning of these calves is more likely to be dipping-related than product-related.

3.2.3 Diazinon

The final four reports involved the use of a product containing an older, unstable formulation of diazinon. In all reports, soon after treatment with the product, numerous cattle developed signs of organo-phosphate poisoning (ataxia, recumbency, salivation and diarrhoea). It appears that in all cases the product had passed the expiry date and had not been disposed of or returned to the supplier. On expiry of the use-by date, diazinon can break down into toxic by-products, particularly if any exposure to moisture has occurred, as can happen with a container that has been partly used and improperly sealed.

3.3 Hormones

Four reports of suspected adverse experiences were received concerning hormonal treatments in cattle.

3.3.1 Chorionic gonadotropin and progesterone combined

In one report, a compound containing chorionic gonadotropin and progesterone was given by intravenous injection to four cattle for treatment of ovarian problems. Soon after injection, the cattle began staggering and developed breathing difficulties, became restless and started shaking their heads. Wheals also developed on the skin. This was determined to be a product-related hypersensitivity reaction. This type of reaction is very rare and consequently, no further action was considered necessary except continued monitoring of the product.

3.3.2 Dinoprost trometamol

Two similar reports were received regarding the development of bacterial infections at the sites of injections with a product containing the hormone dinoprost trometamol. In all, 128 cattle were treated with intra muscular injections of this product. In 30 cattle, post injection muscle lesions occurred that were consistent with bacterial infections. Three of these cattle died as a result. In the second case, 18 cattle developed bacterial infections at the injection site, which subsequently extended down the leg in a number of animals. Two cows in this case were euthenased.

It was concluded that none of these incidents could be attributed directly to the product used. It is possible that during the course of the injections, the contaminating bacteria were drawn under the skin via the insertion of the needle, as a number of cattle were injected with the same needle and the skin was not sterilised prior to injection. Therefore the outcome was that this problem was most likely related to the injection technique, not the product itself.

3.3.3 Oxytocin

In the fourth report, a farmer gave a cow an intravenous injection of oxytocin to stimulate milk letdown as the cow had a mastitis problem. The cow showed classical signs of anaphylaxis (staggering, frothing from the nose and mouth and collapsed) within thirty minutes of the injection, and subsequently died. This incident was considered to product related as a result of an anaphylactic reaction. It should be noted that the use of this product by the intravenous route is not recommended unless under direct veterinary supervision, although the NRA is of the opinion that the choice of the intravenous route was not the prime cause of the reaction.

3.4 Anti-bloat therapies

3.4.1 Monensin

Four reports were received regarding the use of an anti-bloat capsule containing the active constituent monensin. In three incidents, a very small percentage of the cattle treated died within two to three months of being treated and subsequent post mortems found that the body and cap of the capsules had separated. As a direct result of these incidents, an extensive review was made into the manufacturing procedure of this product. A change made to the mould used in the manufacture of these batches has now been rectified. Two of incidents were classified as product-related.

The third of these incidents was classified as possibly product-related as a sample of the dead animal’s stomach contents was analysed and not found to have significantly abnormal levels of monensin present. Therefore the cause of death remains undiagnosed.

In the fourth incident, one animal died 45 days after treatment, allegedly as a result of capsule separation. This capsule was manufactured previous to the above capsules, and using a different mould for which there have been no similar incidents reported. The cause of death was inconclusive, as a post mortem was not conducted by a qualified person, and other

evidence could not conclusively substantiate this incident. This report was therefore classified as possibly product-related.

3.5 Anthelmintics

Only one report was received regarding suspected adverse reactions following use of an anthelmintic product.

3.5.1 Nitroxynil

The farmer treated 42 cattle with a product containing the anthelmintic nitroxynil, and 25 of them allegedly developed large lumps at the site of injection. No veterinary observation was made of the reported reactions so no definitive diagnosis was able to be made. On this basis, the incident was classified as possibly product-related, although highly unlikely as no other similar reports have been recorded for this product.

3.6 Vaccines

Only one report was received regarding the use of vaccines in cattle.

3.6.1 Leptospiral and clostridial organisms combined

In this report, sixteen cattle were treated and two cows reacted. The first cow to react started frothing at the mouth, its eyes sank back in its head and the mucous membranes became blue in colour. The second cow developed laboured breathing and whorls appeared on the skin all over the body.

These reactions were considered to be hypersensitivity reactions and directly product- related. These types of reactions have been reported previously and have been well documented in the literature and are considered to be an unavoidable possible side effect that may occur with any vaccine in any species.

As previously mentioned, continued monitoring of these types of situations is required to detect any increase in incidence early.

3.7 Corticosteroids

A letter was received by the AERP from a dairy farmer who had concerns about products containing the active constituent dexamethasone trimethylacetate. These products are occasionally used in dairy herds to induce cattle to calve as part of the general herd management program. The letter indicated that in a number of herds cattle had died after receiving this treatment. To date, no other similar reports have been received by the AERP and an extensive literature search failed to locate any published reports on such incidents occurring. This report is still under investigation and our findings into the matter will be published in the 1999 Annual Report.

4 ADVERSE EXPERIENCES REPORTED FOR DOGS IN 1997 AND 1998

TABLE 3 – DOGS

Product Category	No. of Reports Received	No. Treated	No. Affected	No. Died	Product Related	Possibly Product Related	Not Product Related	Caused by not using product according to label directions
Vaccines	26	41+	36+	8+	27	0	9+	0
External parasiticides	15	36	23	6	7	9	1	6
Anthelmintics	5	5	5	2	2	2	0	1
Anti-inflammatory agents	5	5	5	3	1	2	1	1
Anti-arthritics	4	4	4	0	3	1	0	0
Antimicrobials	4	4	4	2	1	1	1	1
Sedatives	2	3	3	0	0	2	1	0
Anaesthetics	1	1	1	0	0	0	1	0
Corticosteroids	1	1	1	0	1	0	0	0
Hormones	1	1	1	0	0	1	0	0

4.1 Vaccines

Vaccines represent the largest number of adverse experience reports submitted for dogs in 1997/98. There were 26 reports received, in which over 41 dogs were treated and more than 36 suspected adverse reactions were observed.

4.1.1 Various

In 27 of the dogs treated, the reactions that occurred were considered to be product-related, as a result of hypersensitivity reactions to a component of the vaccine. In most of these incidents, the signs observed were facial oedema (swelling), particularly the ears and around the eyes, and urticaria (redness of the skin). In three cases, the dogs developed pruritus (irritation) of the face and ears as well. Another dog began vomiting. One dog became weak and appeared to show signs of pain. One dog started shivering and staggering when walking. In most cases the signs ceased after treatment with an appropriate anti-inflammatory, and in some cases, the animals recovered without any treatment. In one report a pup died from choking, while eating soon after being vaccinated. In this incident, there may have been some oedema of the throat that caused the pup to have difficulty in eating but it was impossible to confirm this as no post mortem was performed.

Adverse reactions such as these have been reported relatively frequently in the literature. Such reactions are rare, but unavoidable, and occur only in a small percentage of the canine population.

In two cases, lumps developed at the injection sites in two dogs approximately eight to nine days after the dogs were vaccinated. This type of reaction has been reported in a rare number of cases previously and is suspected to be a localised reaction to the adjuvant used in the formulation of the vaccine. As these reactions pose no major or life-threatening consequences and they only occur very rarely, then no further action was taken except ongoing monitoring of the vaccines for any further similar reports.

In one report, which was classified as not product related, the puppy vaccinated developed acute gastroenteritis three days after vaccination. Treatment was initiated, but the dog died seven days later, of suspected canine parvovirus. It was suspected that the pup was exposed to the disease approximately one week prior to vaccination, at which stage it would have no protective antibodies, either maternal or induced.

In another report, three pups died within three days of being vaccinated with varying signs of depression, diarrhoea and abdominal pain. On post mortem, the signs were consistent with parvoviral enteritis, although the vaccine was not considered to have caused the disease. These vaccines utilise non-virulent strains of the virus that have been extensively attenuated (weakened) by repeated passage through tissue culture and it is virtually impossible for any reversion to virulence to occur. Extensive safety testing has failed to show any evidence of this occurring.

4.2 External parasiticides

This was the second most commonly reported category of products in 1997/98. Fifteen reports were received, in which 36 dogs were treated and 23 suspected adverse reactions were observed.

4.2.1 Amitraz

In one report, a collar containing the active constituent amitraz was placed on a dog to control ticks. Soon after this, the dog chewed the collar off and started to eat it. Two other dogs also started to chew on the collar. Within a few hours of this occurring one dog began staggering around, lost bladder control and then collapsed in respiratory distress. This dog continued to have respiratory difficulty for some hours and was weak for several days. The owner attempted mouth-to-mouth resuscitation on the dog, but he became nauseous and began to vomit soon after, which lasted for two hours. The other two dogs involved became weak, vomited and lost bladder control. The owner queried the adequacy of the label safety directions and expressed concern about what the consequences would be if a child were to chew on a piece of the collar or even handle it.

Following investigation of this complaint, the following conclusions were made:

- The current label instructions and warning statements on the packaging are adequate. These instructions state clearly that the product is a poison, and that it should be handled carefully and kept out of reach of children.

- These label instructions were approved for use on the packaging under the former State registration system and the NRA has given approval for their continued use as per the State registration.

- Nevertheless it has been recommended that the NRA conduct a review of this product which considers its toxicity, labelling, packaging and its safety to children.

4.2.2 Carbaryl

One dog treated with a carbaryl-containing product showed signs of excitement and acute pruritus (irritation) causing it to continually run around and not settle. As this reaction occurred within a few hours of being treated with this product it was considered to be product related and most likely an hypersensitivity reaction.

4.2.3 Cythioate

In another report, a dog had been treated with a product containing cythioate, according to the label instructions, to control fleas and ticks. As the dog increased in weight, the owner increased the dose rate appropriately, but three days later, the dog developed a change in behaviour and had difficulty standing. After seven days, the dog could not stand, developed diarrhoea and was trembling. While the dog was hospitalised, it did not receive the cythioate product and subsequently improved slightly. When the dog was returned to the treatment the clinical signs returned. Initially it appeared that there was a clear cause and effect relationship between the product and the clinical signs observed, but on further questioning of the owner, it was revealed that the dog may have been washed in a shampoo that contained an anticholinesterase compound. The label directions for this product clearly state that other anticholinesterase compounds must not be used concurrently with this treatment. It appears that at the lower dose rate, the combination of treatments was not toxic for this dog; but when the dose rate was increased, the dog developed toxicity. As this was deemed a case of accidental overdose, no further action was considered necessary.

4.2.4 Fenthion

One dog treated with fenthion showed signs of anorexia (depressed appetite) and lethargy several hours after application. The dog collapsed the following day, and was diagnosed with pancreatitis by the attending veterinarian. One month later the dog was diagnosed with Diabetes mellitus. As it was impossible to determine whether these events resulted from treatment with the fenthion, this incident was classified as possibly product-related but unlikely.

4.2.5 Fipronil

Four reports were received regarding the use of the external parasiticide, fipronil.
In the first report, a dog was treated with a concentrated form, which is applied to the back of the neck. Approximately two weeks after treatment, the dog developed small crusty sores at the application site. Due to the length of time that elapsed between treatment and the development of the sores, it is difficult to say whether the reaction was due to this product or not. It was clearly indicated by the reportee that the lesions were at the application site. In view of this, the incident was classified as possibly product-related.

In a second report, an owner treated three pups with a similar product containing fipronil in a spray form. One pup died within twenty-four hours of application and the other two pups exhibited neurological signs. They were salivating, had muscular tremors and dilated pupils.

A second pup died three days after treatment. It is highly unlikely that this product was the cause of the reactions, as these signs have not been seen before with this product. No blood tests or post mortems were carried out on any of the pups; therefore it was impossible to determine the cause of death. This incident was classified possibly product-related, although very unlikely.

In the third report, a dog started screaming from an apparent skin irritation immediately after application of the product. It continued for approximately one hour. The signs of irritation reappeared later when the dog became wet in the rain. Some dogs are averse to being sprayed with anything, particularly around the face, so it is possible this dog was reacting simply to the act of being sprayed. Although the attending veterinarian reported that the dog appeared to be highly distressed and he felt the reaction was more severe than would occur from just being sprayed, he could see no evidence of skin irritation to the product. This incident has been classified as possibly product-related, but it is impossible to determine the exact cause of the reaction.

In the fourth report, the puppy was vaccinated at the same time as the fipronil was applied. Forty minutes after the treatments the pup appeared to choke while eating and died five minutes later. The post mortem changes were consistent with an anaphylaxis-like reaction, most likely to the vaccine.

4.2.6 Imidacloprid

Four reports were received regarding a product containing the active constituent imidacloprid, which is applied as a concentrate on the back of the neck to control fleas.

In the first report, a raised, hairless, scabby and intensely pruritic dermatitis developed at the application site approximately thirty-six hours after the product was applied. This incident was considered to be product-related as there was a clear cause and effect relationship. It was most likely an allergic or irritation reaction to the product.

In the second report, an owner accidentally applied the product to a dog’s eye, which caused irritation and damage to the superficial layers of the cornea. This product is known to be irritant to eyes and has adequate warnings on the label.

Another dog seemed to develop a change in behaviour approximately one day after being treated with this product. It became quiet and lay out in the sun for most of the day. The owner noticed that the dog’s skin became very pink after this. Over the following eleven days, the dog became lethargic and developed diarrhoea and red ears. A veterinary examination took place fourteen days after the initial treatment. The diagnosis was heat stroke and intense erythema of all skin surfaces, the conjunctiva and the mucous membranes. The dog was hospitalised for the following five days, during which time it became weak and recumbent, with a painful abdomen, pale mucous membranes and oedema of the lungs. Skin ulcers formed on day eighteen and covered 50% of the abdominal skin by day nineteen. The dog recovered fully with treatment. This incident was classified as possibly product-related. The initial behavioural changes were unlikely to have been related to the product and the subsequent reactions were all part of a chain reaction that occurred after this.

In the fourth report three dogs treated with imidacloprid became quiet, their appetites were depressed and they would not settle easily, within twelve hours of application. The changes in

behaviour were considered to be product-related and have been reported in a very small number of dogs treated with this product. The behavioural changes are considered to be only transient and will resolve within 24 hours in most cases.

4.2.7 Maldison

One dog was treated with maldison and died during the night following treatment. It is impossible to say whether the death could be attributed to the use of this product as no post mortem was performed. A large number of other dogs had been treated with the same product by the same person with no reports of adverse reactions.

4.2.8 Milbemycin and lufenuron combined

Two reports were received regarding the use of a product containing milbemycin and lufenuron as a combined treatment for heartworm and fleas. The first dog reportedly developed a rash on the belly, paws and back within two days of being treated. This type of reaction is very rare and is therefore described as an idiosyncrasy. However, it is clear that there is a cause and effect relationship between the use of this product and the subsequent reactions, therefore it was classified as product-related.

Another dog developed loose, black stools after treatment with this product. The dog was treated once a month for two months, and these signs occurred within one to two days of both treatments. Similar reactions have been recorded in a very small number of dogs treated with these chemicals in other countries. The reaction was classified as possibly product related.

4.3 Anthelmintics

There were five reports received concerning the use of anthelmintics during 1997/98. Five dogs were treated, five were reported to have reacted adversely and two dogs died.

4.3.1 Ivermectin

One dog consumed an unknown quantity of a horse worming paste, containing ivermectin, and developed excessive salivation and incoordination. The dog died approximately three hours after the onset of clinical signs. This was an accidental exposure to this product and therefore caused by not using the product correctly.

4.3.2 Praziquantel, pyrantel embonate and oxantel embonate

In another report, an adult cattle dog was treated with an oral broad-spectrum worming product containing pyrantel embonate, oxantel embonate and praziquantel. Thirty minutes after the recommended dosage was given, the dog began to vomit. On presentation to the veterinarian, the dog also had diarrhoea. The dog was hospitalised overnight, treated accordingly and then released the following day. It is possible that the product was at least partly responsible for these clinical signs. Two weeks later, the dog vomited again and the owner felt that this was a relapse of the previous problem. It had not been treated with the product again, so it was unlikely that the product played any part in this.

4.3.3 Pyrantel embonate

A third report concerned eight pups treated with a product containing pyrantel embonate, a broad-spectrum wormer for dogs. The pups were treated initially at two weeks of age with a tablet formulation. The owner noticed that these tablets passed through the pups undigested, therefore indicating that they were ineffective. The owner treated the pups again at four weeks of age with the same brand of product in a liquid form. All the puppies developed signs of discomfort and diarrhoea, which persisted until the following day. Two of the pups developed vomiting, more severe diarrhoea and anorexia the next day. All pups recovered after medical treatment with fluids to prevent dehydration. In these cases, the reactions were probably product-related, although there are a number of factors to consider. Firstly, the owner should have re-treated the pups at two weeks old, as it was obvious that the product was ineffective at this time. At the second treatment at four weeks old, the pups may have had a large worm burden that was possibly partially responsible for the discomfort, vomiting and diarrhoea experienced (a summary of this report is provided in the Lack of Efficacy appendix).

4.3.4 Milbemycin

The last two reports involved the use of the chemical milbemycin, which is combined with lufenuron to control heartworm and fleas. These reports are detailed earlier under the external parasiticides section.

4.4 Anti-inflammatory agents

Five reports were received regarding the use of anti-inflammatory agents and suspected adverse reactions occurred in five dogs treated. Three of the dogs died.

4.4.1 Carprofen

In the first two reports, the dogs were treated with a product containing the active constituent carprofen, a potent painkiller. In one case, the dog became weak soon after treatment with this product and began to vomit that night. It continued to vomit the following day, which was not reported to the veterinarian, and then it died the following day. It is highly unlikely that the single injection given to this animal would have caused these signs or its death. No similar reports to this have been received and consequently this incident was classified as possibly product-related, but unlikely.

In the second report, the dog was treated twice daily for four days. After two days, the owner noticed that the dog would start panting rapidly and that the heart was visibly pounding. The dog would take approximately two hours to recover each time. No similar episodes occurred after the medication was stopped. The report was classified as product-related due to the relationship between the treatment and the timing of the reactions.

4.4.2 Copper indomethacin

The next report involved the use of a topical anti-inflammatory therapy containing copper indomethacin, in a dog’s eye. The dog had a corneal ulcer, blepharospasm and corneal vascularisation. The principal of the practice indicated that he would not have used this

product in this situation as he felt that other treatments would have been more appropriate. The owner noticed a deterioration in the condition soon after commencing treatment, but did not report this to the veterinarians early enough. There are a number of other factors involved in this incident that eventually led to the removal of the eye, so it was classified as caused by not using the product according to label directions.

4.4.3 Phenylbutazone

Another dog was treated with an anti-inflammatory agent for post-operative swelling that occurred after removal of a vaginal tumour. The dog developed severe vomiting and gastroenteritis in the evening after being given the product. The owner treated the dog at home with anti-emetics, fluids and eggs but it died three days later. There were clearly a number of other factors involved in this case that made it impossible to clearly identify the cause of the death of this dog, thus the conclusion was that the incident was possibly product-related but unlikely.

4.5 Anti-arthritics

4.5.1 Pentosan polysulfate

Four reports were received concerning the use of the anti-arthritic agent pentosan polysulfate sodium. Three reports were considered product-related and one possibly product-related.

In the first two reports, two dogs developed lethargy and inappetence for about thirty-six hours after being treated, and one dog started vomiting. Similar reactions to these have been recorded previously after use of this chemical, but they are rare and usually only transient. Both reports were classified as product-related.

In another report a dog became quite weak after treatment with pentosan polysulfate and was found recumbent by the owners and too weak to lift its head or wag its tail. It appeared to be trembling and had laboured breathing. This dog was given three injections of this product and similar reactions occurred after each treatment, and were worse when an injection of a larger volume was given. This is reported as an individual idiosyncratic drug reaction.

A fourth dog was treated with a similar product on two occasions for treatment of degenerative joint disease. Vomiting occurred for twenty-four hours following injection, and then diarrhoea developed about thirteen hours after treatment. At the time of the first treatment, the dog was also given anti-inflammatory tablets, which are contraindicated. These were not given at the second treatment; therefore, the conclusion was that this case was possibly product-related.

4.6 Antimicrobials

Antimicrobials were implicated in four reports submitted during 1997 and 1998. Four dogs were treated, four suspected adverse reactions were reported and two dogs died.

4.6.1 Amoxycillin

One dog was treated with a number of products, including a sedative, an anaesthetic and an antimicrobial, during the course of a routine surgery. Within two hours of the surgery, the dog developed an urticarial reaction (redness), which resolved after administration of an antihistamine. After a further 12 hours, oedema developed in the right foreleg, right hindleg and down the right side of the body. The skin of these areas started to peel within 48 hours. Similar reactions to all these chemicals have been reported in the literature (5), although it appears to be more common with the particular antimicrobial used (amoxycillin). This case was classified as a possible product reaction.

4.6.2 Amoxycillin and clavulanic acid combined

Another dog treated with an amoxycillin/ clavulanic acid combination for pneumonia and pericarditis. Sixteen hours later, the dog was returned to the veterinary clinic after becoming very depressed. On presentation, the oral mucous membranes were very pale. A diagnosis of autoimmune haemolytic anaemia was made from a blood test. This continued to worsen despite treatment with corticosteroids and the dog died in the following few days. This course of events was highly unlikely to have been as a result of the antibiotic therapy, and was therefore classified as not product-related.

Another dog developed facial swelling, which is a common sign of an allergic reaction, soon after treatment with an amoxycillin and clavulanic acid product. This incident was considered product-related because the swelling occurred soon after administration of the product and the signs observed were classical allergic responses.

4.6.3 Trimethoprim and sulfatroxazole combined

Five minutes after being given an injection of a product containing trimethoprim and sulfatroxazole, a dog began Cheynes-stokes breathing. The signs worsened despite treatment and the dog died approximately ten minutes later. According to one source (8), acute toxic effects to sulphonamide-trimethoprim combinations are most commonly associated with overdose or too rapid rates of intravenous drug administration. The amount of product administered in this case was twice the recommended dose, therefore the conclusion is that the product was not used according to label directions.

4.7 Sedatives

Two reports were received concerning suspected adverse reactions after use of sedatives during 1997 and 1998.

4.7.1 Diazepam

In the first report, a dog was treated concurrently with a sedative (diazepam), an anaesthetic agent (ketamine) and an antimicrobial product (amoxycillin) for a routine desexing operation. This incident has been outlined above in the antimicrobial section (4.6).

4.7.2 Medetomidine hydrochloride

Two dogs were given medetomidine hydrochloride as a pre medication and sedative in preparation for general anaesthesia. Both dogs developed profound apnoea (slow respiratory rate) and bradycardia (slow heart rate) soon after administration. Due to the mechanism of action of this chemical, heart rate and body temperature decrease. It is likely that these incidents were product-related as the reactions observed occurred soon after administration of the product.

4.6 Anaesthetics

4.6.1 Ketamine

Only one report was submitted concerning the use of an anaesthetic agent in dogs. In this case, the reaction that occurred was not considered to be related to the use of the anaesthetic agent. This incident has been outlined above in the antimicrobial section.

4.8 Corticosteroids

4.8.1 Dexamethasone

One dog was treated with a corticosteroid by intravenous injection. The dog immediately showed signs of agitation and irritation at the site of injection, then it collapsed. This reaction was considered to be, an idiosyncratic allergic reaction to the product.

4.9 Hormones

4.9.1 Oestradiol monobenzoate

One bitch was treated with the hormone oestradiol monobenzoate to prevent conception occurring after an unwanted mating. Six weeks later she developed vaginal bleeding. The use of this hormone is known to alter the oestrus cycle of animals significantly. This alteration to the oestrus cycle may have predisposed to the development of a uterine infection, which may have caused the vaginal bleeding. The conclusion is that the reaction was possibly product-related.

5 ADVERSE EXPERIENCES REPORTED FOR GOATS IN 1997 AND 1998

TABLE 4 – GOATS

Product Category	No. of Reports Received	No. Treated	No. Affected	No. Died	Product Related	Possibly Product Related	Not Product Related	Caused by not using product according to label directions
Internal parasiticides	35	35	35	29	0	0	0	35

5.1 Internal parasiticides

5.1.1 Ivermectin

A herd of 35 milking goats was treated off-label with a product containing ivermectin as an internal parasiticide (drench).

For two to three days following treatment, the goats became depressed and went off their milk. Three days after treatment two goats died, and a total of 29 goats died over the following few days. Post mortems were performed on the dead goats including laboratory work. The pathology results suggested severe, acute and recent hepatopathy (liver disease) in the dead goats. Clinical pathology of the remaining undrenched goats indicated mild hepatopathy as well. No other reports of liver damage have been recorded following the use of ivermectin in goats. It is also unlikely that the ivermectin product would have contributed to or exacerbated the liver damage.

A number of important issues are relevant in this case:

- the farmer was using this product in a species for which it is not registered for in Australia;
- the product should not have been used in lactating animals where the milk was used for human consumption; the label clearly states this;
- these goats had pre-existing liver disease and the deaths that occurred appear to be more related to this disease than product-related.

This incident was therefore classified as not using the product according to label directions.

6 ADVERSE EXPERIENCES REPORTED FOR HORSES IN 1997 AND 1998

TABLE 5 – HORSES

Product Category	No. of Reports Received	No. Treated	No. Affected	No. Died	Product Related	Possibly Product Related	Not Product Related	Caused by not using product according to label directions
Parasticides (Oral)	15	77	76	2	67	5	0	4
Parasiticides (External)	1	1	1	0	1	0	0	0
Antimicrobials	13	17	16	6	12	4	0	0
Vitamins, amino-acids and mineral supplements	4	7	6	3	2	4	0	0
Anabolic steroids	1	5	1	1	0	0	0	1
Corticosteroids	1	1	1	0	1	0	0	0
Sedatives	1	1	1	0	1	0	0	0
Smooth muscle relaxants	1	3	2	0	2	0	0	0

6.1 Parasiticides (Oral)

The largest number of reports received in 1997/98 concerning suspected adverse reactions in horses involved oral parasiticides. All these products are used for routine worming procedures. Fifteen reports were received involving the treatment of 77 horses, with 76 reported reactions and two reported deaths.

6.1.1 Moxidectin

Eight reports were received concerning the use of a product containing moxidectin, affecting ten horses in total. In four cases the horses were accidentally overdosed with the product. One miniature pony foal died after receiving twice the recommended dose, one horse was accidentally administered approximately ten times the recommended dose, but survived and two further foals were overdosed, but recovered. An improvement to the labelling of this product is to be made to reduce the possibility of accidental overdose occurring.

In another three reports, one horse developed swelling around the eyes twenty four hours after treatment, another developed lumps over the neck and back the day following treatment, and two other horses developed weeping skin lesions in the axillae (underneath the elbows) and groin twenty four hours after treatment. In all these cases it was suspected that the effects observed were due to a possible allergic reaction to the product.

In another report a horse developed a swollen mouth the day following administration of a product containing moxidectin. The next day, the horse developed colic, which progressive worsened despite veterinary treatment. The horse was euthenased three days after treatment due to severity of clinical signs. A post mortem was performed and an area of ischaemic necrosis (bowel death due to interrupted blood supply) 75-100 centimetres long was discovered in the small intestine. This type of reaction has not been reported before for this product, and it is impossible to say whether the product was the cause of these signs.

6.1.2 Oxfendazole and pyrantel embonate combined

One particular brand of horse wormer containing the chemicals oxfendazole and pyrantel embonate was implicated in five reports, affecting 65 horses. The reported symptoms involved inappetence, mild colic, scouring (diarrhoea) or loose consistency of the faeces. The registrant undertook a study to determine whether the product was the cause of these problems or not. It was decided that the product could cause faecal softening in a very low percentage of horses (0.06%), being most significant at approximately twelve hours post administration. The safety margins of both active constituents (oxfendazole and pyrantel embonate) are very high and neither of these chemicals is thought to be the cause. The base carrier may also be responsible for these findings, and investigations are ongoing. On this basis, the reactions were classified as product-related.

6.1.3 Morantel tartrate

In another report, a foal treated with a product containing morantel tartrate, developed signs of colic the day following administration. Despite veterinary treatment, the foal required surgery and was found to have developed enteritis (inflammation of the bowel). The foal continued to have relapses of lethargy, temperature fluctuations and abnormal blood counts. This reaction was classified as possibly product-related. A review of the previous three years adverse drug reaction reports indicates that this is the first report of its kind for this product.

6.1.4 Oxfendazole and trichlorfon combined

In the final report a horse treated with a preparation containing oxfendazole and trichlorfon developed ulceration inside the mouth the day following treatment. The face and lips became swollen and there was excessive salivation. The horse also became dull and depressed. It appears that in a small percentage of cases the ingredient trichlorfon can cause transient irritation to the sensitive oral mucous membranes. This is stated on the label under Directions for use. Worming products, in particular pastes are quite often poorly administered – eg the paste is put inside the mouth between the gum and teeth of the horse rather than being placed on the back of the tongue. With these types of products, containing boticides, this poor administration has the potential to cause mild irritation to the soft tissue of the mouth. This incident was classified as product related.

6.2 Parasiticides (External)

6.2.1 Permethrin

One case involving the use of a product containing permethrin resulted in the skin of a horse becoming scalded where the product was applied two to three days earlier. The reaction was classified as product-related and may have been due to a possible chemical and ultraviolet light interaction. The registrant is testing new formulations in an attempt to overcome this problem.

6.3 Antimicrobials

A total of thirteen reports were received during 1997 and 1998 concerning the use of antimicrobial agents (mostly antibiotics) in horses and suspected adverse reactions. Procaine penicillin was implicated in ten of the reports, ceftiofur in two reports and a combination of trimethoprim and sulfadiazine in the final report.

6.3.1 Procaine penicillin

In nine of the ten reports concerning procaine penicillin, the reactions were classified as product-related. Horses reacted with varying signs of excitation in five of the incidents. The main clinical signs in these cases were collapse, nervousness, head tossing and muscular twitching. These types of excitation reactions have been observed previously in a small percentage of horses treated with procaine penicillin products.

In two of the reports, the horses died within minutes of treatment. They were classified as anaphylactic reactions, which have been recorded previously in the literature. Reactions such as this are rare, but unavoidable. They occur in a very small percentage of the very large number of horses that are treated yearly.

In one report, the horse reacted ‘violently’ (as described by the attending veterinarian), which was considered to be an extreme hypersensitivity reaction and therefore classified as product related.

In another report, two horses developed painful swellings at the injection sites and became mildly ataxic and anorexic. There may have been some local reactions to these injections and some pain response, which resulted in the ataxia and anorexia, therefore they were classified as possibly product-related.

The final report involved the treatment of a horse for a suspected respiratory infection. It was in poor condition and had a slight cough. After approximately two weeks the horse became lethargic, its breathing became laboured and its heart rate was elevated. A clinical examination revealed a normal temperature, elevated heart rate and respiratory rate, slight dehydration and poor condition. A blood sample revealed an elevated white blood cell count. The horse was treated with a procaine penicillin product at this stage for a suspected infection. The following day the horse was still lethargic and its heart rate was still elevated. A lump appeared where the injection had been given. The next day the lump had increased in size, the horse was reluctant to move, stopped eating and drinking, and its heart rate was still elevated.

The horse was found dead in the paddock the next morning. While the cause of the lump at the injection site was almost certainly product-related, the cause of death in this case is unknown. The horse was obviously seriously ill at the time of examination by the attending veterinarian, and there is no obvious relationship between the death and the use of the product.

6.3.2 Ceftiofur

In the two reports concerning the use of ceftiofur in horses for treatment of bacterial infections, both horses developed acute febrile diarrhoea during the course of treatment. It is important to note that there are a number of extenuating circumstances in both these incidents. The horses were in work and therefore under a certain level of stress and they were also being treated for bacterial infections. Acute febrile diarrhoea can occur in horses not receiving treatment with an antimicrobial product, although it also known to occur in horses under stress when treated with antimicrobial products. There have been a number of other reports of acute febrile diarrhoea associated with use of ceftiofur and other antimicrobials. It is difficult to determine the cause of the reaction in these incidents and for this reason the reactions were classified as possibly product-related.

6.3.3 Trimethoprim and sulfadiazine combined

In the final report, which involved an intravenous injection of trimethoprim and sulfadiazine, the horse reared and fell shortly after the injection was administered. It relaxed after approximately five minutes and then made a complete recovery. This incident was classified as product-related and appears to have been an idiosyncratic hypersensitivity reaction.

6.4 Vitamins

Four reports were received during 1997 and 1998 regarding administration of products containing vitamins, amino acids and/or mineral supplements. A total of seven horses were treated, six were observed to have reacted and three horses reportedly died.

6.4.1 Various

In the first report, a horse had been treated one week previously with the recommended dose of a product containing aminoacids and vitamins. On this occasion the owner only gave 10-15mL and the horse immediately became disorientated, collapsed, had white oral mucous membranes and died within one to two minutes. Post mortem examination revealed white froth in the airways and no other abnormalities. The method and route of administration of this product in this case may have had some bearing on the death of the horse. This type of reaction has been reported before after intra-arterial injections and it is possible that the reaction was caused by accidental intra-arterial injection. As it is impossible to confirm that the injection was administered intra-arterially, the incident was therefore classified as possibly product-related.

6.4.2 Arginine hydrochloride and sodium glucuronate combined

In the second report, a horse was given an intravenous injection of a product containing arginine hydrochloride and sodium glucuronate. Within two minutes, the horse collapsed. It subsequently died about five minutes later. This was considered to have been an anaphylactic reaction and therefore classified as product-related.

6.4.3 Multi-vitamin

One horse developed signs of trembling, staggering and collapse within three minutes following injection of a multi-vitamin preparation. The horse died and the cause was considered to be an acute anaphylactic reaction to the product.

6.4.4 Vitamin e and selenium combined

In the final report, four other horses were treated with a product containing vitamin E and selenium. Three horses showed signs of acute stress and pain within hours of the intramuscular injections. Swellings developed at the injection sites in the three horses, and the signs continued for approximately 24 hours. This is possibly product-related, although there are a number of factors to take into account:

- horses react to painful stimuli in a number of different ways, and a deep intramuscular injection (such as these horses received) can cause signs of acute pain;

- local reactions occur at the site of many injections, and the swellings that occurred in these horses would not be considered unusual.

6.5 Steroids (Anabolic)

6.5.1 Stanazolol

One horse was accidentally injected intra-arterially with a suspension containing stanazolol. This caused the horse to rear, fall and hit its head. Later the horse developed neurological signs, it did not respond to treatment and was euthenased. This incident was therefore caused by accidental misuse of the product.

6.6 Steroids (Corticosteroids)

6.6.1 Flumethasone and dimethyl sulfoxide combined

A product containing a synthetic flucorticoid (flumethasone) and dimethyl sulfoxide (an analgesic and anti-inflammatory) was applied to a horse’s leg to reduce swelling. Blistering occurred to the legs where the product was applied, and scarring was present when the skin grew back. The conclusion in this case was that this reaction was product-related. It was clear that the site of application of this product was where the lesions and scarring developed, although it should be noted that this type of reaction is extremely rare.

6.7 Sedatives

6.7.1 Romifidine

One horse was given an intravenous sedative containing the chemical romifidine in preparation for facial surgery. The horse was discovered the following day with paraphimosis (swelling and extrusion of the penis). This swelling persisted, despite various treatments by the attending veterinarian for a further fourteen days. This type of reaction is a recognised side effect of a number of sedatives for horses and is considered to have been product related.

6.8 Smooth muscle relaxants

6.8.1 Propantheline bromide

It is a recognised side effect of smooth muscle relaxants that intestinal motility may be reduced after administration, which can lead to build up of gas and flatulent colic. Three horses were treated with propantheline bromide to facilitate rectal palpation, and two horses developed signs of colic within 45 minutes of administration. Both horses recovered six to eight hours after treatment. Other factors may have been involved as the horses were from the same property. These factors such as feeding of high concentrate diets, dietary change, enteritis, parasite infestation and electrolyte imbalances may contribute to gas production. These reactions were therefore classified as product-related.

7 ADVERSE EXPERIENCES REPORTED FOR RABBITS IN 1997 AND 1998

TABLE 6 – RABBITS

Product Category	No. of Reports Received	No. Treated	No. Affected	No. Died	Product Related	Possibly Product Related	Not Product Related	Caused by not using product according to label directions
External parasiticides	2	2	2	2	0	0	0	2
Vaccines	2	2	2	0	1	1	0	0

7.1 External parasiticides

7.1.1 Fipronil

Two reports were received late in 1998 regarding the off-label use of a product containing the external parasiticide fipronil in rabbits. In both cases the rabbits showed neurological signs of jaw champing and seizures within forty-eight hours of treatment and died despite being washed with soap and water and being treated with a sedative. An increase in reports similar to these began to occur late in 1998, and it appears there is evidence that a small percentage of rabbits treated with this product may develop similar signs. A warning was issued to the veterinary profession, through various publications, on this possible link and risk.

7.2 Vaccines

7.2.1 Rabbit calicivirus vaccine

Two adverse experience reports involving vaccines were received in 1997 for rabbits. Both reports concerned the use of an inactivated rabbit calicivirus vaccine.

One rabbit developed an abscess at the site of injection and a fever two days after being vaccinated. This type of problem can occur with any injection, as bacteria can be transported under the skin along with the insertion of the needle. Consequently, this report was classified as possibly product-related, and there is no indication that this brand of vaccine is any more likely to cause this type of reaction than any other.

The second case involved the development of a hairless, crusty, reddened area, approximately six centimetres in diameter, at the site of injection two weeks after administration of the vaccine. This type of reaction is classified as product-related, and is most likely due to a hypersensitivity reaction to the product.

8 ADVERSE EXPERIENCES REPORTED FOR SHEEP IN 1997 AND 1998

TABLE 7 – SHEEP

Product Category	No. of Reports Received	No. Treated	No. Affected	No. Died	Product Related	Possibly Product Related	Not Product Related	Caused by not using product according to label directions
Internal parasiticides	5	35815+	788+	607	0	0	0	788+
Internal parasiticides (containing mineral supplements)	2	750	82	82	80	0	0	2

8.1 Internal parasiticides

A total of seven reports were received during the 1997/98 reporting period concerning suspected adverse reactions occurring in sheep after the use of internal parasiticides.

8.1.1 Ivermectin

Four reports concerned the use of slow-release capsules containing the chemical ivermectin. Over 35000 sheep were treated in these reports and more than 600 died. Post mortems conducted on the dead sheep revealed that during drenching, the capsules were incorrectly administered and caused severe damage to the throats, which eventually led to the death of the sheep. The label of this product has been changed to emphasise the importance of keeping the neck of the sheep being treated straight to prevent injuries to the pharynx.

8.1.2 Moxidectin

Another report involved the use of a product containing moxidectin in 515 sheep. Three sheep died approximately two weeks after drenching, and others were noticed to have pale gums and swelling under the necks. A veterinary post mortem indicated that the sheep still had a heavy worm burden. The sheep were drenched a second time with the same product under the supervision of the product representative and faecal samples indicated that the drench was 100% effective. It was therefore decided that a number of sheep may have been missed at the initial drenching, and the incident was classified as caused by not using the product according to label directions.

8.1.3 Levamisole combined with a number of minerals

The last two reports involved the use of levamisole mixed with a number of minerals, which was used as an internal parasiticide and mineral supplement.

In one report, approximately 400 lambs were drenched with this product by a very experienced sheep farmer. Initially the lambs were drenched, given a vitamin B injection and then marked, but when some of the lambs started to die, the farmer ceased giving the drench. Of the lambs that did not receive the drench, there were no deaths. The only deaths that occurred were of the group treated with the drench. As there was a clear cause and effect relationship between the administration of this product and the resulting clinical signs.

In the second report, 350 sheep were drenched and two of the treated sheep died shortly after they were drenched. In this case, the farmer returned a sample of the product he was using. The sample returned turned out to be another registered product. It therefore appears that the farmer may have inadvertently drenched the sheep with an incorrect product.

9 ADVERSE EXPERIENCES REPORTED FOR HUMANS IN 1997 AND 1998

TABLE 8 - HUMAN REACTIONS

Product Category	No. of Reports Received	No. Affected	Product Related Reactions	Possibly Product Related Reactions	Not Product Related
Parasiticide	1	1	0	1	0
Feed additive	1	1	1	0	0

9.1 Parasiticides

9.1.1 Moxidectin

A farmer used a product containing moxidectin, which is applied topically to cattle for internal and external parasite control, on two occasions. Approximately four days after each use, the farmer developed a swollen left eyelid, a “head cold” feeling, a raw feeling to the nose with some crusting and peeling and had some diarrhoea which persisted for about one week. In both instances, the farmer also indicated that areas of skin that did not come into contact with the product began to peel. The farmer’s doctor made a diagnosis of “industrial dermatitis”. This is considered possibly product-related, and is thought to be due to an allergic response of the farmer to the product.

9.2 Feed additives

9.2.1 Olaquindox

A man employed at a piggery in Victoria for 23 years developed a skin reaction that caused florid, widespread, itchy, erythematous and weeping skin eruptions affecting his hands, forearms and neck. This occurred soon after the piggery began using a feed premix containing olaquindox, which improves liveweight gains and feed conversion efficiency and reduces scouring outbreaks caused by organisms sensitive to olaquindox in pigs. This was diagnosed initially as an allergic contact dermatitis.

A dermatologist examined the man and used a series of patch tests to determine the cause of the allergy, and a positive reaction occurred to olaquindox. The dermatologist then diagnosed the problem as Olaquindox photodermatitis.

There have been a number of cases of similar reactions occurring after the use of olaquindox-containing compounds in Australia and overseas (6, 7). Olaquindox is a derivative of the compounds quindoxin and quinoxaline. Quindoxin was withdrawn from the European Economic Community market in 1973 because of its carcinogenic properties in experimental animals (7). It has also been implicated in a number of photosensitivity reactions in people (7).

This information resulted in label changes being recommended in eighteen products containing this chemical. The label now carries a warning statement indicating that care must be taken when handling these products as there is the potential for such allergic reactions.

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Appendix A

Summary of Adverse Experience Reports
1997 and 1998
(Animal Reaction Category)

The following summary sets out the details of those reports where it has been decided that the adverse experience is product-related, possibly product-related, not product-related or caused by not using the product according to label directions. Included are reported reactions involving off label use. Reports classified as not product related have previously not been included, but those reports of interest have been included in this annual report for completeness.

The table lists the animal species affected; the generic chemical/active constituent; route of administration; number of animals involved; a description of the adverse experience; the classification of the reaction and comments. In evaluating the reports the NRA also takes into consideration climatic conditions at the time of treatment, and health and management of the animal. In situations where a number of products were administered concurrently, the active constituents of all products used are named.

This summary table is intended only to provide general information about the types of reactions that veterinarians, animal owners and others have voluntarily reported to the NRA or the manufacturer after use of the product. The information in the table is not by itself a basis for determining the safety and efficacy of a given product or for comparing one product with another, nor can it be used to predict the frequency of occurrence of a reaction.

CATS

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Alphaxalone Alphadolone	Intravenous	1	1	1	Apnoea and bradycardia occurred immediately following administration of this product. The cat did not respond to resuscitation techniques and died.	Product-related. The cause of death in this cat appears to be directly related to the administration of this product, and is most likely due to an anaphylactic reaction.
Bethanechol	Oral	1	1	1	Used to treat urinary retention. Three hours after treatment the cat began vomiting, salivating and had diarrhoea. Atropine was given as an antidote and response was good. Cat was stable when checked seven hours after treatment, but deteriorated three hours later. Veterinary attention not sought at this time. The cat died eighteen hours after the product was administered.	Caused by not using the product according to label directions. This was an off label use of a human drug used to stimulate muscle tone in the bladder of this cat.
Carprofen	Oral	1	1	Nil	Three days after being treated with this product twice daily the cat became lethargic, anorexic, jaundiced and laboratory tests revealed haemolysis, renal failure and non-regenerative anaemia. One week after removal of treatment, signs resolved.	Caused by not using the product according to label directions. This product is unregistered for use in cats. The elimination half-life of this chemical is possibly 48 hours in cats, therefore the dosage given may have been 4-8 times overdose.
Doxycycline Carprofen	Oral Sub-cutaneous	1	1	Nil	The cat was treated with these products for fight wounds, cellulitis and arthritis. Presented one week later with swollen eyelids, swollen ears and head shaking. Condition resolved when doxycycline was stopped, antihistamines given parenterally and antibiotic/anti-inflammatory ointment applied to eyes and ears.	Possibly product-related. Although the cat was treated with two products it appears that the reaction may have been due to the administration of the product containing the antimicrobial agent doxycycline. The reaction only occurred after the cat was treated with the doxycycline for a period of one week, and these clinical signs have been seen very rarely with doxycycline before.
Enrofloxacin	Oral	1	1	Nil	Cat was being treated for deep pyoderma of abdominal fat pad and tongue. Had been given daily injections of enrofloxacin until oral solution arrived. Prolonged, excessive salivation was observed after oral administration of the product.	Product-related. This active constituent has a very bitter taste, which is most likely responsible for the excessive salivation.

CATS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Enrofloxacin	Oral	1	1	Nil	Cat began to salivate when given one drop of product. Veterinarian did not continue with full dose.	Possibly product-related. This active constituent has a very bitter taste, which is most likely responsible for the excessive salivation.
Enrofloxacin	Oral	1	1	Nil	After two days of treatment with this product, the cat began to salivate excessively. On day 3 the cat collapsed once or twice and stopped eating. On day 4 the cat was not eating, drinking defecating or urinating and owner ceased administration of tablets. On day 5 the cat was ataxic. Cat stopped frequently for a rest when walking. On day 6 the cat was ataxic, falling and appeared to have a perpetual neuropathy. Legs were knuckling.	Possibly product-related. Reactions such as these (vomiting, inappetence, incoordination and convulsions) have been recorded but only after receiving 10 times the recommended dose or greater.
Feline panleucopenia virus; feline rhinotracheitis virus; feline calicivirus (combined live attenuated) **Plus** Purified recombinant vaccinal antigen of feline leukaemia virus	Subcutaneous	1	1	Nil	After being vaccinated, the cat was very quiet and became aggressive when patted. When examined the next day by a veterinarian, the cat was pyrexic (temperature 40^0 C), and inappetent. By the next morning the cat's temperature was 39^0C.	Product-related. An allergic reaction.
Imidacloprid	External	1	1	Nil	A bald patch appeared on back of neck of this cat where this product was applied.	Product-related. This type of reaction has been reported before with this product in a very small percentage of cases (approximately 0.002% incidence).
Lufenuron	Subcutaneous	2	1	Nil	A cat had been treated with the oral formulation of this product without ill effects for some time, but when it was treated with the injectable form of this product a reaction occurred (a description of the reaction was not reported). It was reported that the cat has since been returned to the oral formulation of this product and has had no further problems.	Product-related. There appears to be a clear relationship between the administration of the injectable formulation of this product and the reaction and that there have been no further problems since being returned to the oral formulation.

CATS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Lufenuron	Oral	1	1	Nil	Cat vomited the night of treatment and during the next day. Cat was dehydrated when seen by veterinarian two days after administration of the product. Clinical pathology showed haemoconcentration, inflammation and multiple biochemical changes.	Possibly product-related. All the clinical signs observed in this cat (vomiting, dehydration and biochemical changes) have been reported after use of this product in a very rare number of cases. It was not recorded whether this treatment was given with a full meal as directed on the label, and this may have contributed to the reaction observed.
Medroxyprogesterone acetate	Oral	1	1	Nil	Gross enlargement of entire mammary chain occurred with cracking of one nipple. Enlargement began six weeks after cat was given product. Condition appeared to respond to treatment with diuretics and antibiotics.	Possibly product-related. This type of reaction, described as feline mammary hypertrophy, is very rare and has not been reported before in Australia. This case was also unusual for a number of reasons (see Part A of this report).
Megestrol acetate	Oral	1	1	Nil	Three weeks after discontinuing treatment two mammary lumps developed on this cat. Surgical resection was necessary and biopsies were submitted for laboratory evaluation. Diagnosis – Benign mammary growth.	Product-related. Use of progestagens have been known to cause mammary hyperplasia regardless of neutering state.
Polymyxin B Nitrofurazone Neomycin sulfate Lignocaine Pyrethrins	Topical (ears)	1	1	Nil	When the drops were applied to this cat's ears it caused the cat to cry and paw at its ears. Two days later the owners noticed the cat's ears were bright red and there were ulcerations in the ear canals. The ears were painful to the touch. The cat started panting and its pupils became dilated at this time.	Possibly product-related. The cat was described as having a heavy infestation of mites at the time of treatment. For this reason, the application of these eardrops would have caused the mites to become aggravated and irritate the ears. The presence of local anaesthetic in the drops would have minimised this irritation, but with a heavy mite infestation this might not have occurred.
Praziquantel, pyrantel embonate	Oral	1	1	Nil	Within two hours of treatment, the cat became lethargic, ataxic, hyperaesthetic, the pupils dilated and it seemed to be in a trance.	Product-related. This type of reaction has been reported before with a previous formulation. The current formulation has a much lower incidence of problems. The label has also been changed to warn of these possible transient effects.

CATS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Purified recombinant vaccinal antigen of feline leukaemia virus	Subcutaneous	1	1	1	Cat found dead in garden by owner one hour after vaccination in clinic. Permission for autopsy not given. Other cats vaccinated by clinic using same batch have shown no ill effect.	Not product-related. Insufficient evidence to link death with administration of product. Note that there have been previous reactions to this vaccine, but sudden death has not occurred.
Purified recombinant vaccinal antigen of feline leukaemia virus	Sub-cutaneous	1	1	Nil	One week after the cat was vaccinated the owner noticed a non-painful lump at the site of the injection. During the day it appeared to increase in size. Seen by veterinarian fourteen days after injection. The lump was 18mm diameter, firm and circumscribed. On needle aspiration a small amount of seropurulent fluid was recovered. Two days later lump was removed under general anaesthetic. On cross section it was seen as solid but oedematous. Recovery was routine.	Product-related. A type of hypersensitivity reaction.

CATTLE

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Ceftiofur sodium	Intramuscular	1	1	1	Fifteen minutes after receiving the eighteenth injection on consecutive days this bull exhibited dyspnoea and became recumbent after a further fifteen minutes. The animal died approximately thirty minutes later.	Possibly product-related. The attending veterinarian reported that this animal may have had an underlying cardiovascular abnormality that may have contributed in some way to the death. It is therefore only possible to classify this incident as possibly product related as there are a number of factors involved.
Chlorfenvinphos	External	40	5	Nil	Five of the smallest poddy calves started to salivate and became uncoordinated which is consistent with organo phosphate poisoning. They were treated with approximately one litre of solution per animal. Recommend dose rate is 200ml per animal.	Caused by not using the product according to label directions. The calves were inadvertently overdosed.
Chlorfenvinphos	External	50	?	Nil	A number of cattle became recumbent and started thrashing their legs around soon after being treated with this product. All cattle recovered after being washed down with soap and water.	Caused by not using product according to label direction. Cattle were dosed with five times the recommended quantity.
Chorionic gonadotropin, progesterone	Intravenous	4	3	Nil	Soon after injection, the cattle began staggering, had difficulty breathing, became restless and started shaking their heads. They then developed wheals over their entire bodies.	Product-related. A hypersensitivity reaction.

CATTLE contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Cloxacillin	Intramammary	100	2	Nil	Cows were treated at least seventy days prior to calving. Blue dye was still present in the milk seven days after calving (three days beyond the recommended with holding period).	Product-related. There are a number of reasons that may have caused persistence of the blue dye such as: • Cow problems – old cows (both cows were nine years old) and cows with chronic infections have a tendency to pocket intramammary formulation in damaged parts of the udder, potentially slowing the washout of dye with milk. • Cow variability – the excretion of blue dye and antibiotic are not linked and not precisely predictable. Taking into account the age of the cows, and that the product tested within specifications, the reason for the persistent blue dye excretion is most likely to be due to cow problems/ variability.
Cloxacillin	Intramammary	30	10	6	Cows calved six weeks after this dry cow therapy was used. Mastitis discovered when cows calved. Milk samples were positive for Pseudomonas.	Not product-related for the following reasons: • Investigations into the batch of intramammary product used in this case indicated that it met all specifications required and no other reports of problems had been recorded from this batch or any other batch. • The time elapsed between the administration of the product and the detection of infection was six weeks – if the infection had been introduced at the time of treatment, then infection and signs of disease would have occurred much sooner
Cypermethrin Chlorfenvinphos	Plunge dip	240	9	9	Nine calves drowned in a dip charged with this product. The dip concentration was within normal limits on analysis by the Queensland Department of Primary Industries Laboratory.	Not product-related. The product is unlikely to have been responsible for the deaths of these calves. It is more likely to have been as a result of poor dipping technique.

CATTLE contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Diazinon	External	278	230	48	Within one hour of treatment, the cattle became ataxic, recumbent started salivating excessively, developed diarrhoea, colic and subsequently many of them died.	Caused by not using product according to label directions. The attending veterinarian notes that product was out of date. There is the potential for diazinon to break down into toxic by-products, particularly if it becomes contaminated with moisture (eg condensation or inadequate re-sealing of containers).
Diazinon	External	110	110	57	Within one hour of treatment with this product, a number of cattle collapsed and died. The attending veterinarian treated cattle with atropine and washed them down with soap and water.	Caused by not using product according to label directions. This product was out of date and had been recalled in 1996, but this batch must have been missed. There is the potential for diazinon to break down into toxic by-products, particularly if it becomes contaminated with moisture (eg condensation or inadequate re-sealing of containers). This product also has warnings on label not to mix with sump oil, yet this farmer used oil to mix the product with, which is misuse of the product.
Diazinon	External	19	19	3	Approximately one and a half hours after treatment with this product, a number of cattle collapsed and three subsequently died.	Caused by not using product according to label directions. This product was out of date and had been recalled in 1996, but this batch must have been missed. There is the potential for diazinon to break down into toxic by-products, particularly if it becomes contaminated with moisture (eg condensation or inadequate re-sealing of containers).
Diazinon	External	284+	72+	72	Numerous animals showed signs of organo-phosphate poisoning and seventy two animals died. The others were treated with atropine and washed down.	Caused by not using product according to label directions. This product was out of date and had been recalled in 1996, but this batch must have been missed. There is the potential for diazinon to break down into toxic by-products, particularly if it becomes contaminated with moisture (eg condensation or inadequate re-sealing of containers).

CATTLE contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Dinoprost trometamol	Intramuscular	110	30	3	Lesions occurred at the site of injection of this product that were consistent with clostridial infections.	Not product-related. The lesions were most likely caused by skin contamination with clostridial organisms or from spores in the muscle proliferating when tissue oxygen was reduced after injection of the product.
Dinoprost trometamol	Intramuscular	18	18	2	Bacterial infections resulting in abscesses and cellulitis occurred in dairy cows following intramuscular injections of the product. Swellings of various sizes occurred in the hip area at the site of injection and in a number of cases extended to the leg. Two cows had to be destroyed.	Not product-related. The investigation suggests that the problem resulted from infections caused by the introduction of bacteria into muscle during injection of the product under non-sterile conditions.
Leptospiral & clostridial organisms (formalin killed)	Subcutaneous	16	2	Nil	The udder and mucous membranes of this cow became cyanotic, the eyes sank back in the head and it started frothing at the mouth.	Product-related. A Type I hypersensitivity reaction.
Monensin	Oral	40	1	1	Forty-nine days after administration of a capsule this steer was seen to be staggering, depressed and salivating. The steer died the following day. At post mortem, the body and the cap of the capsule had separated.	Product-related. As a direct result of this incident, an extensive review was made into the manufacturing procedure of this product. A change made to the mould used in the manufacture of these batches has now been rectified.
Monensin	Oral	258	4	4	Three steers died about one month after treatment. A further three months later another steer died. Capsules retrieved at post mortem found that the body and cap of the capsules had separated.	Product-related. As a direct result of this incident, an extensive review was made into the manufacturing procedure of this product. A change made to the mould used in the manufacture of these batches has now been rectified.
Monensin	Oral	350	2	1	One steer was noticed by the owner as being unwell two months after being treated with this product. It died within four days of first being observed as unwell. A post mortem revealed that the body and cap of the capsule had separated.	Possibly product-related. Samples of the fluid of the steer's stomach were not significantly abnormal. Therefore the cause of the death of this animal was undiagnosed.

CATTLE contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Monensin	Oral	Herd	1	1	Forty-five days after application of a capsule in this steer, the animal was found to be "swollen up in the belly" for a couple of days. On this day, it regurgitated an incomplete capsule and died later in the day. The capsule body was broken in half length ways with pieces missing.	Possibly product-related. As a direct result of this incident, an extensive review was made into the manufacturing procedure of this product. A change made to the mould used in the manufacture of these batches has now been rectified.
Neomycin sulfate, dihydrostreptomycin, Novobiocin	Intramammary	5	5	Nil	This product was used in a number of cattle to treat clinical mastitis. The milk from some of the treated cattle was described as unusual in appearance, some returned a positive residue test after the withholding period and one quarter was lost in a cow.	Product-related. Analysis of a sample of this milk revealed that the antibiotic levels in the milk were below the maximum residue levels. There is no physical evidence to indicate that this product caused the abnormal appearance of the milk, but the cause and effect relationship cannot be discounted.
Nitroxynil	Subcutaneous	42	25	Nil	The owner reported that affected cattle developed large lumps at injection sites. Lesions reported to, but not seen by, veterinarian.	Possibly product-related. No veterinary observation was made of the reported reactions so no definitive diagnosis could be made. On this basis, the incident was classified as possibly product-related, although highly unlikely as no other similar reports have been recorded for this product.
Oxytetracycline	Intramuscular	1	1	1	Within five minutes of injection the bull showed profuse salivation, progressive muscle tremor, incoordination leading to recumbency with severe breathing difficulties and death (approximately eight minutes after injection).	Product-related. A Type I hypersensitivity reaction.

CATTLE contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Oxytetracycline	Intramuscular & Sub-cutaneous	18	18	7	Within two minutes of injection of product all cattle reacted. All showed signs of depression, head dropping, intense salivation, flapping ears, intense forehead irritation leading to self-mutilation. The steer that was injected by the intra muscular route reacted more violently and became recumbent for two and a half hours. Seven cattle died two days later while in holding for movement onto ship for transport.	Product-related. Anaphylactic reactions. Investigations are continuing into this incident to determine more precisely the cause of the reactions and whether they relate to interaction with excipients of vaccines used previously on the animals..
Oxytetracycline	Intramuscular	2	2	1	The owner treated both animals. One bull showed head shaking, salivation and distress soon after treatment. The symptoms lasted approx. forty minutes. The other bull was found dead ten minutes after being treated.	Product-related. A Type I hypersensitivity reaction.
Oxytetracycline	Intramuscular	1	1	Nil	This bull was treated for an abscess on its jaw. As this bull had reacted to this product six months previously a low dose (approx 56% recommended dose) was given and the bull then watched closely. Within three minutes of injection the bull reacted in the following way - head shaking, tail swinging, salivation, foaming at mouth, nasal discharge, swollen face, wrinkling of skin over body and swelling of anus. The bull became recumbent within fifteen minutes. It recovered after treatment with adrenaline, antihistamine and corticosteroid, and was able to stand within ninety minutes.	Product-related. A Type I hypersensitivity reaction.
Oxytetracycline	Intramuscular	1	1	Nil	Product was administered to treat a footrot infection. Half an hour after treatment the bull was weak, leaning on a building, then sat down and started salivating profusely from the mouth and nostrils. The bull then started breathing rapidly and let its head hang down weakly.	Product-related. A Type I hypersensitivity reaction.

CATTLE contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Oxytetracycline	Intramuscular	1	1	1	This bull died very suddenly within five minutes of being treated with this product after receiving only a partial dose.	Product-related. A Type I hypersensitivity reaction.
Oxytocin	Intravenous	1	1	1	The owner administered this product by intravenous injection to stimulate milk letdown, in accordance with a veterinarian's written instructions. The cow began staggering within thirty seconds of injection. Bloody froth was seen coming from mouth and nostrils. Cow collapsed after one minute and was dead within three minutes of injection. Veterinarian attended one hour later and diagnosed anaphylactic reaction.	Product-related. This was determined to have been an anaphylactic reaction as the cow showed classical signs of anaphylaxis, although the intravenous route of administration is not recommended unless under the direct supervision of a veterinarian.
Procaine penicillin	Intramuscular	1	1	1	The bull died suddenly soon after treatment with this product. The clinical signs observed were consistent with an anaphylactic reaction.	Product-related. The description of events and the clinical signs observed by the owner indicate that this was a case of anaphylactic shock.
Procaine penicillin	Intramuscular	1	1	Nil	Fifteen minutes after treatment the bull staggered and fell down a number of times before become prostrate and bloating rapidly.	Product related. A type I hypersensitivity reaction.
Procaine penicillin	Intramuscular	1	1	1	Bull died within 60-90 seconds of injection.	Product-related. A Type I hypersensitivity reaction.
Procaine penicillin	Intramuscular	2	2	1	Ten minutes after treatment the bull began snorting blood from the nostrils.	Product-related. A Type I hypersensitivity reaction.
Procaine penicillin	Intramuscular	1	1	Nil	This animal collapsed immediately after the injection was given. It recovered quite rapidly, but was very agitated. It progressively recovered after being let out of the yards.	Product-related. A Type I hypersensitivity reaction.
Procaine penicillin	Intramuscular	3	3	Nil	Immediately after being injected, the bulls began salivating and ran around the yard bashing their heads against the fences.	Product-related. A Type I hypersensitivity reaction.

CATTLE contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Procaine penicillin, benzathine penicillin	Intramuscular	1	1	1	This animal was treated for footrot. It was found dead the morning after treatment. A post mortem revealed oedema and small haemorrhages in the eyelids, trachea, peritracheal tissue; pleura and diaphragm; and oedema and emphysema of the lungs. These post mortem findings are consistent with an anaphylactic reaction.	Possibly product-related. A Type I hypersensitivity reaction is suspected as being the cause of death, although no post mortem was performed to confirm this.
Procaine penicillin, dihydrostreptomycin sulfate	Intramuscular	4	3	1	A bull and two heifers were given a single intramuscular injection. The bull started staggering, salivating and lay down within five to seven minutes of the injection. A heifer lay down started convulsing and died within two minutes of injection. It died before veterinary treatment was available approximately ten minutes after treatment. Another heifer reacted twenty minutes after being injected, was treated for anaphylaxis and survived.	Product-related. A Type I hypersensitivity reaction.

DOGS

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Amitraz	Oral (inadvertent)	3	3	Nil	Three dogs inadvertently ate a tick collar. Within a few hours the dogs urinated and collapsed. One dog staggered, lost control, urinated, collapsed screaming and in respiratory distress. It had respiratory difficulty for some hours and was weak for several days. The owner gave dog mouth-to-mouth resuscitation; he then began vomiting, which lasted for two hours. Two other dogs involved became weak, vomited and lost bladder control.	Caused by not using product according to label directions. During our investigation of this complaint, the following conclusions were made: • The current label instructions and warnings statements on the packaging appear to be adequate. These instructions state clearly that the product is a poison and it should be handled carefully and kept out of reach of children. • These label instructions were approved for use on the packaging under State legislation and the NRA has given approval for their continued use as per the State registration. Nevertheless we have recommended that the NRA conduct a review of this product to address its toxicity, labelling, packaging and especially its safety to children.
Amoxycillin Clavulanic acid	Subcutaneous	1	1	1	Dog presented with signs consistent with pneumonia and pericarditis. Sixteen hours after initial treatment dog was depressed with pale mucous membranes. Blood tests indicated autoimmune haemolytic anaemia. Treatment with corticosteroids was started. Blood tests three days later indicated that the autoimmune haemolytic anaemia was getting worse. The dog died.	Not product-related. It is clear that there were many other factors involved in the death of this dog and it does not appear that this product played any part in it.
Amoxycillin Clavulanic acid	Oral	1	1	Nil	Facial swelling occurred the day injection was given and persisted until the next day.	Product-related. A Type I hypersensitivity reaction.
Bordetella bronchiseptica	Subcutaneous	2	2	Nil	Within one hour of vaccination, facial swelling and irritation occurred to both dogs. One dog started to vomit a number of times. The second dog developed ocular and scleral oedema.	Product-related. A Type I hypersensitivity reaction.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Bordetella bronchiseptica	Subcutaneous	2	2	Nil	After annual vaccination, two mature dogs showed urticaria, facial swelling and oedema within one hour.	Product-related. A Type I hypersensitivity reaction.
Bordetella bronchiseptica & canine parainfluenza virus (inactivated)	Subcutaneous	1	1	Nil	A lump two centimetres in diameter appeared at the injection site nine days after injection.	Product-related. The cause of the formation of the lump was most likely to have been a reaction to the adjuvant in the vaccine.
Bordetella bronchiseptica strain 55 (living) **Plus** Canine distemper virus, canine adenovirus type2, canine parvovirus and canine influenza type 2 virus (attenuated) Fipronil	Subcutaneous External	1	1	1	A healthy puppy was vaccinated and taken home by the owner. Forty minutes later it appeared to choke when eating and died five minutes later. Post mortem changes were consistent with an anaphylaxis-like process.	Product-related. A Type I hypersensitivity reaction to the vaccine.
Canine distemper virus, canine adenovirus type 2 (CAV2) and canine parvovirus (attenuated)	Subcutaneous	1	1	Nil	Dog showed signs of pain and weakness within one hour of vaccination. Dog continued to remain quiet and appeared to be in pain for four to five hours.	Product-related. A Type I hypersensitivity reaction.
Canine distemper virus, canine adenovirus type 2 (CAV2) and canine parvovirus (attenuated)	Subcutaneous	1	1	Nil	Dog appeared quiet and started shivering and staggering within two hours of vaccination. Recovered two to three hours after symptoms first appeared.	Product-related. A Type I hypersensitivity reaction.
Canine distemper virus, canine adenovirus type 2 (CAV2) and canine parvovirus (attenuated)	Subcutaneous	1	1	Nil	After vaccination the puppy became lethargic and facial oedema developed.	Product-related. A Type I hypersensitivity reaction.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Canine distemper virus, canine adenovirus type 2 (CAV2) and canine parvovirus (attenuated)	Subcutaneous	1	1	1	Routine vaccination given to twelve week old puppy. Owner said puppy had previously had two vaccinations with a product from a different manufacturer. Presented to vet with severe gastroenteritis three days after vaccination. Parvoviral gastroenteritis was suspected. Puppy died despite treatment.	Not product-related. Laboratory tests performed on this pup indicated it was incubating the disease before the vaccination was administered.
Canine distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus and canine influenza type 2 virus (attenuated)	Subcutaneous	1	1	Nil	Fifteen minutes after vaccination the dog showed the following symptoms: urticaria, angioneurotic oedema and intense facial pruritus. Forty-five minutes later vomiting, weakness and agitation were observed. One hour and ten minutes after vaccination dog was still weak and vomiting and had diarrhoea.	Product-related. A Type I hypersensitivity reaction.
Canine parainfluenza virus (living), Bordetella bronchiseptica (inactivated)	Subcutaneous	1	1	Nil	Soon after the puppy was vaccinated with this product, it developed facial swelling (oedema).	Product-related. A Type I hypersensitivity reaction.
Carbaryl	External	1	1	Nil	On two occasions, a few hours after treatment was applied, the dog became very excited, ran around uncontrollably and showed signs consistent with acute pruritus.	Product-related. A Type I hypersensitivity reaction.
Carprofen	Subcutaneous	1	1	1	The dog became weak soon after administration of product. Over night the dog vomited several times. It continued to vomit the next day and died the following night.	Possibly product-related. The cause of death is unknown. It is very unlikely that a single injection of this product would have caused the death of this dog. No other similar reports have been received.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Carprofen	Oral	1	1	Nil	This dog commenced treatment twice daily for four days. After two days on medication, the owner noticed dog reacted half an hour after tablets were given. The dog would lay down; start panting rapidly and the heart would start visibly pounding. It recovered in two hours each time. The effect continued the following day when re-treated. No similar episodes occurred once the medication stopped.	Product-related. There is an obvious cause and effect relationship between the administration of this product and the signs observed.
Copper indomethacin	Topical (eye)	1	1	Nil	This dog was treated for a corneal ulcer, blepharospasm and corneal vascularisation. One week after beginning treatment with this product, the dog was presented to the veterinarian again with a full thickness corneal ulcer (desmetocoele) covering half the cornea. On attempting a third eyelid flap, the globe ruptured.	Caused by not using product according to label directions. The practice principal indicated that he would not have used this product in this situation as he felt that other treatments would have been more appropriate. The owner noticed a deterioration in the condition soon after commencing treatment, but did not report this to the veterinarians early enough.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Cythioate	Oral	1	1	Nil	This dog had been treated with the recommended dose rate of this product for some time. When dog reached 19kg bodyweight, the owner increased the dose rate to the appropriate level. Three days after starting the higher dose rate the dog showed a change in behaviour and had difficulty standing. After seven days, the dog could not stand, had developed diarrhoea and was trembling. Treated by veterinarian at this time with antibiotics and diazepam. The tablets were stopped during hospitalisation and dog was able to stand. The following day she was given two more tablets and was unable to stand the following day. The dog almost fully recovered two weeks after the tablets were stopped. It was revealed that the dog may have been washed in a shampoo that contained an anticholinesterase compound. The label directions for this product clearly state that other anticholinesterase compounds must not be used concurrently with this treatment.	Caused by not using the product according to label directions. The label clearly states that other anticholinesterase compounds must not be used concurrently with this treatment.
Dexamethasone	Intravenous	1	1	Nil	Immediately after injection dog showed signs of irritation at injection site and appeared to become quite agitated. The dog collapsed briefly after this, but recovered.	Product related. This was an idiosyncratic allergic reaction.
Diazepam Ketamine hydrochloride Amoxycillin trihydrate	Subcutaneous & Intravenous Intravenous Subcutaneous	1	1	Nil	The dog developed a generalised urticarial reaction of the entire body about two hours after a routine desexing operation during which the treatments were given. This resolved following treatment with an antihistamine. Twelve hours later, oedema formed in the right foreleg, right hindleg and the right mammary chain. After forty-eight hours, the skin of these affected areas began to peel badly.	Possibly product related. The reaction observed in this case is very unusual, but skin reactions such as urticaria and pruritus have been seen after administration of amoxycillin, so it has been concluded that the reaction may have been associated with this product.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Distemper virus, adenovirus and parvovirus (attenuated)	Subcutaneous	3	3	3	All three pups vaccinated died within three days of being vaccinated, with varying signs of depression, diarrhoea and abdominal pain. On post mortem signs, were consistent with parvoviral enteritis.	Not product-related. These vaccines utilise non-virulent strains of the virus that have been extensively attenuated (weakened) by repeated passage through tissue culture and it is virtually impossible for any reversion to virulence to occur. Extensive safety testing has failed to show any evidence of this being possible.
Distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus type 2 (CPV2) (living attenuated) and living canine parainfluenza virus **Plus** Bordetella bronchiseptica	Subcutaneous	1	1	Nil	Urticaria developed over the entire body of the dog within one hour of being vaccinated.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus type 2 (CPV2) (living attenuated) and living canine parainfluenza virus **Plus** Bordetella bronchiseptica	Subcutaneous	1	1	Nil	Swellings developed around both eyes and the ears became red and hot one hour after injection of the product.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus type 2 (CPV2) (living attenuated) and living canine parainfluenza virus **Plus** Bordetella bronchiseptica	Subcutaneous	2	2	Nil	Both dogs developed oedema of the head shortly after being vaccinated.	Product-related. A Type I hypersensitivity reaction.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus type 2 (CPV2) (living attenuated) and living canine parainfluenza virus **Plus** Bordetella bronchiseptica	Subcutaneous	1	1	Nil	Two hours after vaccination the dog developed an itchy swollen face.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus type 2 (CPV2) (living attenuated) and living canine parainfluenza virus **Plus** Bordetella bronchiseptica	Subcutaneous	1	1	Nil	Two hours after vaccination puppy developed swellings around both eyes. This returned to normal eight to twelve hours after treatment with an intravenous corticosteroid.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus type 2 (CPV2) (living attenuated) and living canine parainfluenza virus	Subcutaneous	2	2	Nil	Both dogs developed facial oedema and generalised urticaria soon after treatment.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2 (CAV2), canine parvovirus type 2 (CPV2) (living attenuated) and living canine parainfluenza virus	Subcutaneous	2	2	Nil	These two dogs had been vaccinated with this product once before. Soon after vaccination, both dogs developed facial oedema and generalised urticaria.	Product-related. A Type I hypersensitivity reaction.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Distemper virus, canine adenovirus type 2, parvovirus type 2 (living attenuated) **Plus** Canine parainfluenza virus (living), Bordetella bronchiseptica (attenuated)	Subcutaneous	1	1	Nil	The dog was presented to the local veterinarian eight days after administration of this product, with a thickened plaque at the injection site approximately 5cm in diameter, 1.5cm thick. The lesion was non-painful.	Product-related. The timing post-vaccination and the fact that this was not a painful reaction would suggest that this was a reaction to the adjuvant in the vaccine.
Distemper virus, canine adenovirus type 2, parvovirus type 2 (living attenuated) **Plus** Canine parainfluenza virus (living), Bordetella bronchiseptica (attenuated)	Subcutaneous	1	1	Nil	Within one to two hours post-vaccination, the ears and face of this dog began to swell with oedema.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2, parvovirus type 2 (living attenuated), canine parainfluenza virus (living)	Subcutaneous	10	5	3	This breeder has had recurring problems with dogs reared in his kennels dying after being vaccinated. Deaths usually occur twenty-four hours to one week after vaccination. In this incident three pups died – within seven days of treatment. A post mortem of the second pup indicated gross signs of parvovirus and subsequent laboratory testing was positive for parvovirus. The third pup died showing similar signs. Other pups were treated with antibiotics and fluids and survived.	Not product-related. These vaccines utilise non-virulent strains of the virus that have been extensively attenuated (weakened) by repeated passage through tissue culture and it is virtually impossible for any reversion to virulence to occur. Extensive safety testing has failed to show any evidence of this being possible. The history also suggests that other factors may have been involved.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Distemper virus, canine adenovirus type 2, parvovirus type 2 (living attenuated) **Plus** Canine parainfluenza virus (living), Bordetella bronchiseptica (attenuated)	Subcutaneous	1	1	Nil	This dog was presented to the attending veterinarian approximately one and a half hours after being vaccinated with oedema of the ears and lips, skin irritation and itching. The dog was treated with cortisone, antihistamine and adrenaline and the oedema and irritation slowly resolved.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2, parvovirus type 2 (living attenuated) **Plus** Canine parainfluenza virus (living), Bordetella bronchiseptica (attenuated)	Subcutaneous	1	1	Nil	Within thirty minutes of vaccination, the dog developed skin irritation, facial oedema and swelling of the vulva. The itching and oedema resolved within twenty minutes of treatment with antihistamine, cortisone and adrenaline.	Product-related. A Type I hypersensitivity reaction.
Distemper virus, canine adenovirus type 2, parvovirus type 2 (living attenuated) **Plus** Canine parainfluenza virus (living), Bordetella bronchiseptica (attenuated)	Subcutaneous	1	1	Nil	Approximately four hours post vaccination, the dog developed facial oedema. This was treated successfully with corticosteroids.	Product-related. A Type I hypersensitivity reaction.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Distemper virus, canine adenovirus type 2, parvovirus type 2 (living attenuated) Plus Canine parainfluenza virus (living), Bordetella bronchiseptica (attenuated)	Subcutaneous	1	1	Nil	Approximately two hours post vaccination, the dog developed facial oedema and urticaria on the head. The dog also became disorientated and vomited once.	Product-related. A Type I hypersensitivity reaction.
Fenthion	External	1	1	Nil	Dog displayed signs of anorexia and lethargy several hours after the application of the product. The next day dog collapsed and was taken to a veterinarian who diagnosed pancreatitis. One month later the dog developed diabetes mellitus.	Possibly product-related. It is highly unlikely that this product played any part in this reaction and it appears that it was coincidental, although it is impossible to rule it out entirely.
Fipronil	External (back of neck)	14	1	Nil	Two weeks after the dog was treated with this product, small crusty sores appeared at the application site. The crusts came off revealing dark brown skin beneath.	Possibly product-related. A type of hypersensitivity reaction.
Fipronil	External	3	3	2	Twenty-four hours after application, one pup had died, and two others were showing neurological signs with excessive salivation, tremors and dilated pupils. One further pup died three days after treatment.	Possibly product-related although it is highly unlikely that this product was the cause of the reaction in these pups. No blood work or post mortems were performed, so it is impossible to determine the cause of death in these pups.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Fipronil	External	1	1	Nil	Dog screamed from apparent skin irritation immediately after application of product, which continued for one hour. Irritation reappeared later when dog became wet.	Possibly product-related. Some dogs are averse to being sprayed with anything, particularly around the face, so it is possible this dog was reacting simply to the act of being sprayed. The attending veterinarian in this incident reported that the dog appeared to be highly distressed and he felt the reaction was more severe than would occur from just being sprayed, although he could see no evidence of skin irritation to the product. This incident has been classified as possibly product related, and it is impossible to determine the cause of the reaction.
Imidacloprid	External	1	1	Nil	A raised, hairless, scabby and intensely pruritic dermatitis developed at the site of application of product, approximately thirty six hours after application.	Product-related. This incident was considered to be product related as there was a clear cause and effect relationship. It was most likely an allergic or irritation reaction to the product.
Imidacloprid	External	1	1	Nil	Owner accidentally applied product to dog's eye. Dog was presented at veterinary surgery with blepharospasm, watery eye, red eye, corneal oedema, miosis and slow pupillary reflex. Keratitis and uveitis was diagnosed.	Caused by not using the product according to label directions.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Imidacloprid	External	1	1	Ni1	One day after application of product, the owner noticed a change in the dog's behaviour. The dog became quiet and lay out in the sun for most of the day. The owner noticed that the dog's skin became very pink after this. Over the following eleven days, the dog became lethargic and developed diarrhoea and red ears. A veterinary examination took place fourteen days after the initial treatment took place. The diagnosis was heat stroke and intense erythema of all skin surfaces, the conjunctiva and the mucous membranes. The dog was hospitalised for the following five days, at which time it became weak and recumbent, with a painful abdomen, pale mucous membranes and oedema of the lungs. Skin ulcers formed on day 18 and covered 50% of the abdominal skin by day 19. The dog recovered fully with treatment.	Possibly product-related. The initial behavioural changes may have been related to the application of the product, although unlikely and the subsequent reactions were all part of a chain reaction that occurred after this.
Imidacloprid	External	3	3	Nil	The three dogs, from different households were treated at different times with this product. Within twelve hours the dogs appeared quiet, their appetites were reduced and they would not settle easily. No evidence of skin irritation was present.	Product-related. A clear cause and effect relationship between the administration of this product and the reactions observed tends to indicate that the incidents were product related.
Ivermectin	Oral	1	1	1	Dog consumed an unknown quantity of an ivermectin-containing product registered for use in horses. One and a half hours later it became ataxic and started salivating. The dog then went into a coma. The dog died three hours after onset of symptoms.	Caused by not using the product according to label directions.
Maldison	External	1	1	1	Some hours after being rinsed with this product the dog started vomiting and chewing at the top of its right front paw. The dog was treated by a veterinarian the following day, but died despite treatment. Post mortem results were inconclusive.	Possibly product-related. There is no evidence to indicate that this product was responsible for the death of this dog.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Medetomidine hydrochloride	Intravenous	2	2	Nil	Product was given as a sedative prior to desexing. Shortly after the injection the bitch developed profound apnoea and bradycardia (heart rate 40 beats per minute) and this continued for fifteen minutes. Appropriate treatments were given and the dog recovered. A male dog treated on the same day developed rapid onset of mucous membrane blanching; inaudible heart beat and distressed breathing. Recovered on administration of reversing agent.	Possibly product-related. Due to the mechanism of action of this chemical, heart rate and body temperature decrease. It is likely that these incidents were product related as the reactions observed occurred soon after administration of the product.
Milbemycin oxime Lufenuron	Oral	1	1	Nil	The dog was treated with this product monthly for six months. Approx. two days after each treatment, the dog developed a rash on the ventral abdomen, paws and back. The owner started using a different treatment regime on this dog and no further problems have been reported.	Product-related. This type of reaction is very unusual and was therefore determined to have been an idiosyncratic reaction.
Milbemycin oxime Lufenuron	Oral	1	1	Nil	This dog was treated twice with this product and after each treatment the dog developed black, loose faeces and became listless and off food within one to two days. Recovered within a day on each occasion.	Product-related. This is a very unusual reaction, although similar reactions have been reported overseas in dogs treated with these chemicals. There is a clear cause and effect relationship in this incident, which indicates that the reaction was most likely due to the administration of this product.
Oestradiol monobenzoate	Subcutaneous	1	1	Nil	Blood clots were passed from the dog's vagina approximately six weeks after product was administered according to label instructions for mesalliance. Resolved over the next week after treatment with a vitamin K preparation and antibiotics.	Possibly product-related. The use of this hormone is known to alter the oestrus cycle of animals significantly. This alteration to the oestrus cycle may have predisposed to the development of a uterine infection, which may have caused the vaginal bleeding.
Pentosan polysulfate	Subcutaneous	1	1	Nil	The dog became inappetent and lethargic on the day of treatment, which persisted for twenty four to thirty six hours. This reaction has occurred after each treatment.	Product-related. Similar reactions to these have been recorded previously after use of this chemical and are quite rare and usually only transient.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Pentosan polysulfate	Subcutaneous	1	1	Nil	Dog began vomiting three to four hours after treatment and continued for thirty six hours. The dog was lethargic and inappetent for a further thirty six hours.	Product-related. Similar reactions to these have been recorded previously after use of this chemical and are quite rare and usually only transient.
Pentosan polysulfate	Subcutaneous	1	1	Nil	This dog was treated three times with this product. After each treatment, the dog became weak, started trembling and had laboured breathing. On the third occasion the dog could not stand, lift its head or wag its tail, the eyes became very dull and both front legs became stiff, unable to voluntarily extend the carpal joints. The rectal temperature at this time was slightly elevated (39.1 degrees C).	Product-related. This was considered to be an idiosyncratic reaction.
Pentosan polysulfate	Subcutaneous	1	1	Nil	Product given on two occasions for treatment of degenerative joint disease of left coxofemoral joint. On each occasion vomiting occurred for the first 24-hour period. Diarrhoea commenced thirteen hours after injection and occurred six to eight times daily. On the first occasion tablets containing carprofen were given concurrently.	Possibly product-related. The use of non-steroidal anti-inflammatory agents concurrently with this product is contraindicated and this is clearly stated on the label.
Pethidine	Subcutaneous	1	1	1	An eleven-year-old papillon was presented to the veterinarian seriously ill with a suspected renal tumour. The dog underwent surgery to remove the affected kidney and was also desexed and had some teeth removed under the anaesthetic. The dog was given an injection of this product after the surgery. The dog died approx. four hours after this injection. The reporting veterinarian indicated that the dog was in a serious condition when presented prior to the surgery, and feels that the death was unrelated to this product. It was more likely due to the cancer and the stress of the operation.	Not product-related. Numerous factors were involved (eg high-risk patient, under went long anaesthetic and surgery). Nothing to indicate that the death was related to this product.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Phenylbutazone	Oral	1	1	1	The dog developed severe vomiting and gastroenteritis in the evening after being given the product for post operative swelling. Dog did not respond to owner's treatment of anti-emetics, fluids and eggs, and died three days after product was administered.	Possibly product-related. It is highly unlikely that a single dose of this product would cause these gastrointestinal signs. As no further assessment of the dog was made by the attending veterinarian it is impossible to determine the cause of death.
Pyrantel embonate Oxantel embonate Praziquantel	Oral	1	1	Nil	Thirty minutes after being given this product, the dog vomited. On presentation to a veterinarian the dog also had diarrhoea. The dog was hospitalised overnight and treated. It was released the following day. Two weeks later, the dog vomited again. It had not been treated with the product again. The dog had tolerated treatment with this product on two previous occasions. The attending veterinarian indicated that the dog might have had an underlying undiagnosed condition.	Possibly product-related. It is very unlikely that this product caused this dog to vomit. The attending veterinarian indicated that it was more likely that the dog had an underlying disease.
Pyrethrins Piperonyl butoxide MGK 264	External	2	2	Nil	This product was used three times on these dogs. After each application the skin of the dogs became red and they started to scratch.	Product-related. A Type I hypersensitivity reaction.

DOGS contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Pyrethrins Piperonyl butoxide	External	2	2	2	1. Product was applied carefully by owner with cloth to a pup. Within one minute of treatment, pup started yelping, running into the walls and frothing at the mouth. Over the next thirty minutes, the pup started convulsing, collapsed and stopped breathing. On veterinary examination the pup had pinpoint pupils, was salivating and convulsing. Despite treatment with sedatives and intravenous fluids, the pup died that night. 2. A second pup was purchased the next week. It ate some of the vomitus of the first pup and exhibited the same signs and died – a post mortem was performed which indicated a severe diffuse pulmonary oedema and congestion.	1. Possibly product-related. The cause and effect relationship between the application of this product and the pup becoming ill suggests that the product may have been responsible for the reaction observed. 2. The death of the second pup did not appear to have anything to do with use of this product..
Trimethoprim Sulfatroxazole	Intravenous	1	1	1	Five minutes after injection dog began Cheyne-Stokes breathing and died ten minutes after injection. Post mortem findings – Pyelonephritis.	The signs worsened despite treatment and the dog died approximately ten minutes later. According to one source (8), acute toxic effects to sulphonamide-trimethoprim combinations are most commonly associated with overdose or too rapid rates of intravenous drug administration. The amount of product administered in this case was twice the recommended dose, therefore the conclusion is that the product was not used according to label directions.

GOATS

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Ivermectin	Oral	35	35	29	Lactating goats were treated with this product in two groups three days apart. This off-label use of the product had been a practice of the owner for a number of years. Animals were depressed for two to three days after treatment. Deaths began three days after treatment. Symptoms prior to death included salivation, teeth grinding and vocalisation. The pathology report indicated severe, acute and recent hepatopathy. Clinical pathology results suggested mild hepatopathy in the un-drenched goats.	Caused by not using product according to label directions. A number of important issues are relevant in this case: • The farmer was using this product in a species it is not registered for in Australia, • The product should not have been used in lactating animals where the milk was used for human consumption, • It was found that these goats had pre-existing liver disease and the deaths that occurred appear to be related to this disease and unlikely to have been a direct result of the administration of this product.

HORSES

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Aminoacids Vitamins	Intravenous	1	1	1	The horse had been treated one week previously with the recommended dose of this product intravenously. On this occasion the owner only gave 10-15mL and the horse immediately became disorientated, collapsed, had white oral mucous membranes and died within one to two minutes. Post mortem revealed white froth in airways and no other abnormalities.	Possibly product-related. The method and route of administration of this product in this case may have had some bearing on the death of this horse. This type of reaction after intra-arterial injection has been reported before. It is therefore probable that the reaction caused by accidental intra-arterial injection.
Arginine hydrochloride Sodium glucuronate	Intravenous	1	1	1	Within two minutes of being given an intravenous injection of this product, the horse collapsed. It subsequently died about five minutes later.	Product-related. An anaphylactic reaction.
Ceftiofur sodium	Intravenous	2	2	2	1. On the fourth day after starting treatment, the first horse developed acute, febrile diarrhoea. The horse was hospitalised, intensive intravenous fluid therapy was commenced, plasma was given (I/V) and flunixin was given. By the third day of treatment for diarrhoea, the horse was improving. The next day, severe laminitis was diagnosed and the horse was euthenased. 2. Five days after starting treatment, the horse stopped eating and became depressed and developed diarrhoea. Fluids, electrolytes and probiotics were given by mouth. Anti-inflammatory doses of flunixin were given two to three times prior to death. The horse died about nineteen hours after signs were first seen.	Possibly product-related. It is important to note that there are a number of extenuating circumstances in both these incidents. The horses were in work and therefore under a certain level of stress and they were also being treated for bacterial infections. Acute febrile diarrhoea is known to occur in horses under stress when treated with antimicrobials, but it can also occur in horses not receiving treatment with an antimicrobial product. Therefore it is difficult to determine the cause of the reaction in these incidents.
Flumethasone Dimethyl sulfoxide	External	1	1	Nil	This product was applied to treat swelling of the forelimbs. Blistering occurred where the product was applied. Scarring occurred when the skin healed. White marks remain on both forelegs at the site of blistering.	Product-related. It is clear that the site of application of this product is where the lesions and scarring developed, although it should be noted that this type of reaction is extremely rare.

HORSES contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Iron ammonium citrate Cobalt gluconate Cyanocobalamin Copper gluconate Pyridoxine hydrochloride Choline chloride Riboflavine sodium phosphate Biotin Niacinamide Inositol d-panthenol l-lysine hydrochloride Racemethionine Glycine	Intramuscular	1	1	1	Rapid onset of anaphylaxis - trembling staggering and collapse three minutes after intramuscular injection of the product. Veterinarian confident that accidental intravenous injection did not occur. Previous record of exposure to the product is unknown.	Product-related. A Type I hypersensitivity reaction.
Morantel tartrate	Oral	1	1	Nil	The day after treatment the foal showed signs of colic. It was treated under veterinary advice with an analgesic. Three and a half hours later the symptoms of colic returned and veterinary advice was sought. One hour later the foal was taken to the veterinary hospital. The next day a laparotomy was performed and proximal enteritis was discovered. The foal continues to have relapses of lethargy, fever spikes, and abnormal blood counts.	Possibly product-related. A review of the previous three years adverse drug reaction reports indicates that this is the first report of its kind for this product.
Moxidectin	Oral	1	1	Nil	This horse became lethargic approximately eight hours after being treated with this product. It was still able to stand.	Caused by not using the product according to label directions. The horse was treated with approximately ten times the recommended dose.

HORSES contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Moxidectin	Oral	2	1	1	Two geldings were treated with this product. The following day one was swollen around its mouth. The owner reports it has happened in the past. The horse developed severe colic the next day and was admitted to hospital. It was euthanased the following day due to severity of signs. Post mortem examination revealed ischaemic necrosis of part of small intestine.	Possibly product-related. This horse may have developed an allergic reaction to the product, particularly as the owner had noticed that the horse had reacted previously.
Moxidectin	Oral	1	1	1	An eight week old miniature pony was given twice the recommended dose by mistake. The foal was found dead the next day.	Caused by not using the product according to label directions. Accidental overdose.
Moxidectin	Oral	1	1	Nil	A six week old foal was given a full tube of this product by mistake. It became ataxic approximately twelve hours after treatment. It then collapsed and became comatose. It improved with veterinary treatment and recovered six days after being given the product.	Caused by not using the product according to label directions. Accidental overdose.
Moxidectin	Oral	1	1	Nil	A four week old foal was given five times the recommended dose of this product. A reaction occurred fourteen hours after the treatment. It developed profound depression and ataxia.	Caused by not using the product according to label directions. Accidental overdose.
Moxidectin	Oral	1	1	Nil	Twenty fours after treatment this horse developed swelling around the eyes. The symptoms disappeared twenty four hours after being first noticed.	Possibly product-related. This reaction is most likely an anaphylactic reaction.
Moxidectin	Oral	1	1	Nil	This horse developed “lumps” on the neck and back the day after treatment. This progressed to a generalised “lumpy” skin the following day.	Product-related. A Type I hypersensitivity reaction.
Moxidectin	Oral	2	2	Nil	Both horses treated with this product developed oozing skin lesions in the axilla/groin areas twenty four hours after treatment.	Possibly product-related. A Type I hypersensitivity reaction.

HORSES contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Oxfendazole Trichlorfon	Oral	1	1	Nil	Ulceration occurred inside the mouth of the horse the day following treatment. The face and lips became swollen and there was excessive salivation. The horse also became dull and depressed.	Product-related. It is clearly stated on the label that care must be taken when administering this product and to place the application syringe on the back of the tongue and not between the teeth and gums.
Oxfendazole Pyrantel embonate	Oral	1	1	Nil	The horse became inappetent soon after treatment and developed mild scouring and colic.	Product-related. Faecal softening is most significant at twelve hours post administration. The cause is unknown. Incidence of 0.06% of treated horses. Veterinary attention sought in 0.01% of horses treated.
Oxfendazole Pyrantel embonate	Oral	4	4	Nil	These horses all developed signs of diarrhoea soon after treatment.	Product-related. Faecal softening is most significant at twelve hours post administration. The cause is unknown. Incidence of 0.06% of treated horses. Veterinary attention sought in 0.01% of horses treated.
Oxfendazole Pyrantel embonate	Oral	1	1	Nil	This horse developed diarrhoea and signs of colic and abdominal pain.	Product-related Faecal softening is most significant at twelve hours post administration. The cause is unknown. Incidence of 0.06% of treated horses. Veterinary attention sought in 0.01% of horses treated.
Oxfendazole Pyrantel embonate	Oral	4	4	Nil	These horses all developed diarrhoea.	Product-related. Faecal softening is most significant at twelve hours post administration. The cause is unknown. Incidence of 0.06% of treated horses. Veterinary attention sought in 0.01% of horses treated.
Oxfendazole Pyrantel embonate	Oral	55	55	Nil	All these horses developed diarrhoea.	Product-related. Faecal softening is most significant at twelve hours post administration. The cause is unknown. Incidence of 0.06% of treated horses. Veterinary attention sought in 0.01% of horses treated.
Permethrin	External	1	1	Nil	Two to three days after application the skin became scalded where the product had been applied - neck withers, back, rump. The skin came off in dry sheets and left scarring.	Product-related. Possible chemical and ultraviolet light interaction. New formulations are being tested by registrant to determine possible cause.

HORSES contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Procaine penicillin	Intramuscular	1	1	Nil	Within one minute of administration horse showed extreme nervousness, slight incoordination and muscular twitching. Recovered within thirty minutes.	Product-related. This type of reaction has been known to occur in a very small percentage of horses being treated with this product.
Procaine penicillin	Intramuscular	1	1	Nil	Horse collapsed within one minute of administration, struggled to feet, struck out at walls repeatedly. Appeared blind. Settled after approximately three-quarters of an hour. Then recovered fully over the next four hours.	Product-related. This type of reaction has been known to occur in a very small percentage of horses being treated with this product.
Procaine penicillin	Intramuscular	1	1	Nil	Within minutes of treatment horse began tossing head and became unsteady.	Product-related. This type of excitation reaction has been reported before in a very small percentage of horses treated.
Procaine penicillin	Intramuscular	1	1	1	The horse was presented with a suspected respiratory infection – it was in poor condition and had a slight cough. After approx. two weeks the horse became lethargic, its breathing became laboured and its heart rate was elevated. A clinical examination revealed a normal temperature, elevated heart rate and respiratory rate, slight dehydration and poor condition. A blood sample revealed an elevated white blood cell count. The horse was treated with this product for a suspected infection. The following day the horse was still lethargic and its heart rate was still elevated. A lump appeared where the injection had been given. The following day the lump had increased in size, the horse was reluctant to move and stopped eating and drinking, and its heart rate was still elevated. Horse was found dead in the paddock the next morning.	The cause of the lump at the site of the injection was product related. The cause of death in this case is unknown. The horse was obviously seriously ill at the time of examination by the attending veterinarian, and there is no obvious relationship between the death and the use of this product.

HORSES contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Procaine penicillin	Intramuscular	2	2	Nil	Painful diffuse swellings developed at the injection sites in both these horses. The horses became mildly ataxic and developed lameness and anorexia.	Possibly product-related. There may have been some local reactions to these injections and some pain response, which resulted in the ataxia and anorexia.
Procaine penicillin	Intramuscular	2	1	Nil	The attending veterinarian who described it as an extreme hypersensitivity reaction reported a 'violent reaction'. The horse settled after about ten minutes.	Product-related. A Type I hypersensitivity.
Procaine penicillin	Intramuscular	1	1	1	Horse died within two minutes of treatment, no post mortem was performed.	Product-related. Most likely an anaphylactic reaction.
Procaine penicillin	Intramuscular	2	2	Nil	Penicillin was given by intramuscular injections twice daily for five days. After this, the horses became uncontrollable and highly nervous.	Product-related. These types of excitation reactions have been observed in a small percentage of horses treated with products containing procaine penicillin.
Procaine penicillin	Intramuscular	1	1	1	Approximately two minutes after injection the horse became weak, fell to the ground and stopped breathing. Its heart continued to beat for three to four minutes before it died.	Product-related. An anaphylactic reaction.
Procaine penicillin	Intramuscular	1	1	Nil	Two minutes after injection the horse developed hyperaesthesia, twitching and miosis. Horse was very alert and returned to normal in five to ten minutes.	Product-related. These types of excitation reactions have been observed in a small percentage of horses treated with products containing procaine penicillin.
Propantheline bromide	Intravenous	3	2	Nil	Two mares developed colic within forty-five minutes of administration of product by veterinarian for pregnancy diagnosis. One was classified by veterinarian as severe and the other moderate. Recovery occurred six to eight hours after treatment.	Product-related. It is recognised that by reducing intestinal motility development of ileus, which may lead to a build up of gas and flatulent colic is possible. Occurrence in two horses at same time on same property may indicate other factors known to contribute to increased gas production eg high concentrate diets, dietary change, enteritis, parasite infestation and electrolyte imbalance, particularly hypokalaemia.

HORSES contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Romifidine	Intravenous	1	1	Nil	This horse developed paraphimosis the day following treatment. The condition was still present fourteen days later.	Product-related. Reversible partial penile prolapse is a possible side effect with these types of sedatives in horses.
Stanozolol	Intramuscular	5	1	1	Injection inadvertently given intra-arterially. The animal became excited, reared, fell and hit its head. Flaccid hind limb paralysis and spastic front limb paralysis resulted along with nystagmus. Treatment for the cerebral injury was unsuccessful and the animal was destroyed.	Caused by not using the product according to label directions.
Trimethoprim, Sulfadiazine	Intravenous	1	1	Nil	After a slow intravenous injection of 12mL of this product, the horse reared and fell. It lay with its legs in extension and jerking. It held its breath and tucked up its abdomen and its eyes rolled back into its head. Relaxed after five minutes and stood. Recovered with no ill effects.	Product-related. Appears to have been an acute hypersensitivity reaction.
Vitamin E acetate Selenium	Intramuscular	4	3	Nil	Three of the four horses given this product by intramuscular injection showed signs consistent with acute stress and pain. One filly went down, was in acute distress for three hours and stopped eating. All horses were still affected the next day. All horses showed very large swellings at the injection sites, ranging in size from twelve to twenty five centimetres in diameter, on the neck at the injection sites.	Possibly product-related, although there are a number of factors to take into account: • Horses react to painful stimuli in a number of different ways, and a deep intramuscular injection (such as these horses received) can cause signs of acute pain. • Local reactions occur at the site of many injections, and the swellings that occurred in these horses would not be considered unusual.

RABBITS

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Fipronil	External	1	1	1	The rabbit began jaw champing approximately forty-eight hours after administration of this product. It then had a seizure twelve hours later, was treated with diazepam and washed with soap and water. Four days later the rabbit had another seizure and died.	Caused by not using product according to label directions.
Fipronil	External	1	1	1	Twenty-four hours after treatment, this rabbit showed signs of jaw champing and seizures. Despite rabbit being washed and treated with diazepam, it died.	Caused by not using product according to label directions.
Inactivated HVD virus	Subcutaneous	1	1	Nil	Two weeks after vaccination an area of alopecia, redness, crusts and scales, approximately six centimetres in diameter, was discovered on the back of the neck and shoulder area, in the vicinity of the vaccination site.	Product-related. This reaction is most likely due to a hypersensitivity reaction to the product.
Inactivated HVD virus	Subcutaneous	1	1	Nil	An abscess was noticed at the injection site two days after vaccination. The rabbit had a slight fever (temperature 39.8 degrees C).	Possibly product-related. This type of problem can occur with any injection, as bacteria can be transported under the skin along with the insertion of the needle. This report is classified as being possibly product related, and there is no indication that this brand of vaccine is any more likely to cause this type of reaction than any other.

SHEEP

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Ivermectin	Oral	34000+	700	574	Numerous reports have been received concerning injuries that have occurred to sheep after treatment with these two products. It appeared that during application of the capsule, the pharynx of the sheep had been damaged causing death in a number of cases. The wings at the junction with the capsule have square, sharp edges that may have contributed to perforations of the pharynx in some cases. Most post mortems performed indicated the capsule was positioned retropharyngeally during application.	Caused by not using the product according to label directions. The label of this product has been changed to emphasise the importance of keeping the neck of sheep being treated straight to prevent injuries to the pharynx.
Ivermectin	Oral	1000	28	22	Eight sheep were found dead on the day following treatment. Post mortems of six sheep showed severe, acute necrosis, abscessation and cellulitis of the neck associated with pharyngeal perforation thought to be due to misplacement of capsules during administration.	Caused by not using the product according to label directions. The label of this product has been changed to emphasise the importance of keeping the neck of sheep being treated straight to prevent injuries to the pharynx.
Ivermectin	Oral	Not recorded	Not recorded	Approx 1%	Sheep in very good condition were treated four weeks prior to lambing. An average mortality of 1% was seen in the treated animals. Post mortems showed capsules lodged in throats.	Caused by not using the product according to label directions. The label of this product has been changed to emphasise the importance of keeping the neck of sheep being treated straight to prevent injuries to the pharynx.

SHEEP contd.

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Ivermectin	Oral	300	10	7	Nine days after treatment, twelve-month-old ewes were found dead. All three post mortems carried out showed capsule penetration of cervical oesophagus or retropharyngeal area, with lodgement of the capsule in the hypaxial musculature of the neck.	Caused by not using the product according to label directions. The label of this product has been changed to emphasise the importance of keeping the neck of sheep being treated straight to prevent injuries to the pharynx.
Levamisole Copper Cobalt Selenium Iodine Zinc	Oral	400	80	80	Within minutes of drenching, the lambs started shivering, frothing at the mouth, became incoordinated and some had mild convulsions before dying. All ages and weights of lambs were affected (ie some of the older and heavier lambs died). Some lambs were not treated with this drench and there were no deaths amongst these.	Product related. There is a clear cause and effect relationship between the administration of this product and the resulting clinical signs observed.
Levamisole hydrochloride Cobalt, selenium, iodine & zinc	Oral	350	2	2	Two sheep from a mob of 350 died soon after being treated.	Caused by not using the product according to label directions. In this case, the farmer returned a sample of the product he was using to drench these sheep. The sample returned was not this product, but another registered product. So it appears that the farmer may have inadvertently drenched the sheep with an incorrect product.
Moxidectin	Oral	515	Approx 10%	4	Lambs were drenched in two groups on different days. Three died and others noted to be pale with sub-mandibular oedema.	A veterinary post mortem indicated that the sheep still had a heavy worm burden. The sheep were drenched a second time with the same product under the supervision of the product representative and faecal samples indicated that the drench was 100% effective. It was therefore decided that a number of sheep may have been missed at the initial drenching, and the incident was classified as caused by not using the product according to label directions..

Appendix B

Summary of Suspected Adverse Experience Reports (Lack of Efficacy Category) 1997 and 1998

All reports of lack of efficacy received in 1997 are presented in this appendix, including those where it was considered that a lack of efficacy was not proven and those where it was not possible to decide on a classification.

As stated for the previous category, this summary table is intended only to provide general information about the types of reactions that veterinarians, animal owners and others have voluntarily reported to the NRA or the manufacturer after use of the product. The information in the tables is not by itself a basis for determining the safety and efficacy of a given product or for comparing one product with another, nor can it be used to predict the frequency of occurrence of a reaction.

CATTLE

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Cloxacillin	Cattle Intra-mammary	5	3	2	Five cows were treated at drying off with this dry-cow therapy. Three days after application, three cows were diagnosed with toxic mastitis. A multi-resistant strain of bacteria was isolated from the affected cows.	Possibly product-related, although highly unlikely. The report indicated that the batch of product in question was sterile at manufacture. The bacteria that was isolated from the milk is an environmental pathogen which is part of normal faecal flora and is commonly found as a teat contaminant. There is also question about the experience of the person who applied the dry cow therapy.
Hydrolysed Linseed Fatty Acids	Cattle External	5	3	2	The teats of five cows were cleaned with product before application of a dry cow therapy. Three days later three cows were diagnosed with mastitis.	Possibly product-related, although highly unlikely. The report indicated that the batch of product in question was sterile at manufacture. The bacteria that was isolated from the milk is an environmental pathogen which is part of normal faecal flora and is commonly found as a teat contaminant. There is also question about the experience of the person who applied the dry cow therapy.
Monensin	Cattle Oral	?	1	1	One steer died two months after application of capsule for control of bloat. Capsule was examined after retrieval. Testing showed payout for this capsule to be lower than acceptable. In vitro testing of batch Of capsules prior to release indicates normal release rate.	Product-related. The reason for the slow payout of this capsule is unknown, but clearly there was a defect in the product, which contributed to the death of this animal.
Monensin	Cattle Oral	?	1	1	Two months and two weeks after the application of a capsule the steer died. The capsule was retrieved and had paid out completely seventy seven days after application.	Product-related The capsules should continue to pay out for 100 days at least. Reason for increased rate of payout of this capsule is unknown, but again it is clear that the defect in the product contributed to the death of this animal.

DOGS

Active constituent	Route of administration	No. Treated	No. Reacted	No. Died	Reported Adverse Reaction	Classification and comments
Cythioate	Oral	6	6	6	The owner of a boarding kennel reports that some of her clients have lost dogs from tick paralysis despite being on this preventative treatment. No further details available.	Possibly product-related. The label of this product indicates that searching the dog thoroughly each day is vital as ticks can attach and inject toxin before they are killed by this product, although this is rare.
Fipronil	External	1	1	1	The dog was presented to the vet with Grade II Tick paralysis fifteen days after being treated with this spray. Six days after being treated with the Top Spot the dog developed tick paralysis again and died.	Possibly product-related. The label of this product indicates clearly that searching the dog thoroughly each day is vital as ticks can attach and inject toxin before they are killed by this product, although this is rare.
Fipronil	External	1	1	Nil	Twenty days after application of top spot for tick control a live tick was removed from the dog.	Caused by not using product according to label directions. Tick control by top spot application is only fourteen days and it appears that the tick attachment occurred outside effective life of treatment.
Pyrantel embonate	Oral	8	8	Nil	1. Pups were treated at 2 weeks old with tablets. The owner noticed that the tablets passed through completely unchanged (undigested). 2. The pups were treated again at 4 weeks of age with a puppy suspension (same brand). After two hours all pups were unhappy and whining. They started groaning and had diarrhoea. The next day, two pups continued to pass diarrhoea, started vomiting and stopped eating. They were treated with electrolytes orally and improved over the next ten days.	1. Product-related. It is clear that as the tablets passed out undigested then they would have been ineffective. It is important to note that the digestive transit time of pups can vary considerably especially if they have diarrhoea, which dramatically reduces the time in which the tablets can be digested. 1. Possibly product-related. It appears that the treatment given at two weeks of age was ineffective and ideally the pups should have been re-wormed sooner.

Appendix C

Summary of Reports of Human Adverse Experiences Related to use of Veterinary Chemicals

Active Constituent	Route of Exposure	No Reacted	No. Affected	Reported Adverse Reaction	Comments
Moxidectin	Skin contact	1	1	After using this product on two occasions, the farmer developed skin irritations, feelings of a "head cold" and diarrhoea.	This was diagnosed by the doctor as "industrial dermatitis", which is a form of contact allergy.
Olaquindox	Skin contact	1	1	Man developed photo-sensitisation of his hands and neck soon after handling this product on a number of occasions.	This was determined to have been as a result of an allergic reaction to this product.

Conclusions

During the first four years of operation of the AERP, the number of voluntary reports has remained constant, averaging 112 reports per annum. While this number of reports is relatively low, considering the quantity of veterinary chemicals used each year, it has been possible to identify and address specific concerns with individual products in the market place.

Although approximately half of the reports received during 1997 and 1998 were classified as product related, many of them related to unpredictable or idiosyncratic reactions. Such reactions include anaphylaxis, direct toxic effects on organs that are associated with actions unrelated to any desired therapeutic effect and aberrant responses in different species. These adverse reactions will continue to be monitored to detect possible defects with these products.

About one quarter of the reports were classified as possibly product related (where the NRA is not satisfied that the product was responsible for the reaction but the possibility that the product was implicated cannot be excluded). As no clear conclusions could be drawn from these reports, they did not result in regulatory action or outcomes.

Approximately one quarter of the reports received during 1997 and 1998 were classified as either not product related or related to products not being used according to label directions (which includes poor or incorrect use and off label use). Evaluation of these types of reports resulted in a number cases where regulatory action was taken. These included:

- Label changes

Twelve products were identified as requiring a change to their labels. Some reports involved allergic responses by factory and farm workers being exposed to a pig feed premix. A label change was recommended after evaluation of these reports and other scientific literature. The revised label will carry a warning statement indicating that care must be taken when handling these products as there is the potential for such allergic reactions.

Other reports included sheep drenching products that were often being administered incorrectly. A warning statement has been included on the label of these products to increase user awareness of these potential problems.

- Notification to veterinarians on restrictions on use

The AERP received a number of adverse reaction reports involving a flea treatment for cats and dogs being used off-label on rabbits. In these reports, after the rabbits were treated, they developed neurological signs and in most instances died within two days. The registrant has been requested by the NRA to inform the veterinary profession of possible links between the product and adverse reactions in rabbits.

- Review of active constituent

In one report three dogs chewed on a tick collar containing the active constituent amitraz. Within a few hours of this the dogs became disorientated, collapsed and required veterinary

attention. While it was concluded that the current label instructions and warning statements on this product are adequate, further consideration of these details is to be undertaken.

It is important that the veterinary profession, the public and manufacturers of veterinary chemical products continue to support the AERP by reporting **all** suspected adverse experience reports so that appropriate steps can be taken to maintain the high quality of veterinary products in the Australian market.

GLOSSARY

Analgesic	pain relieving treatment
Anaphylaxis	an exaggerated allergic reaction of an animal to a foreign protein or other substances
Angioneurotic	large painless areas of swelling in the subcutaneous tissues, usually as a result of hypersensitivity reactions
Apnoea	a period of cessation of breathing
Ataxic	unsteady walking action due to muscular incoordination
Blepharospasm	spasm of the muscle of the eyelid, resulting in continued blinking
Bradycardia	a decrease in the heart rate, below 60bpm for cats and dogs
Cellulitis	an inflammatory process within solid tissues
Cervical	pertaining to the neck
Cheyne-Stokes breathing	breathing characterised by rhythmic waxing and waning of the depth of respiration
Colic	a general term for abdominal pain
Coxofemoral joint	hip joint
Cyanotic	blue discolouration of the mucous membranes and other tissues due to a lack of circulating oxygen in the blood
Emphysema	pathological accumulation of air in the tissues
Enteritis	inflammation of the intestinal lining causing diarrhoea, dehydration and abdominal pain
Haemoconcentration	an increase in the formed particles in the blood, usually due to a decrease in the fluid content – eg clinical dehydration
Haemolysis	breakdown of the red blood cells with release of haemoglobin
Hepatopathy	disease of the liver
Hypaxial	beneath the spinal column
Hyperaesthetic	a state of abnormally increased sensitisation to touch and other stimuli
Ischaemic	deficiency of blood supply
Jaundice	yellow discolouration of the skin, mucous membranes etc, due to a high level of liver enzymes in the blood as a result of liver disease or injury
Keratitis	inflammation of the iris
Laparotomy	surgery of the abdominal cavity
Mésalliance	mismating
Miosis	excessive contraction of the pupil
Necrosis	death of an area of tissue
Neuropathy	a general term denoting disturbances in the peripheral nervous system
Nystagmus	involuntary movement of the eyeballs in unison
Ocular	pertaining to the eye
Oedematous	abnormal accumulation of fluid in body cavities and under the skin
Paraphimosis	swelling of the penis resulting in the inability to retract it

Parenteral	administration of a treatment by one of the following routes – subcutaneous, intramuscular, intrasternal intravenous
Parvovirus	viral infection of dogs that is characterised by diarrhoea, dehydration and pyrexia
Pericarditis	inflammation of the tissue that surrounds the heart
Peritracheal tissue	tissue immediately surrounding the trachea
Pharynx	the throat
Pleura	the tissue surrounding the lungs in the thoracic cavity
Pruritus	irritation and itching
Pyelonephritis	inflammation of the kidney
Pyoderma	any infected skin disease with production of pus
Pyrexic	animal suffering from a high fever
Retropharangeal	behind the pharynx
Sclera	the hard, white outer coating of the posterior eyeball, which connects anteriorly with the cornea
Seropurulent	mixture of serum (watery blood fluid) and pus
Urticaria	vascular reaction of the skin as a result of contact with a chemical or may be immunologically based
Uveitis	inflammation of the iris