Veterinary Medicines Directorate

Veterinary Pharmacovigilance in the United Kingdom

Annual Review 2016

Protecting animal health, public health and the environment

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Veterinary Pharmacovigilance in the United Kingdom

Annual Review 2016

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Introduction

Within the UK, vets, animal owners and other people who work with animals administer many millions of doses of different types of veterinary medicine to animals every year. In a relatively small number of cases, an adverse event (AE) occurs. This may occur during, or sometime after, the use of a medicine.

Veterinary professionals, animal owners (including farmers) or anyone else who has reliable knowledge of the incident can report an AE either to the company marketing the medicine or to the VMD.

Veterinary pharmacovigilance is the monitoring of all AE reports for emerging patterns of undesirable effects, following the use of veterinary medicines.

An **adverse event** (AE) is any observation in animals or humans that is unfavourable and unintended and that occurs after any use of a veterinary medicine. Even if you think it is unlikely that a medicine was responsible for an AE, you can still report it.

A **suspected adverse reaction** (SAR) is an event that involves the development of side effects in animals or humans after any use of a veterinary medicine. A **safety** report describes an event involving a suspected adverse reaction.

A **suspected lack of expected efficacy** (SLEE) has occurred when a product has not worked as well as expected. Some safety reports also involve an element of lack of efficacy. In these cases, we record 'lack of efficacy' as one of the clinical signs.

A **serious adverse event** results in death, is life-threatening, ends in significant disability or incapacity, a congenital anomaly or birth defect, or results in permanent or prolonged signs in treated animals. All events in which a person experiences an adverse reaction are serious AEs.

An **environmental incident** is an event in which a veterinary medicine affects wildlife or plants. This happens when someone either accidentally or deliberately releases a medicine into the environment.

During 2016, VMD's Pharmacovigilance team received and assessed 6559 adverse event reports. This is an increase of over 15% on the previous year.

Most of these reports describe events that occurred in animals during or after the use of authorised veterinary or human medicines. Many reports involved the use of multiple products, some of which may not have been authorised medicines.

Some reports describe reactions experienced by humans exposed to products used to treat animals. Others involved the detection of the residues of veterinary medicines in a food product intended for human consumption, usually milk, before it enters the food chain.

Figure 1 shows the numbers of different types of report received during 2016 and the animal species associated with those reports. Spontaneous reports are those that occur after normal everyday use of products. Non-spontaneous reports are from scientific literature or from scientific studies.

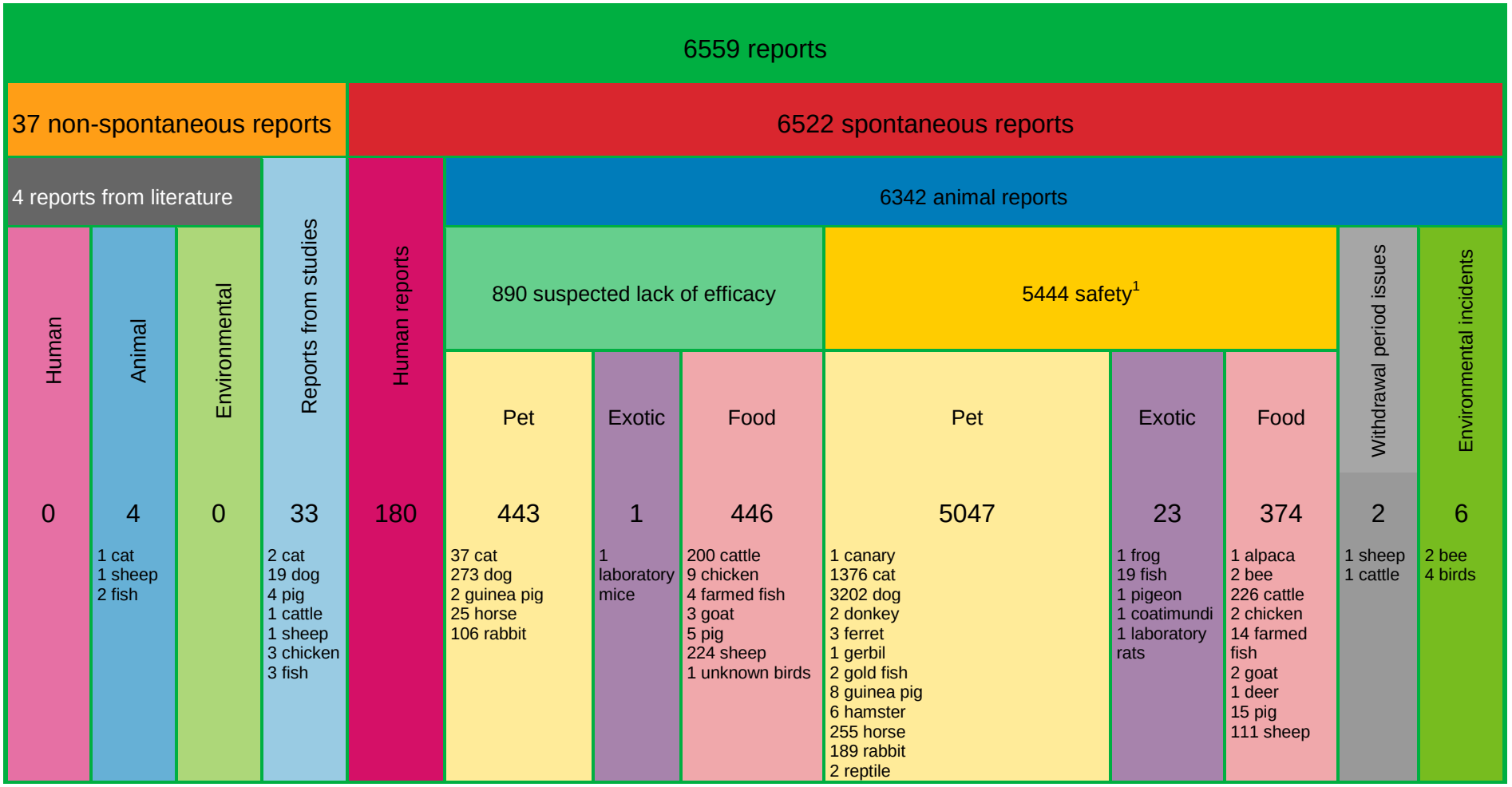


Figure 1 Number of reports of different types received during 2016 and the animal species associated with them

[1] Some safety reports involve a lack of efficacy element; in these cases, we record 'lack of efficacy' together with any other clinical signs observed.

Important points to note

This review summarises the spontaneous and non-spontaneous reports received by the VMD's Pharmacovigilance team during 2016.

Information from Periodic Safety Update Reports, which companies that own or market authorised veterinary medicines (known as Marketing Authorisation Holders or MAHs) submit to us for each product at intervals of between 6-months and 3-years, is not included in this review. These reports summarise all adverse events involving each product during the period of the report. We are unable to extract this information into individual incident reports in order to add them into our database.

MAHs are obliged to send all serious animal and all human AE reports to us within 15 days of becoming aware of an incident. Although there is no legal obligation, according to their Code of Professional Conduct[2], vets should report all adverse events either to the VMD or to the company that markets the product involved.

In the Annex of this review you will find a glossary explaining some of the more technical clinical terms used.

Remember:

- The number of treatments per year for some types of product is much higher than other types of product. It is likely that there will be more reports associated with those types of product.
- All reports from MAHs, most of which are serious, are included in this annual review, together with those received directly from vets and other people. The information summarised in this review relates to the most severe events that may occur following the use of different types of veterinary products.
- Each report may involve one or a combination of different types of product.
- We record all clinical signs described in a report, even if some may have been unrelated to the products used.
- We acknowledge that many of the clinical signs, reported in a particular case, relate to the products used. If we find a pattern of signs not previously related to a particular product, we will take regulatory action to add the new sign(s) to the product information.
- The use of multiple products, both medicinal and non-medicinal, will complicate the interpretation of the information summarised in this review, as each product may contribute additional clinical signs.
- Each report may describe adverse events in more than one animal,

[2] Code of Professional Conduct for Veterinary Surgeons and Supporting Guidance, 4. Veterinary medicines, paragraph 4.50 www.rcvs.org.uk/setting-standards/advice-and-guidance/code-of-professional-conduct-for-veterinary-surgeons/supporting-guidance/veterinary-medicines

particularly those involving farm animals.

- We assume that administration of all products was according to the instructions, unless specifically described otherwise.
- A death is not always directly associated with the use of any product involved. Factors other than welfare, such as financial constraints, can affect the decision to euthanase an animal. Reporters often record death by euthanasia simply as death. Some animals are so sick that no treatment is capable of maintaining life, and death is inevitable. Some products used as end-of-life treatments will have a disproportionately high association with death, even though they may not be the cause.
- You cannot use the information provided in this review to compare the safety of one authorised veterinary medicine with another. Veterinary professionals should discuss and agree on the choice of product to use in a particular instance with animal owners.

Who tells VMD about adverse events

Most of the AE reports that we receive come from MAHs (61% in 2016, as in 2015). The majority of reporters contact the MAH of the product involved, as this is the best way to get immediate advice. We received the remaining 39% directly from the reporter.

Social media

We are aware of various groups and campaigns organised through different social media forums. These groups often share experiences of particular brands of veterinary medicine, but they also gather and share information from elsewhere on the internet. Often this information relates to the US market, not the UK's. As the populations of cats and dogs in the US are approaching 10 times those in the UK, the absolute number of reported adverse events is likely to be 10 times higher. Therefore, these figures, without any indication of the number of uses, may stir up a disproportionate level of concern in the UK.

We cannot accept descriptions of adverse events reported through these social media channels. Often it is not clear whether the events occurred within the UK, or the information provided is insufficient to determine any product involvement.

If you are motivated enough to use social media to discuss an adverse event that you have seen, you must also report it to us, using the online reporting form[3].

In this way you will have the opportunity to tell us the full history of the event, including

- the species, breed, age and general condition of the animal involved
- which products were used, why they were used, how much, when and by whom they were administered
- when did you notice that there was something wrong with your animal
- what exactly was wrong
- was any treatment given
- what was the final outcome of the adverse event

Only by gathering sufficient numbers of similar cases, will we be able to determine whether there is actual product involvement, and therefore take regulatory action to change the marketing authorisation of any product, or in extreme circumstances suspend or withdraw the marketing authorisation.

Figure 2 shows the number of reports sent by different types of direct reporter.

[3] Report a problem with an animal medicine, www.gov.uk/report-veterinary-medicine-problem

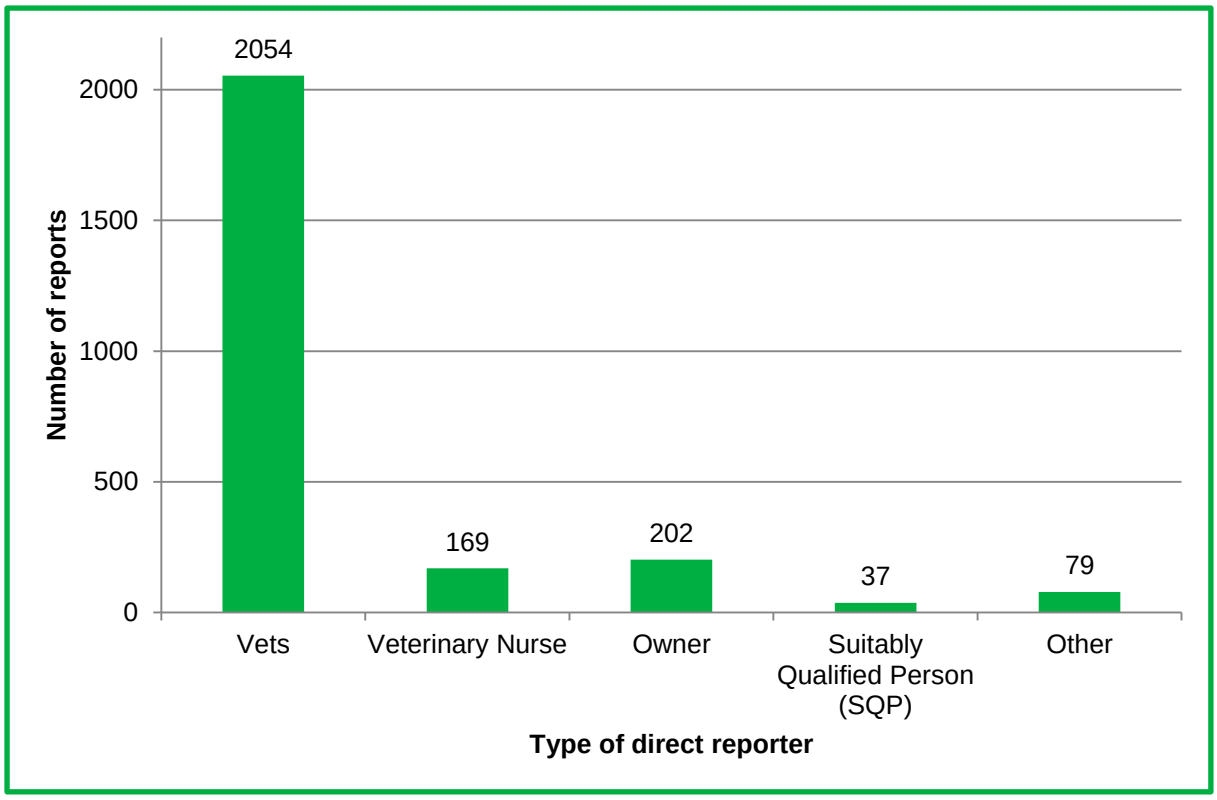


Figure 2 Number of reports from different types of direct reporters

Suitably Qualified Persons (SQPs) are authorised to prescribe and supply certain veterinary medicines. These medicines have mostly preventative uses, for example, internal and external anti-parasitic medicines, farm animal vaccines and nutritional supplements. They often work in vet surgeries, livery stables or agricultural merchants. Most 'Other' reporters were other vet practice staff.

There should be no need to report an event to both the MAH and us, but if you do, please tell us. When, as either a vet or an animal owner, you report an adverse event, we recommend that you let any other parties know that you have done so. This will help reduce the number of duplicate reports we receive and have to identify.

When you submit information to us using the online reporting form[4], you will get an automatic acknowledgement and a reference number for your records.

[4] Report a problem with an animal medicine www.gov.uk/report-veterinary-medicine-problem

Types of report

Figure 3 shows that the vast majority of reports that we receive describe events following normal everyday use of veterinary medicines and other veterinary products. These are called ‘spontaneous’ events. Reports involving the environment are usually also spontaneous.

‘Reports from studies’ are associated with clinical or field trials. ‘Reports from literature’ are found by MAHs searching scientific publications for events that may be associated with their or similar products. These are called ‘non-spontaneous’ reports. Some environmental incidents come from scientific literature.

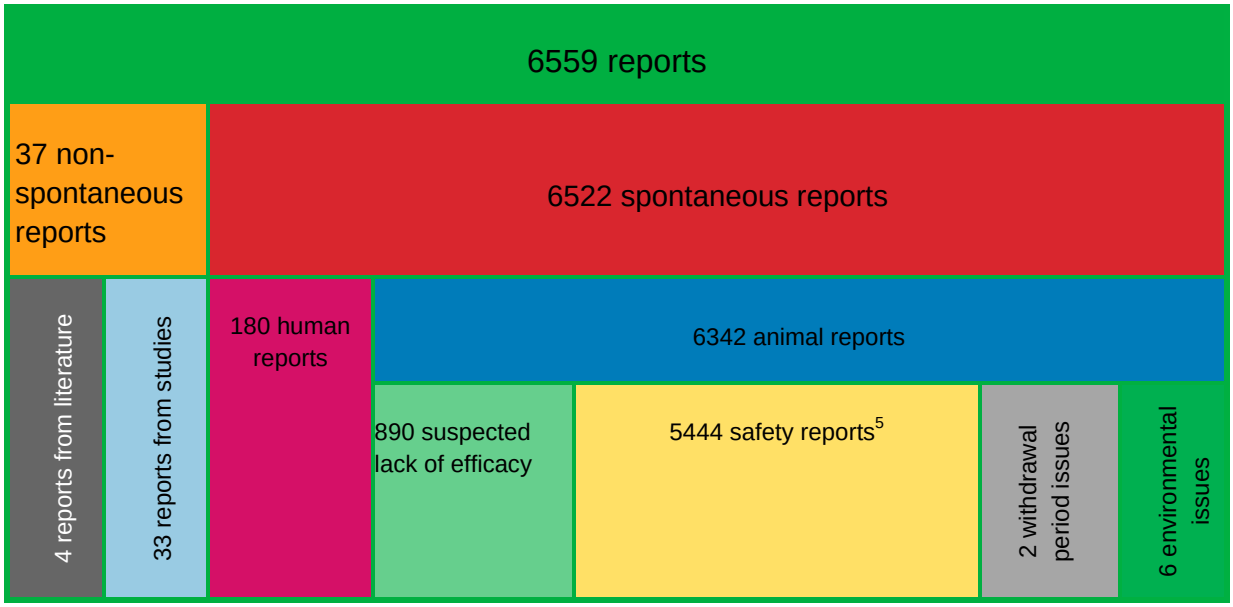


Figure 3 Different types of adverse event report received

Spontaneous animal reports may be:

- Suspected lack of expected efficacy (SLEE) reports
- Safety reports
- Withdrawal period issues
- Environmental issues

Withdrawal period issues involve food-producing animals; we receive reports of veterinary medicine residues detected in meat, milk or other products destined for the food chain. Often these residues are still present because insufficient time has passed between administration of a medicine and residue testing, prior to release of the food product into the food chain.

[5] Some safety reports may involve a lack of efficacy element; in these cases, we record ‘lack of efficacy’ together with any other clinical signs observed.

Medicines and other products reported

Reporters do not always fully identify the medicines and other products in their AE reports.

The complete identification of products ensures that we can make a fully informed assessment of the involvement of products used in each case reported.

Without size/strength information, it is not possible to determine whether under/over-dosing is a factor. In some cases, providing only a brand name will not even identify the dosage form, for example, tablet or oral solution. In these cases, we use whatever evidence is provided in the description of the AE to determine the identity of the product used, such as, animal weight.

The better the product identification is, the more effective the monitoring of all veterinary medicines will be.

Authorised veterinary medicines

There are currently over 2,700 veterinary medicines[6] that are authorised for use in the United Kingdom.

Before authorisation, information about each product is scrutinised by appropriately qualified experts (vets, pharmacists, chemists, toxicologists etc) in the VMD and, where applicable, by equivalent experts in other Member States of the European Union. The use of any medicine carries a risk, but new medicines are only authorised for use when these experts are satisfied that the benefits gained by using them greatly outweigh the risks that may be incurred.

For each product, appropriate experts check the following:

- the quality of the ingredients and the manufacturing process
- how well the medicine performs when used to treat a specific condition or disease
- any safety risks to the person(s) administering the medicines, the animals being treated or the environment

During the authorisation process, a document called the Summary of Product Characteristics (SPC) is agreed. This describes the approved conditions of use of the medicine to ensure its safety and effectiveness. It also includes technical information about the product's pharmacological or immunological properties which veterinary professionals may find useful. **You can access a copy of the SPC for every UK authorised product using the VMD's Product Information Database (PID)[6].**

[6] Product information database, www.vmd.defra.gov.uk/ProductInformationDatabase/

We published a letter[7] in the Veterinary Record in 2015 reminding vets to check for changes to any product's SPC by accessing the VMD's PID. This is where to find the most up-to-date information about veterinary medicines.

A package leaflet, supplied with each medicine, lists important information from the SPC in non-technical terms, such as:

- the animal species it is intended to treat
- how much of the medicine should be administered and how often
- whether it is safe to use the medicine at the same time as another
- the precautions a user should take to protect their safety (eg whether protective gloves should be used whilst handling the medicine).

If a user follows the instructions provided in the SPC for using an authorised medicine, this is '**authorised use'**.

If a user uses an authorised medicine in a way not defined in the SPC, for example:

- at a higher or lower dose than instructed
- more often than recommended
- to treat a species of animal not listed
- to treat a condition not listed

this is '**off-label use**'.

Vets can use their clinical judgement to decide whether the benefit of using a medicine off-label outweighs the risk of using it that way.

If no suitable authorised veterinary medicine is available in the UK to treat a specific condition in a particular species, in the interest of animal welfare, vets are allowed to treat an animal under their care with other products (human medicines or veterinary medicines authorised abroad) in accordance with the Cascade[8].

Distribution categories[9]

Each authorised veterinary medicine belongs to one of four distribution categories. These are

- POM-V: as a vet, you can only prescribe and supply it, if it is for an animal under your care

Vets must remember that **TILMICOSIN** solutions for injection are only for veterinary administration. You must not supply these medicines for use by anyone else.

[7] Using the VMD's product information database, Veterinary Record (2015) **177**, 448
[8] The Cascade: Prescribing unauthorised medicines, www.gov.uk/guidance/the-cascade-prescribing-unauthorised-medicines
[9] Guidance – Retail of veterinary medicines, www.gov.uk/guidance/retail-of-veterinary-medicines

- POM-VPS: as a vet, pharmacist or SQP, you can prescribe and supply it for an indicated use. You do not have to have seen or made a clinical assessment of the animal concerned. But you must have sufficient knowledge of the animal and how it is kept to allow you to prescribe and supply appropriately. As a pharmacist or an SQP, you cannot supply these medicines for use under the cascade, unless a vet has prescribed them.

- NFA-VPS: as a vet, pharmacist or SQP, you can supply these medicines without prescription, but only for an indicated use in companion animals. For use under the cascade, you will have to provide a prescription.

- AVM-GSL: have no legal restrictions on supply; no prescription is required.

Therapeutic groups

A therapeutic group is a group of medicines that have the same, or similar, medicinal actions or effects. There are 14 main groups of medicines; each group is associated with a particular organ or system within the body. Differences in specific sites or modes of action, or active ingredient divide the groups into sub-groups.

Digestion

This group contains a wide variety of medicines for the treatment of problems with

- stomach acid
- colic or vomiting, due to stomach spasms
- nausea and vomiting, due to motion sickness or chemotherapy
- diarrhoea, due to inflammation or infection
- digestive enzyme production
- diabetes
- vitamin or mineral deficiency
- ketosis, toxaemia and bloat

Blood and blood production

These are medicines for the treatment of

- poisoning, due to anti-coagulants
- anaemia, due to vitamin B_{12} or iron deficiency
- dehydration or electrolyte deficiency or imbalance

Heart and circulation

These medicines treat heart conditions or circulatory problems, such as

- congestive heart failure (CHF)

- swelling due to CHF
- high blood pressure
- excessive urinary protein in cats with chronic kidney disease

Skin

These medicines include treatments for

- fungal infections
- superficial wounds
- foot rot
- dermatitis
- hoofs and claws

and also antiseptics, disinfectants and poultices.

Urine and reproduction

- urinary tract infections
- urinary incontinence
- control of reproductive cycles

Vaccines

Vaccines comprise a very wide range of products. Each vaccine protects against one or more specific infections in a particular species. Vaccines are available for use against bacteria, viruses, parasites and even one against a fungal infection in cattle.

Most vaccines are injected but some are given in different ways eg up the nose. They contain a killed or weakened form of whole bacteria or viruses, or just a small part of them. They may prevent an infection, or just reduce the severity of infection.

Ectoparasiticides - treatments for external parasites

Ectoparasiticides are medicines that kill the parasites that live on the skin of animals, eg fleas, ticks, mites and lice.

Endectocides - treatments for internal and external parasites

Endectocides are medicines that kill both the parasites that live on the skin of your animals and those living in their guts or other parts of the body.

Anthelmintics - wormers

Anthelmintics are medicines that kill the parasitic worms that live in animals, eg roundworm, hookworm, whipworm, tapeworm, lungworm and heartworm; they treat internal parasites.

Flukicides – treatments for liver fluke

Flukicide products specifically treat liver fluke infections in cattle and sheep. Parasitic flat worms cause these infections.

Anti-inflammatories

These products treat inflammation. Different sub-groups contain different types of drug to make them work. Different types used in animals include:

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroids
- Immunosuppressive drugs

Antimicrobials

These products treat different types of infection caused by microscopic organisms.

- Antibiotics (used to treat bacterial infections)
- Antifungal agents (used to treat fungal/yeast infections)
- Antiprotozoals (used to treat protozoal infections)

There are some special antimicrobial preparations for use in specific situations, for example intramammary antimicrobials used to treat mastitis in dairy cows.

Neurological agents

These drugs act on the brain and nervous system. Different groups of product have different uses. There are:

- Sedatives
- Pain killers (analgesics)
- Injectable anaesthetics
- Inhaled anaesthetics
- Anti-epileptics

- Spasmolytic drugs (to treat scour and equine colic).

Hormones and hormone regulators

These may stimulate or suppress the production of hormones that are being under or over produced respectively, or replace them. Examples of these are thyroid suppressants for cats with overactive thyroids, and synthetic thyroid hormone replacements for dogs with underactive thyroids, or insulin to control the symptoms associated with diabetes mellitus.

Exempt veterinary medicines

Some medicines intended for use in minor pet species, are exempt[10] from the need to be authorised like other more widely used veterinary medicines. These products contain a restricted range of active substances. Unlike authorised veterinary medicines, we do not assess these products individually, but their manufacture is to the same high standards. Many of their ingredients have treated animals for a long time, and they are safe to use. Nevertheless, it is still important that you follow the instructions that come with the medicine. These types of products treat the following animals:

- small rodents (rats, guinea pigs, gerbils, hamsters etc)
- ferrets
- rabbits
- terrarium animals (terrestrial reptiles and amphibians)
- aquarium animals (aquatic reptiles, fish)
- cage birds (budgies, cockatiels, parrots etc)
- homing pigeons.

Incompletely identified veterinary medicines

It has not been possible to identify these products as a specific authorised veterinary medicine, but using the information provided it has been possible to determine that they really are veterinary medicines. For instance, some active substances are not for use in human medicines. Using all the available information, for example, active substance, pharmaceutical form, dose size, it is sometimes possible to determine the

[10] Exemption from authorisation for medicines for small pet animals, www.gov.uk/guidance/exemption-from-authorisation-for-medicines-for-small-pet-animals

exact veterinary medicine used. Otherwise, we have to record the best information we have, such as, the active substance.

When you do not completely identify products, i.e. you do not identify the specific brand and/or strength; you make it difficult to determine whether any signs observed may be due to a product-specific effect.

There are groups of products that have exactly the same medicinal ingredients, but they may have different amounts or formulations of other non-medicinal ingredients (excipients).

In rare situations interaction between medicinal and non-medicinal ingredients can lead to adverse effects, but without sufficient evidence these unusual situations will remain undetected.

Imported medicines

If you are a vet and wish to use a medicine (meant for animal or human use) that is not available in the UK, but is available elsewhere in Europe or the world, you can apply[11] to the VMD to import it, with the appropriate certificate:

- a Special Import Certificate (SIC), for veterinary medicines authorised elsewhere in the EU
- a Special Treatment Certificate (STC), for veterinary medicines authorised outside the EU or any human medicine authorised outside the UK.

VMD issues appropriate import certificates, which include product specific contraindications, precautions and user safety warnings. The importer must pass this information to anyone who will use the imported product.

You must apply for an import certificate, even if the product you wish to import is not described as medicinal at the point of origin. If you are considering using it under the Cascade, then technically it becomes a medicine, when you import it.

It is illegal to buy authorised veterinary medicines outside of the UK and bring them back to the UK to use. If you buy medicines for your pet whilst you are abroad, you must use them there, or at least start a course of treatment, before you return.

It is also illegal to buy from websites that are not based in the UK. If you buy products from these websites, you cannot be sure that what you receive is a genuine

[11] Guidance – Apply for a certificate to import a medicine for veterinary use into the UK, www.gov.uk/guidance/apply-for-a-certificate-to-import-a-veterinary-medicine-into-the-uk

veterinary medicine. You are not only risking the health of your pet, but are also putting yourself at risk of prosecution.

Non-medicinal veterinary products

There are other products available that are for use in animals, but as they are not medicines and do not make any medicinal claims, they do not have to comply with the rigorous requirements applied to medicines. These products include:

- supplements for joints
- support for liver function
- probiotics
- pheromones for modification of behaviour

Authorised human medicines

There are very many more medicines authorised for human use than there are for animal use. If there is no appropriate veterinary medicine available, a vet may decide that a human medicine is suitable for use in a particular animal. This may be an active substance that is not available as a veterinary medicine, or is not available as a veterinary medicine in the required form, such as an injection.

Extemporaneous products

In exceptional circumstances, a vet or pharmacist can prepare a suitable medicinal product for veterinary use; a smaller size of tablet, a lower strength of a solution, or a specific combination of medicines. We call these extemporaneous products. They are made for use in an individual patient.

Although the maker of an extemporaneous medicine may include safety information in the product packaging, it is the responsibility of the vet prescribing the medicine to ensure that the user is fully aware of all necessary information so that the medicine is used safely.

Other non-medicinal products

These are generally products made for human use, and although legally they may be authorised human medicines[12] or medical devices, they are not in themselves medicinal as they do not treat or prevent disease. Examples include suture materials

[12] Find PILs and SPCs for different medicines, www.gov.uk/pil-spc

(stitches) and contrast agents, used to enhance the imaging of certain organs or tissues for diagnostic imaging (eg MRI scans).

Biocides and disinfectants

Biocides[13] control harmful or unwanted organisms through chemical or biological means. Some control flea and other insect infestations. They are not authorised veterinary medicines. Some of these products are for treating where your animals live, including farm buildings, furniture, carpets and pet beds. Others you can apply to your animal to repel insects. You must not apply any of this type of product to your animals, unless the instructions specifically say you can.

The Health and Safety Executive[14] (HSE) have a database[15] listing biocidal products containing substances approved or authorised under the Control of Pesticide Regulations and the EU Biocidal Products Directive. These products have a reference number with a prefix of 'HSE' or 'BPR' that shows that they are approved or authorised for use.

The HSE provides guidance[16] on the steps to take if you think exposure to biocides has affected you, your family, your pets or wildlife.

If you have information about an adverse event in any animal(s) involving the use of a biocide, you should report this to the Wildlife Incident Investigation Scheme (WIIS) on 0800 321600. You can use this number for reporting events involving pets, farm animals or wildlife.

Products used in clinical/field trials

As a new veterinary medicine is being developed, once safety and efficacy have been demonstrated in laboratory conditions, MAHs are required to show that the same results can be achieved in the 'real world'. Vets in practice sometimes also wish to investigate other treatment options for particular diseases.

MAHs and veterinary researchers must apply[17] to the VMD for an Animal Test Certificate[18] (ATC), which authorises them to conduct studies with non-laboratory animals. One of the conditions of an ATC is that the lead investigator must report all

[13] Biocides: The basics, www.hse.gov.uk/biocides/basics.htm
[14] The Health and Safety Executive, www.hse.gov.uk
[15] How can I find out if a product is already approved/authorised?, www.hse.gov.uk/biocides/faq.htm#productauthorised
[16] Reporting incidents of exposure / possible adverse reactions to biocides, www.hse.gov.uk/biocides/reporting.htm
[17] Apply for an animal test certificate, www.gov.uk/government/collections/apply-for-an-animal-test-certificate
[18] Animal Test Certificates, www.gov.uk/guidance/animal-test-certificates

serious adverse events occurring following use of any product involved in the trial (even control or placebo products) to the VMD within 15 days.

We will not discuss the findings of any adverse events reported to us originating from trials carried out under ATCs in this review, as these are confidential.

Animal species reported

For the purposes of this review:

- Pet animals are cats, dogs, horses, donkeys, small mammals and single caged birds kept in the home.
- Food-producing animals are cattle, sheep, pigs, poultry, farmed fish etc.
- Exotic animals are all other non-food-producing animals, including native wild animals, aquarium fish, zoo animals, aviary or racing/ornamental birds and laboratory animals.

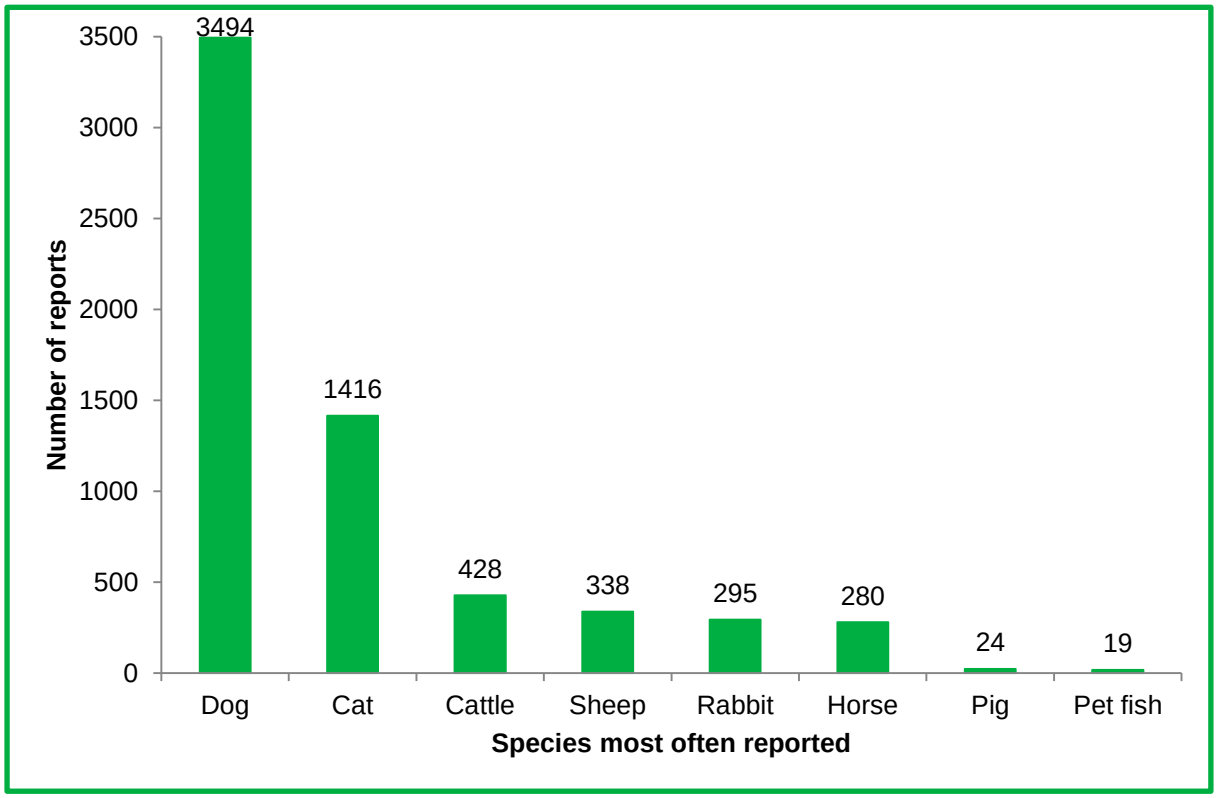


Figure 4 Number of reports received for the most commonly reported species

Other reports involved farmed fish, poultry, furry, scaly or feathered pets, and various, mostly feathered, wildlife. The most unusual species reported was a Coati Mundi.

Pet animal breeds

For pet animals, in approximately 20% of cases, the reporter did not identify the breed of the animal.

Dogs

In 8% of dog cases, the reporter did not identify the breed of a dog, with a further 14% identified as ‘crossbred’. The cross breeds most often identified were Cocker Spaniel crossed with Poodle, Lurcher and Labrador crossed with Poodle.

The top 5 reported breeds were

- Labrador Retriever, 8.9%
- Jack Russell Terrier, 4.2%
- English Cocker Spaniel, 4.1%
- Yorkshire Terrier, 3.0%
- Border Collie, 3.0%

Reports received during 2016 described over 160 different specific dog breeds.

Cats

In 30% of cat cases, the reporter did not identify the breed of a cat, with a further 53% identified as ‘crossbred’. Of the crossbred cats 82% were short-haired and 8% were long-haired.

Reports received during 2016 described only 25 different specific cat breeds, with Ragdoll, Siamese, Bengal, Maine Coon and British being the most commonly identified breeds.

Horses

In 41% of cases, the reporter did not identify the breed of a horse, with a further 10% identified as ‘crossbred’.

The remaining reports received during 2016 identified horse breeds as Thoroughbred, various Sport Horses, various ponies, Welsh Cob, Draught and Quarter horses.

Rabbits

In 35% of rabbit cases, the reporter did not identify the breed, with a further 7% identified as ‘crossbred’.

Fourteen specific breeds were identified, with Dwarf Lop (13%), English Lop (10%), Dutch (9%) and Lion Head (6%) being the most commonly identified breeds.

Food-producing animal breeds

The reporter did not identify the breed of food-producing animal in 75% of cases received during 2016.

Cattle

The reporter did not identify the breed of cattle in 72% of the cattle cases received during 2016, with a further 1% identified as ‘crossbred’.

Three herds were of a mixture of breeds, and a further 12 breeds were identified in reports, with Holstein-Friesian (10%), Limousin (4%) and Aberdeen Angus (3%) being the most commonly identified breeds.

Sheep

The reporter did not identify the breed of sheep in 75% of sheep cases received during 2016, with a further 6% identified as ‘crossbred’.

One flock was of a mixture of breeds, and a further 18 breeds were identified in other reports, with Texel (4%), Suffolk (3%) and Blackface (2%) being the most commonly identified breeds.

Pig

The reporter did not identify the breed of pig in 58% of pig cases received during 2016, with a further 17% identified as ‘crossbred’.

Only three specific breeds were identified in reports; British Landrace, Large White and Commercial Hybrid.

Poultry

Of the 14 cases involving poultry, in only one did the reporter identify the breed of the birds (Leghorn).

Non-spontaneous adverse event reports

Figure 5 shows a breakdown of the 37 reports we received that were not associated with spontaneous adverse events. Thirty three of these described events that occurred during field or clinical trials, and the other four were reports originating from scientific literature.

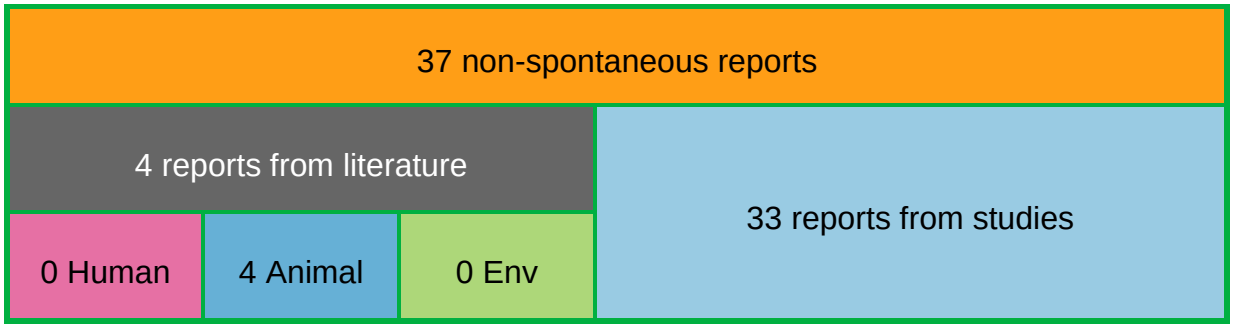


Figure 5 Sources of non-spontaneous reports received

Reports from literature

Reports about people

We received no reports of adverse events involving people originating from scientific literature during 2016.

Reports about animals

One report described a comparative study of long-term oral treatment of chronic kidney disease in cats with either a standard treatment or a novel substance[19].

A second described a study to evaluate the clinical success of whole-flock systemic tilmicosin and enhanced biosecurity in eliminating active contagious ovine digital dermatitis (CODD) from sheep flocks.[20]

One report described a paper that evaluated the sensitivity of successive generations of a particular species of sea-lice to emamectin benzoate[21]. Another

[19] Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease (2015). J Vet Intern Med 2015;29:1479-1487
[20] Whole-flock, metaphylactic tilmicosin failed to eliminate contagious ovine digital dermatitis and footrot in sheep: a cluster randomised trial (2016). veterinaryrecord.bmj.com/content/179/12/308.long
[21] SARF069: Evaluation of sensitivity to chemotherapeutants in successive generations of *Lepeophtheirus salmonis* from a Resistant Population. www.sarf.org.uk/reports/

described two papers investigating the effectiveness of treatment of emamectin benzoate against sea lice infestations in Scotland [22] [23].

Environmental report

We received no environmental reports originating from scientific literature during 2016.

Reports from studies

We received 33 reports associated with studies. As previously stated, we do not discuss findings of clinical trials due to their commercially sensitive nature.

[22] Factors associated with changing efficacy of emamectin benzoate against infestations of *Lepeophtheirus salmonis* on Scottish salmon farms (2008). onlinelibrary.wiley.com/doi/10.1111/j.1365-2761.2008.00969.x/abstract

[23] The efficacy of emamectin benzoate against infestations of *Lepeophtheirus salmonis* on farmed Atlantic salmon (Salmo salar L) in Scotland, 2002-2006 (2008). www.ncbi.nlm.nih.gov/pubmed/18253496

Spontaneous adverse event reports

There was an increase of almost 16% in spontaneous reports received during 2016, compared to 2015. Six thousand, three hundred and forty five of the 6522 reports were associated with animals (15% increase on 2015), 180 with people (45% increase) and 6 with the environment. Figure 6 shows a breakdown of the types of report and the groups of animal associated with those reports.

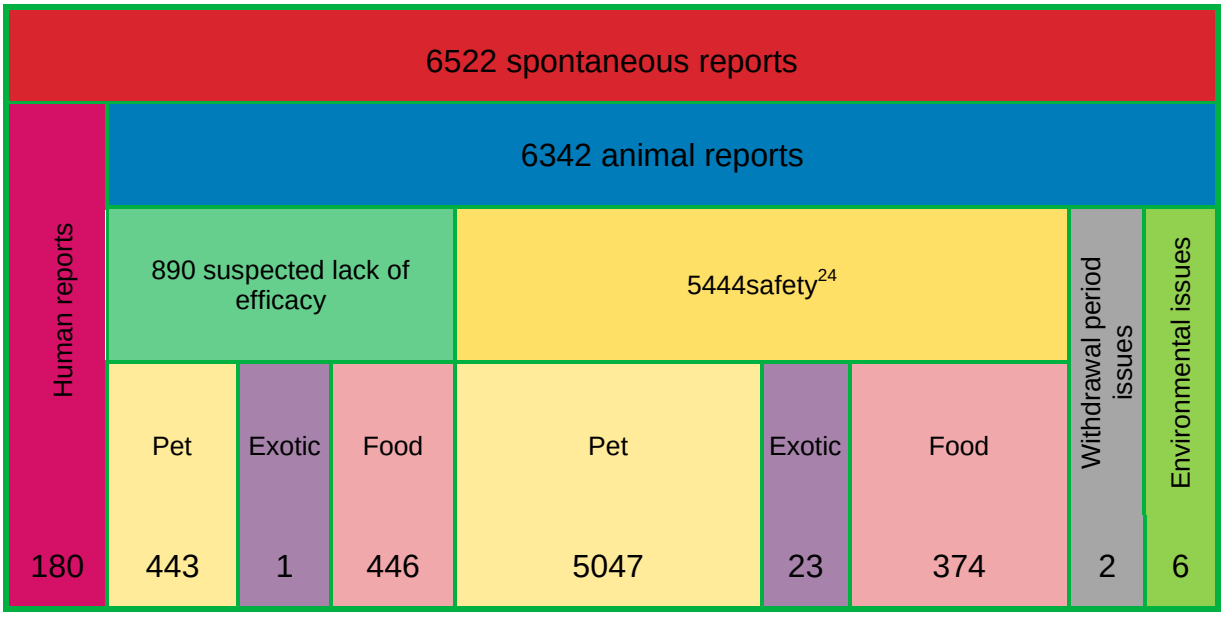


Figure 6 Number of spontaneous reports received, associated with different types of adverse event

Each human report relates to a single person. In some incidents, more than one person is affected. In these situations, we record each person's symptoms in separate records.

Each animal report received related to the treatment of a single species of animal, and in many cases only one animal. But in some cases, particularly those involving food-producing animals, more than one animal was involved. In these cases, we recorded all clinical signs from the group in one report.

Almost 85% of all spontaneous animal reports describe adverse reactions observed after the use of one or more products i.e. undesirable effects have occurred. The remaining 15% of reports describe a lack of efficacy of one or more products used i.e. they have not worked as well as expected.

Figure 7 compares the relative number of safety reports to SLEE reports for pet, exotic and food-producing animals.

[24] Some safety reports may involve a lack of efficacy element; in these cases, we record 'lack of efficacy' together with any other clinical signs observed.

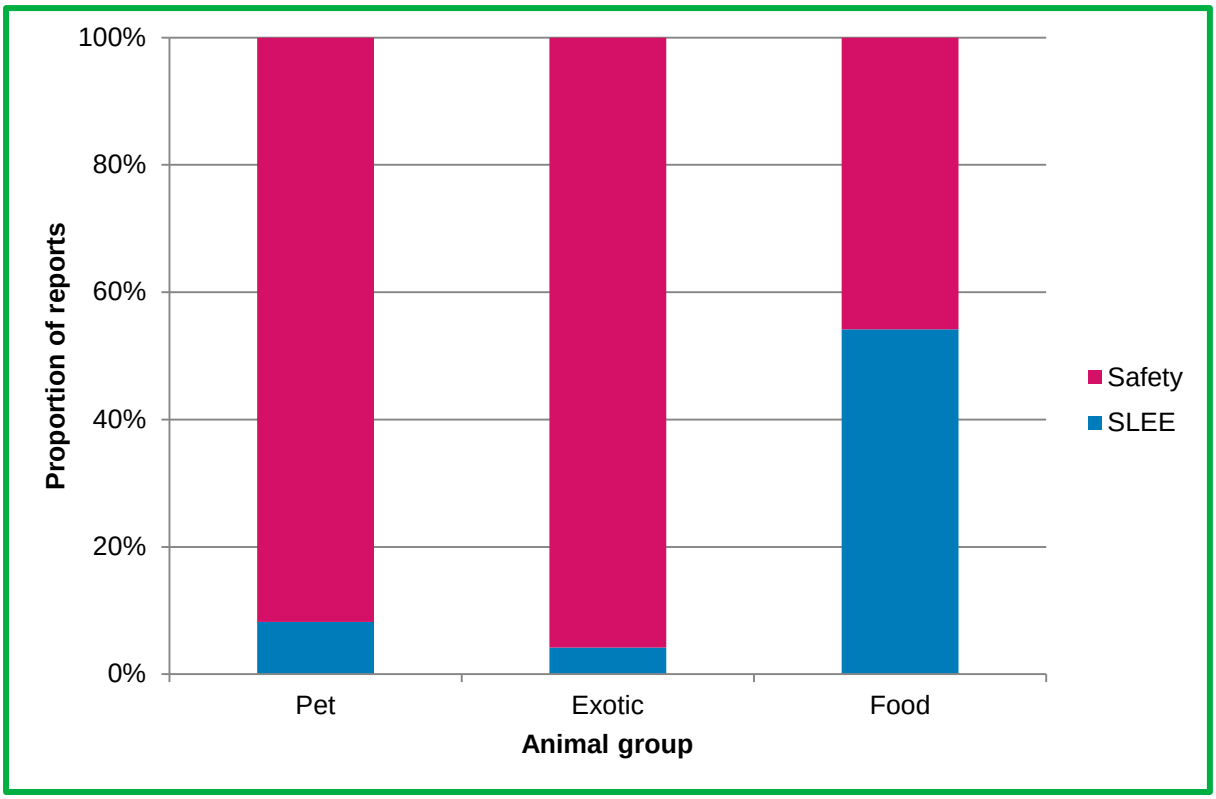


Figure 7 Comparison of numbers of safety and SLEE reports received for different groups of animals

For pet animals, SLEE reports account for less than 9% of reports. For exotic animals, they account for just less than 5% of reports. By contrast, for food-producing animals, SLEE reports represent over 54% of reports.

We received two reports describing potential withdrawal issues during 2016. In these cases, animal tissue or produce intended for human consumption tested positive for residues of veterinary medicines.

WIIS submitted six reports describing potential environmental issues during 2016.

Adverse reactions in people

During 2016, the VMD received a total of 180 reports describing adverse reactions in people. The VMD sometimes received these either from the person who experienced an adverse reaction (the Patient) or from someone reporting on their behalf, usually a vet. Otherwise, the MAH of a product involved in a reaction sent the reports, after receiving information about an incident directly from a patient or from another person.

People affected

Figure 8 shows a breakdown of the types of people affected by the use of different products on animals.

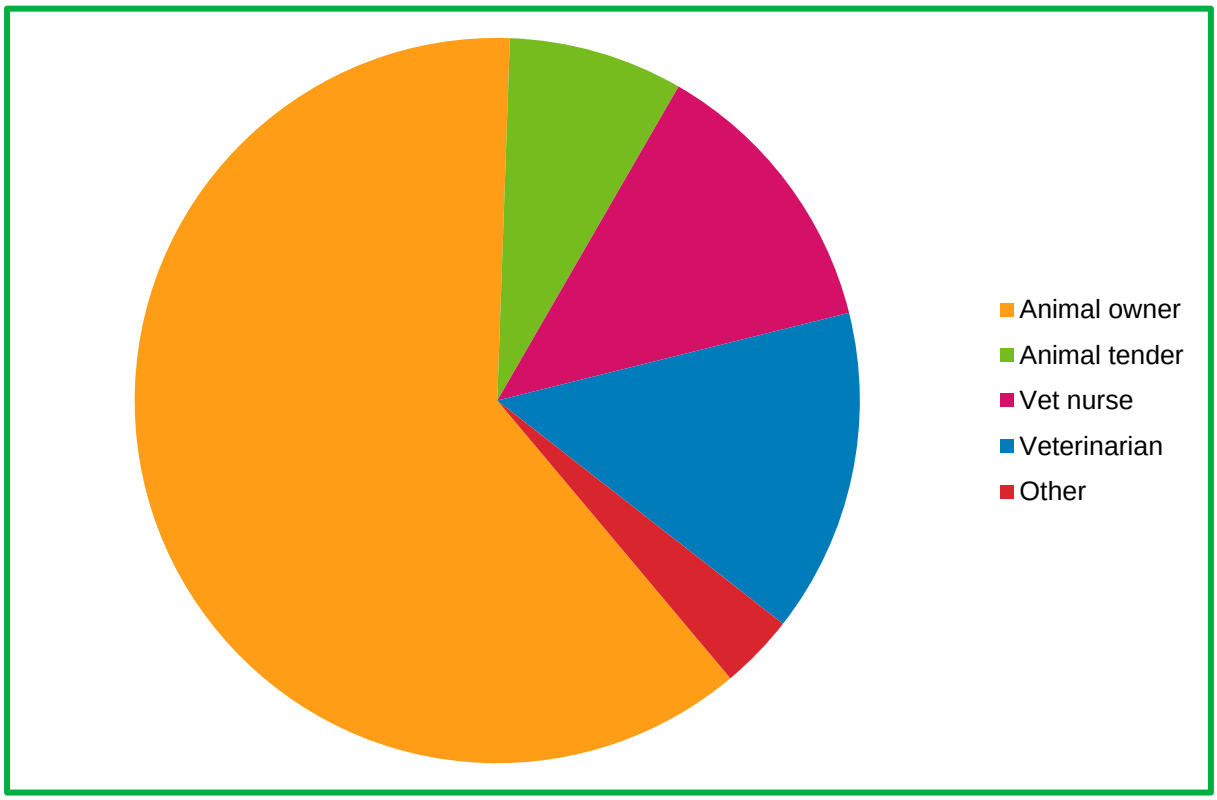


Figure 8 Different types of people appearing in Human adverse event reports

Animal owners are most often the person affected by the medicines used on their pets or stock animals.

For pet owners, those with dogs were affected most often (67%), followed by cat owners (24%) and horse owners (5%). The reporter either did not identify the species treated, or no animal had been treated, in the remaining 4% of cases involving pet animal medicines.

For owners of food producing species, sheep farmers were most often affected (48%), followed by cattle farmers (41%) and pig farmers (11%).

Most of the animal tenders affected by medicines worked with large animals. Thirty six percent worked with pigs and 50% with sheep or cattle. The remainder worked with chickens or on a fish farm.

Most of the cases involving vet nurses or veterinary staff, other than vets, occurred whilst dogs were being treated (35%). A fifth of cases occurred in incidents unrelated to the treatment of specific animals.

For vets, 46% of incidents involved the treatment of dogs with 19% involving cats. Less than 8% involved large animals, horses or cattle.

Accidents during the transit of medicines led to the exposure of the five 'Other' people affected by veterinary medicines. One case involved a postal worker exposed to a cypermethrin product that leaked whilst it was being delivered. In another, four pharmaceutical industry workers were exposed to deltamethrin, when they accepted delivery of a box containing damaged bottles of product, without using protective gloves.

You must ensure that when you are sending veterinary medicines through the post:

- it is permissible for the medicine(s) to be sent by this method[25]
- the contents are sufficiently protected and/or you have taken measures to contain any spillages that may occur.

Medicines and other products

One hundred and eighty reports described the use of a total of 196 products that were associated with adverse events in people. The maximum number of products mentioned in a single report was three, in three reports, with two products in 10 reports and one product in each of the remaining 167 reports.

Authorised veterinary medicines

One hundred and eighty nine of the 196 products associated with adverse reactions in people were authorised veterinary medicines.

[25] Royal Mail – Prohibited and restricted items

It is essential that people using injectable products are aware of the potential dangers these products pose to them. Apart from exposure to infection from dirty needles or the toxic effects of substances not intended for use in humans, some products pose an additional hazard. **Self-injection with a vaccine that contains a mineral oil (liquid paraffin/Montanide) adjuvant could cause life-changing injuries**.

The product information leaflet supplied with these vaccines, including those imported from other countries, explains the specific and prompt action that you must take in the event of accidental self-injection.

You will find a list of injectable products that contain mineral oil in the Annex.

Table 1 shows how many of different types of authorised medicines were associated with adverse reactions in different groups of people.

Administration route	Small animal owner	Large/food animal owner/handler	Veterinary professional	Total
Injection	7	31	40	78
Oral	14	3		17
Collar	17			17
Skin spot-on	38		2	40
Skin pour-on		9		9
Skin dip		1		1
Skin spray		5		5
Inhalation			11	11
Nasal	6		2	8
Ear	2		1	3

Table 1 Number of adverse reaction reports received for different groups of people following administration of authorised medicines by different routes

Other products

The remaining cases were associated with adverse reactions following exposure to products without UK veterinary authorisations:

- injection (2 cases) – imported pig vaccine, extemporaneous adrenal gland function diagnostic preparation
- dermal exposure – surgical tissue glue
- dermal exposure – ear cleaner
- dermal exposure – human eye drops
- dermal exposure – extemporaneous gel product
- inhalation – essential oil vapours.

Adverse reaction reports

Authorised veterinary medicines

Treatments for internal and external parasites were the most often reported type of authorised veterinary medicine (47%) in human reports. Vaccines (34%) were the next most often reported type of product. The remaining 19% of authorised products mentioned included anaesthetics, inflammation control, antibiotics, and hormone regulation.

Internal and external parasites

Thirty nine adverse event reports described symptoms experienced by people following the use of spot-on anti-parasitic treatments in cats (16 cases) and dogs (23 cases). Others involved collars (16) and tablets (6). Skin disorders were most often associated with spot-on products containing moxidectin, including three cases involving children. Spot-on products containing moxidectin were also most often associated with sensory abnormalities and breathing problems.

Parents, and others who have children in their care, should always be aware of the dangers of leaving potentially hazardous medicines and other chemicals within sight and reach of children.

You should also be aware of the warnings to ensure spot-on treatment sites are completely dry before a pet is kissed or cuddled.

Adverse reactions in people, following the treatment of large animals, most often involved the use of pour-on (8) or injectable anti-parasitic products (4). One case involved the use of a product for oral administration. Exposure to pour-ons, synthetic

pyrethroid- or avermectin-based, led mainly to sensory abnormalities or nervous system disorders. But reporters also described skin and lung symptoms. Injection of avermectin-based products led to localised injection site reactions, and injection of milbemycin-based products led to problems with co-ordination or balance. Redness and swelling of the affected limb occurred following skin exposure to a combination wormer and flukicide drench.

Vaccines

We received eight reports of accidental self-injection with mineral oil-based vaccines during 2016. If you have such an accident, it is essential that you get immediate medical attention, to reduce the risk of loss of function, or even amputation, of any affected fingers or thumbs. Three cases occurred during the vaccination of sheep, 3 during the vaccination of pigs, 1 during the vaccination of chickens and 1 during the vaccination of farmed fish.

In one case, unspecified symptoms only resolved after a long period of treatment. In another, a farm worker had a painful wrist, poor hand strength and a stiff arm for a period of time after accidental injection in the arm. The final outcome is unknown. In another, an injured finger was still not fully mobile two and a half months later. A historical report received during 2016, described a thumb injury that occurred over 7 years earlier, but had not yet resolved.

For water-based vaccines, the effects resulting from self-injection were usually shorter lasting. Most symptoms described were localised injury site reactions, but in some cases systemic effects, such as lethargy or high temperature, occurred, possibly due to infection from the dirty needle.

For human reports involving kennel cough vaccines administered nasally, signs of infection were sometimes reported in someone who had been in contact with a treated dog. However, no clinical tests were performed to determine the identity of the infection.

Anaesthetics and sedatives

Adverse events in people, in which anaesthetics or sedatives were involved, were most often due to inhaled vapours. Exposure often occurred during handling of the products (spillages), but also occurred as a result of treatments, during which neither adequate ventilation nor gas scavenger systems were in place. Symptoms of nausea or light-headedness were transient and there were no lasting effects.

Vet practices should ensure that they have adequate and well-maintained anaesthetic gas scavenging systems in place in operating theatres. These ensure that staff working within such areas are not exposed to the potentially harmful effects that can occur through prolonged or repeated exposure to volatile anaesthetic gases.

Those who are pregnant should ensure exposure is kept to the absolute minimum, as exposure to some anaesthetics has been linked to spontaneous abortion and congenital defects.

Symptoms caused by accidental self-injection with injectable products were generally of short duration, but in one case treatment for a corneal ulcer was required after a vet splashed a euthanasia agent into their eye.

Other products

Other cases, involving products that were not authorised veterinary medicines occurred after the use of a tissue-glue used after surgery, an essential oil calming vapour, an ear cleaning solution and some human eye drops.

In this final case, a cat owner developed a swollen tongue and throat lymph nodes after using the eye drops on a cat, and these symptoms worsened when a treatment for hyperthyroidism was administered. The symptoms recurred, later when an oral meloxicam product was administered.

Animal adverse event reports

Figure 9 shows how spontaneous animal reports are distributed between safety and lack of efficacy reports, and between different groups of animals.

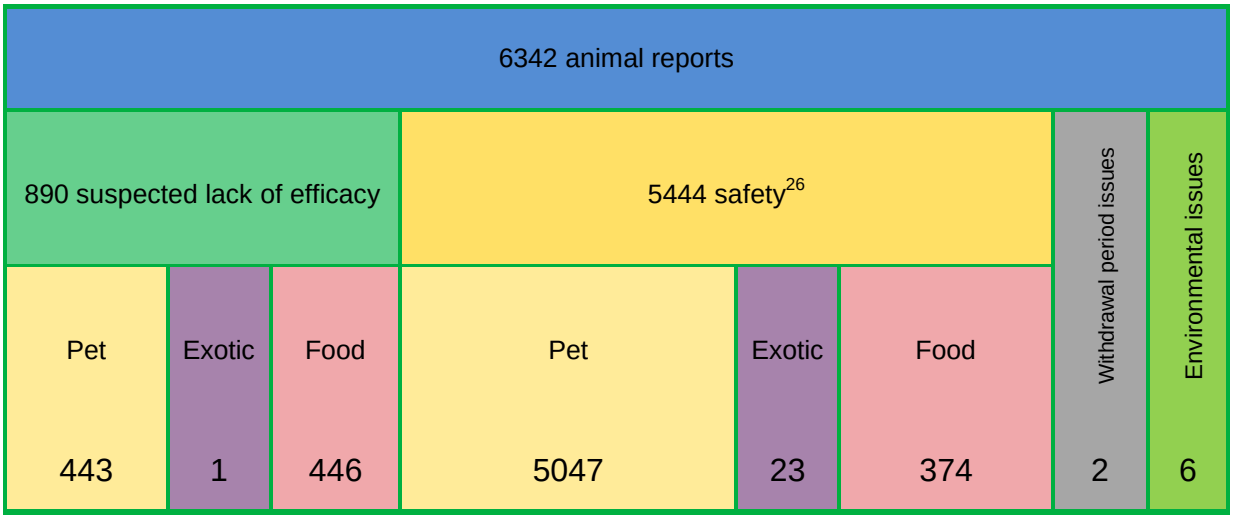


Figure 9 Number of different types of spontaneous animal adverse event reports received

Less than 15% of animal reports received during 2016 described events in which one or more products used to treat an animal did not perform as expected. The vast majority of reports received reported undesirable effects observed following the use of medicines or other veterinary products.

Medicines and other products

Reporters included a total of 8841 products in 6334 reports associated with safety- or lack efficacy-related adverse events in animals. This is an average of 1.4 products per report. The maximum number of products mentioned in a single report was 10; all 10 were authorised veterinary medicines; six anaesthetics or sedatives, two treatments for pain and inflammation, and two homeopathic products. A further four reports involved nine products, with between six and nine authorised veterinary medicines. Almost 70% of reports described events that occurred after the use of a single reported product.

Just over 97% of reports received involved the use of at least one authorised veterinary medicine. Conversely, slightly less than 3% did not involve the use of any authorised veterinary medicines.

[26] Some safety reports may involve a lack of efficacy element; in these cases, we record 'lack of efficacy' together with any other clinical signs observed.

Figure 10 shows the types of products reported in spontaneous animal adverse event reports.

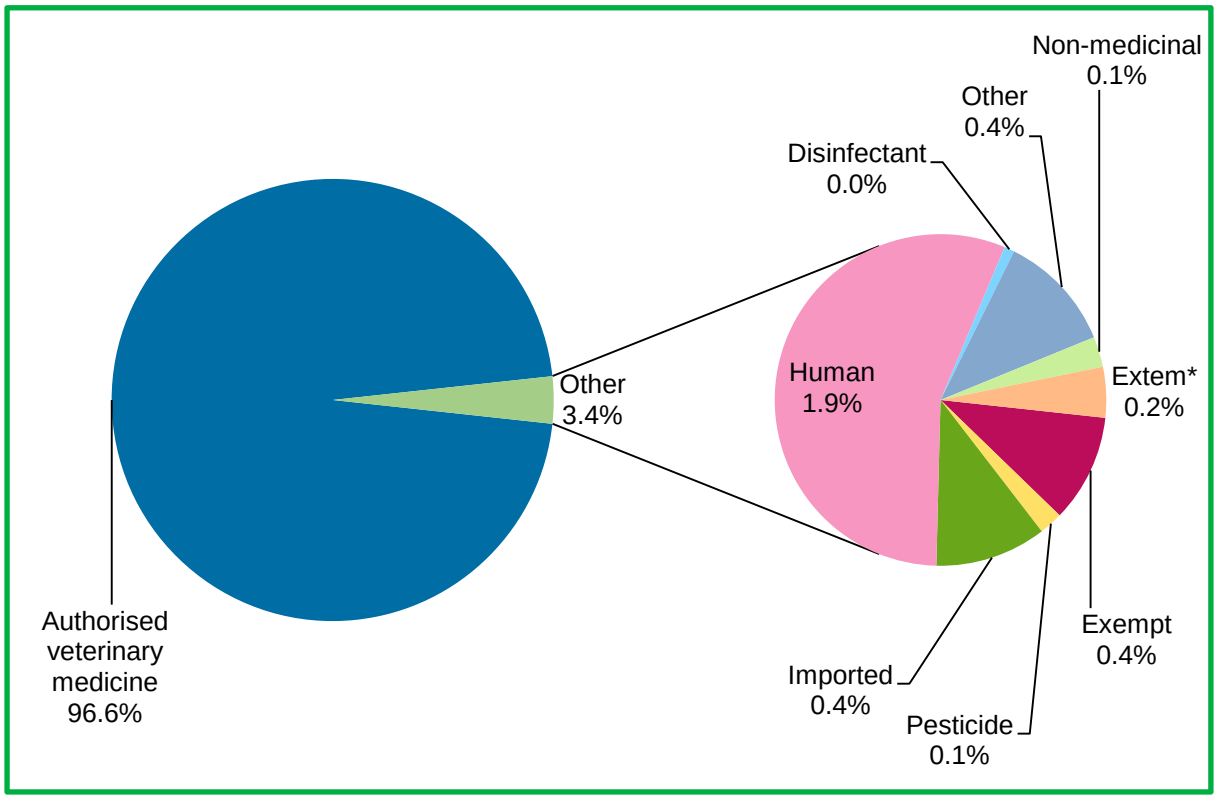


Figure 10. Different types of products appearing in spontaneous animal adverse event reports (* - extemporaneous)

All of the top 20 most commonly reported products were authorised veterinary medicines. Twelve of the top 20, including the top nine, most commonly reported products were vaccines for the following species:

- Dogs (7 different vaccines)
- Cats (3)
- Rabbits (1)
- Sheep (1)

Other products in the top 20 were treatments for Addison's disease (dogs), epilepsy (dogs), hyperthyroidism (cats), a steroidal anti-inflammatory drug, a cat spot-on endectocide and an NSAID (dogs and cats).

In 2015, an amoxicillin/clavulanic acid combination authorised for human use was the 15th most commonly reported treatment associated with an adverse event. In 2016, this product has dropped to 21st place in the list.

Authorised veterinary medicines

Authorised veterinary medicines accounted for over 94% of all products mentioned in spontaneous animal adverse event reports. The reporter did not fully identify a

further 2% of products, but they contained ingredients only available in veterinary medicines. Figure 11 shows the different types of veterinary medicines mentioned in reports, including those not fully identified.

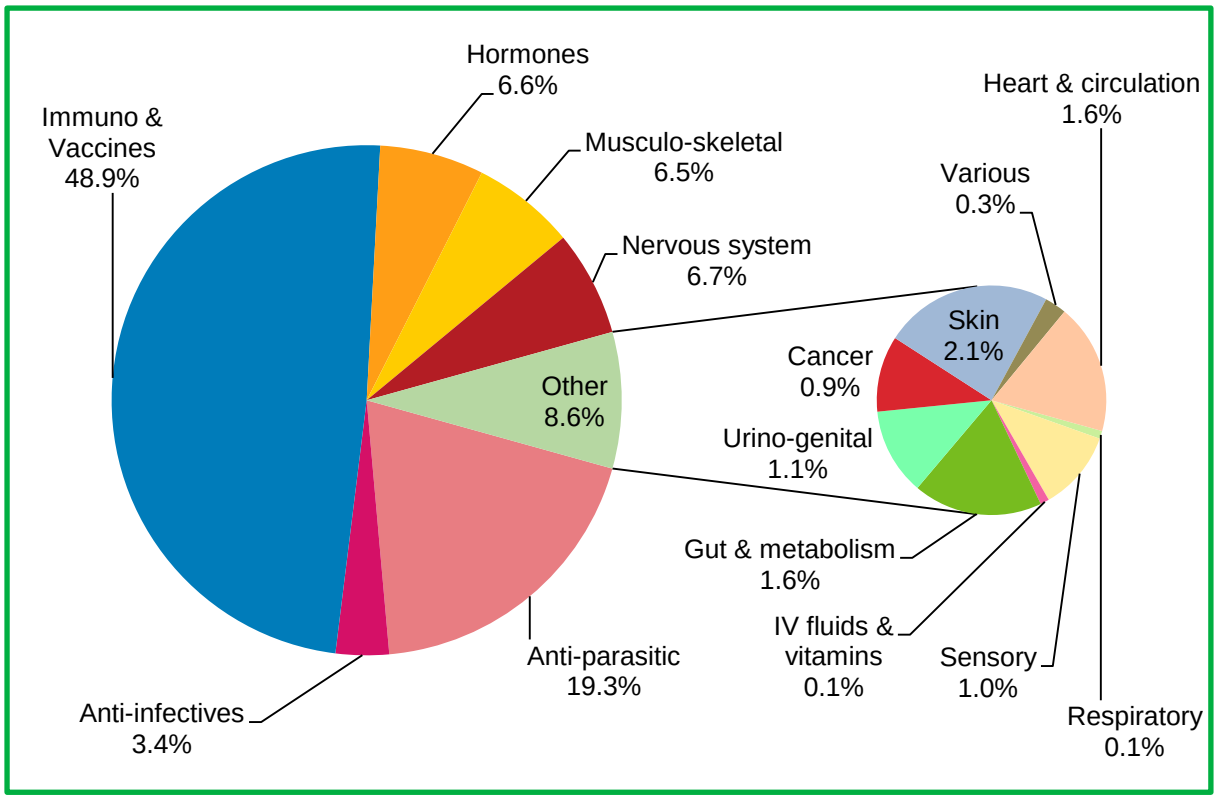


Figure 11 Types of authorised veterinary medicines mentioned in spontaneous animal adverse event reports

This shows that the prevention or treatment of infection accounted for approximately half of all authorised medicines mentioned in spontaneous animal adverse event reports. Almost a fifth of medicines mentioned were for the prevention or treatment of internal and external parasites. Another fifth were almost equally divided between medicines for the treatment of pain and inflammation in muscles or bones, for hormone replacement or control and for epilepsy control, sedatives or anaesthetics. The remaining medicines were for:

- treatment of allergic skin conditions
- heart and circulation support
- gastro-intestinal support
- reproductive hormone control
- eye and ear treatments

- cancer treatment
- sedation reversal
- fluid replacement, vitamins and minerals
- respiratory support.

Incompletely identified veterinary medicines

At least one medicine was incompletely identified in 158 reports (more than 2% of reports), with a total of 190 incompletely identified medicines in those reports. The maximum number of incompletely identified medicines in one report was five. Figure 12 shows the types of incompletely identified medicines reported.

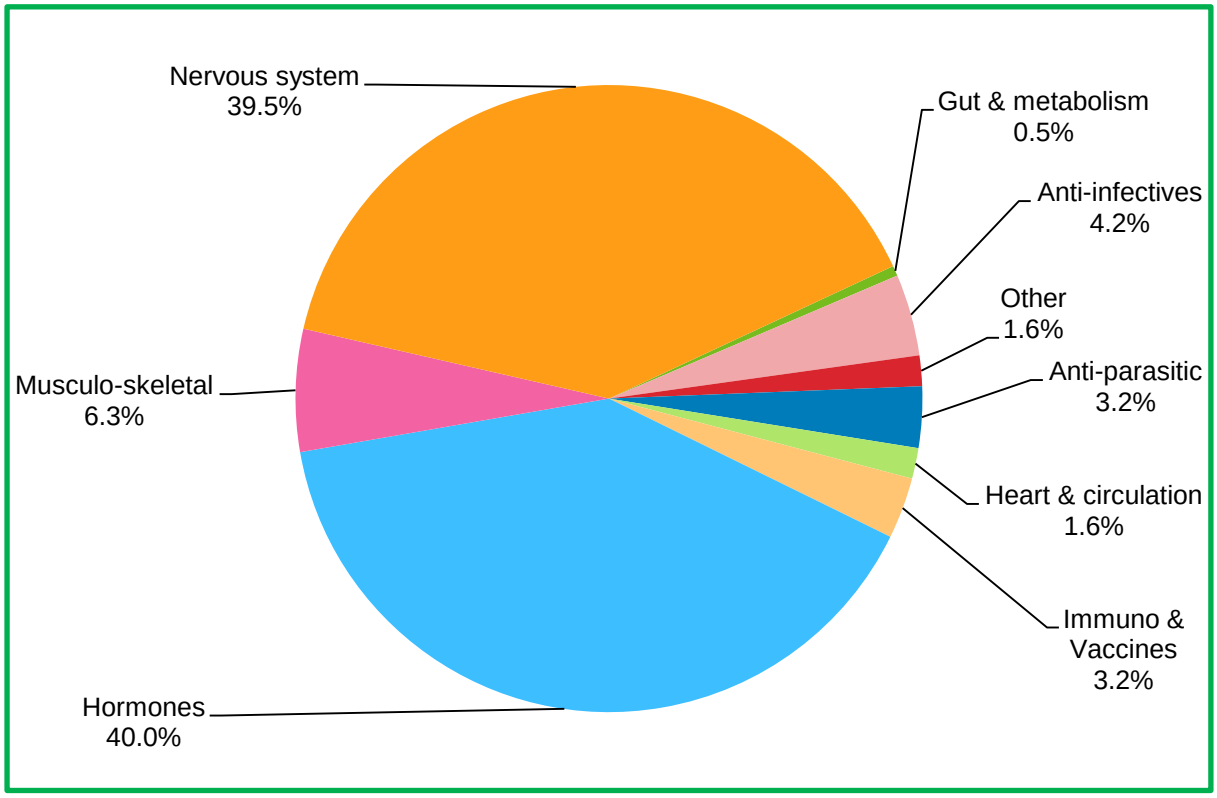


Figure 12 Types of incompletely identified products mentioned in Adverse Event reports

Authorised human medicines)

Reporters mentioned a total of 168 individual human medicines in 153 different adverse event reports, often together with other types of product. Four cases listed three of these medicines; nine listed two and the remainder listed only one.

Many of the human medicines used (46%) were for the control of infection. Others were for sedation, pain relief or epilepsy control (21%) or treatment of digestive problems (13%). Products for the diagnosis or treatment of eye problems accounted

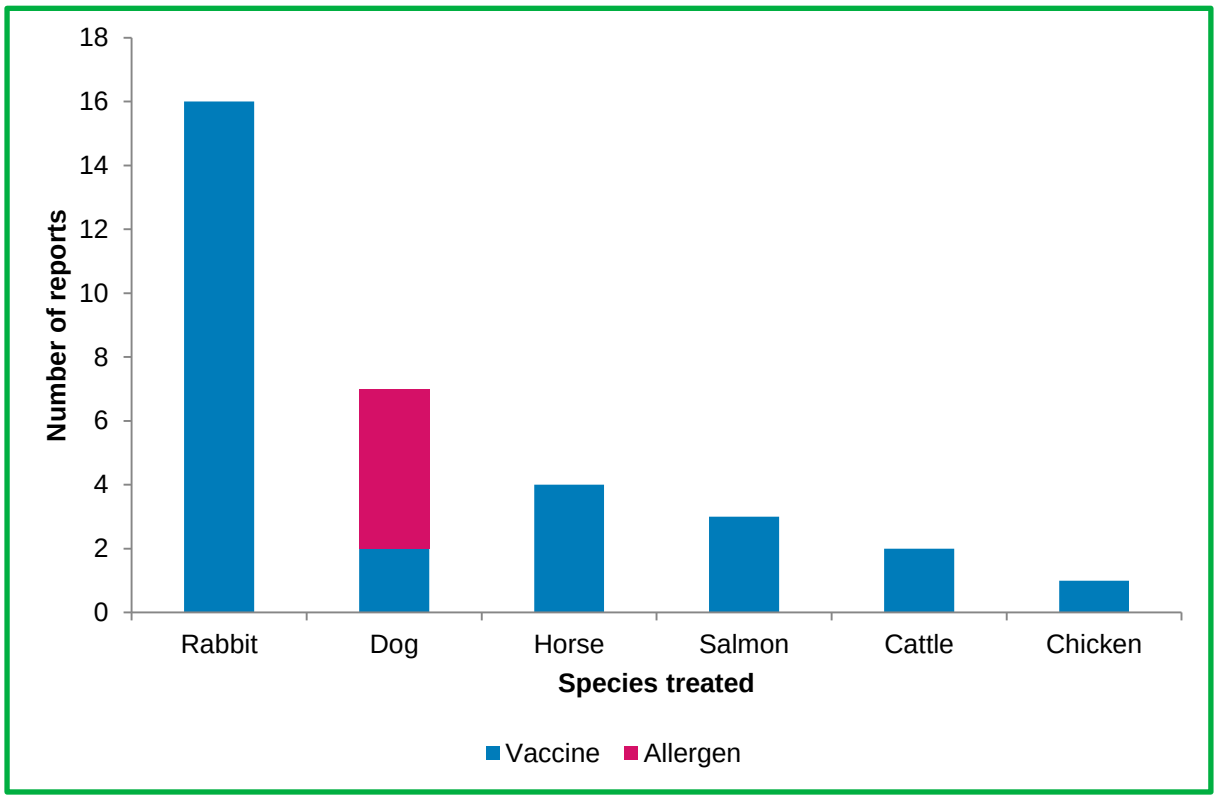
for 4% of human medicines reported, with hormone control (4%), respiratory support (4%), circulatory support (4%) and cancer treatment (2%) being most of the remainder.

Extemporaneous products

Sixteen adverse event reports described clinical signs following the use of a single extemporaneous product. Nine reports involved a tetracosactide diagnostic test for Cushing's disease in dogs. Six reports involved a methimazole gel treatment for hyperthyroidism in cats. The remaining report involved trilostane used to treat Cushing's disease.

Imported medicines

Thirty three reports described the use of imported medicines. Figure 13 shows the number of reports for each type of product and the species treated with those



products.

Figure 13 Number of reports by species received after the use of imported immunological medicines

Exempt veterinary medicines

VMD received 31 reports involving 32 exempt medicines. There were 19 fish treatment cases (one involved 2 products), 7 external parasite treatments, 2 internal and external parasite treatments, 2 wormers and a general anti-parasitic.

Non-medicinal products

We received three reports involving the use of an imaging contrast agent, and one each describing an adverse event following the use of sutures or tissue adhesive.

Biocides

We received seven reports involving the use of biocides. Four of these reports described the use of spot-on products containing margosa oil; another two were household flea treatments and the final report related to the use of an insecticidal spray for bird or dog housing.

Suspected lack of expected efficacy reports

Figure 14 shows how many SLEE reports we received during 2016 for different groups of animals.

890 suspected lack of efficacy		
Pet	Exotic	Food
443	1	446
37 cat [53] 273 dog [350] 2 guinea pig [3] 25 horse [77] 106 rabbit [110]	1 laboratory mice [60]	200 cattle [4200] 10 chicken [13250] 4 farmed fish [11600] 3 goat [35] 5 pig [1020] 224 sheep [6900]

Figure 14 Number of SLEE reports received for pet, exotic and food-producing animals [Number of animals involved]

Pet animals

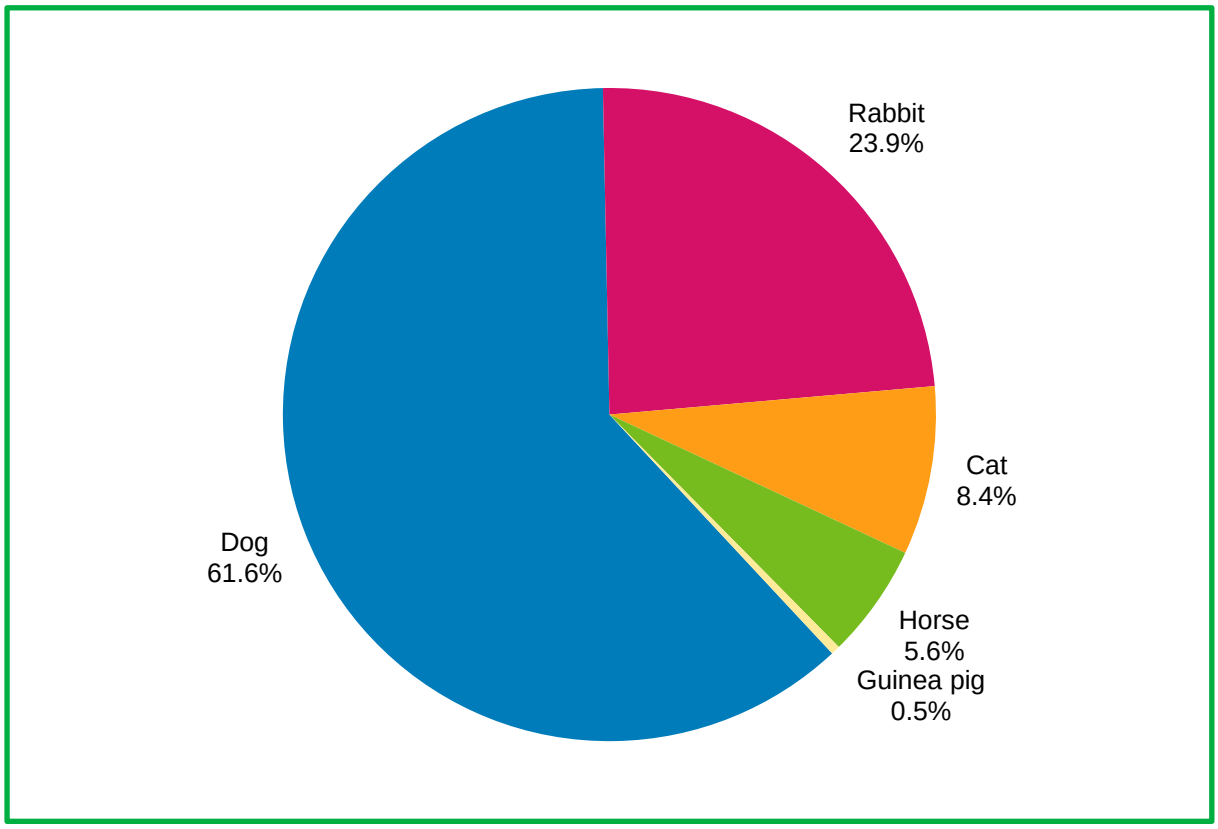


Figure 15 Proportion of SLEE reports per pet animal species

The Pet Food Manufacturers' Association commissions and publishes a Pet Population report, which estimates the numbers of specific species kept as pets over a two year period. Using figures for 2016[27], the number of SLEE reports received for each species was:

- 1 report for every 31,000 dogs, or 1 lack of efficacy in a dog was reported for every 24,300 dogs
- 1 report for every 203,000 cats, or 1 lack of efficacy in a cat was reported for every 141,500 cats
- 1 report for every 7,500 rabbits, or 1 lack of efficacy in a rabbit was reported for every 7,300 rabbits

The number of horses kept in the UK is estimated to be 944,000[28], which means that 1 report is received for approximately every 38,000 horses, or 1 lack of efficacy in a horse was reported for every 12,250 horses.

In only 261 of the 443 reports was there sufficient evidence to suggest that a medicine may not have performed as well as expected.

Table 2 summarises the types of product and species associated with SLEE in the 261 reports in which product involvement was not ruled out.

[27] Pet Food Manufacturers' Association, Pet Population - 2016, www.pfma.org.uk/pet-population-2016
[28] British Equestrian Trade Association, National Equestrian Survey 2015, www.beta-uk.org/pages/industry-information/market-information

Product type	Dog	Cat	Horse	Rabbit	# of reports
Anti-parasitic	21	16	2		39
Reproduction control	4				4
Skin allergy	1				1
Emesis control	1				1
Anxiety control	1				1
Circulation	2				2
Hormone control	15	6			21
Epilepsy control	18				18
Pain & inflammation			1		1
Euthanasia			10		10
Anaesthetic/sedative	5	3	4		12
Vaccine	87	6	3	54	150
Total	155	31	20	54	260

Table 2 Types and number of products associated with SLEE in different pet species

There was also one case describing the lack of efficacy of an isoflurane anaesthetic which reported the death of two guinea pigs. A practice had on-going problems with multiple species waking during procedures, but equipment checks did not reveal any leaks or other failures.

Dogs

Vaccines were the product type most often reported to have failed to work in dogs. But in many cases evidence suggested the vaccine was not at fault; the most common reasons for the vaccine not being responsible for the SLEE were:

- a full vaccination schedule had not been completed
- the SLEE occurred beyond the expected duration of immunity of the vaccine
- the SLEE occurred before effective immunity could be expected to have developed
- incubation of infection was suspected to have started before immunisation
- protection from the infection observed was not covered by the vaccine.

Cats

We received most reports of flea spot-on products used to treat cats not working as well as expected. You may see live fleas on your cat for a period of time after you have applied a spot-on flea product. This is because these products do not immediately kill fleas. You may be seeing fleas before the product has had time to act. Also, a cat's household environment, if not treated at the same time, may harbour live fleas. When the product on the cat gets beyond its normal period of effectiveness, those fleas may then re-infest the cat.

Rabbits[29]

In most of the cases in which vaccination against myxomatosis or rabbit haemorrhagic disease (RHD) appeared to be ineffective, diagnostic tests did not confirm the identity of the infection that developed. Therefore, there was insufficient evidence to support failure of the vaccine. The reasons that cast doubt on vaccine failure in other cases were:

- the clinical signs occurred before effective immunity could be expected to have developed
- the clinical signs occurred beyond the expected duration of immunity of the vaccine
- the positive identification of another cause of the signs seen
- protection from the infection observed was not covered by the vaccine.

Horses

Most SLEE cases in horses (12 reports involving 12 horses) followed the use of euthanasia products. Reporters described delayed onset of effect, both with and

[29] For information about rabbit-related research projects, including testing for Rabbit Haemorrhagic disease, www.harcourt-brown.co.uk/

without prior sedation. In several cases, the vet administered multiple overdoses without effect.

The number of cases involving lack of efficacy, when using euthanasia products in horses, serves as a reminder that an alternative means of administering euthanasia should always be available, in case the chosen method does not proceed as planned.

Exotic animals

The one ‘exotic’ animal SLEE report described a lower level of anaesthesia than expected in laboratory mice over a period of months after using ketamine. It was not clear whether the same batch of the anaesthetic was in use over the period.

Food-producing animals

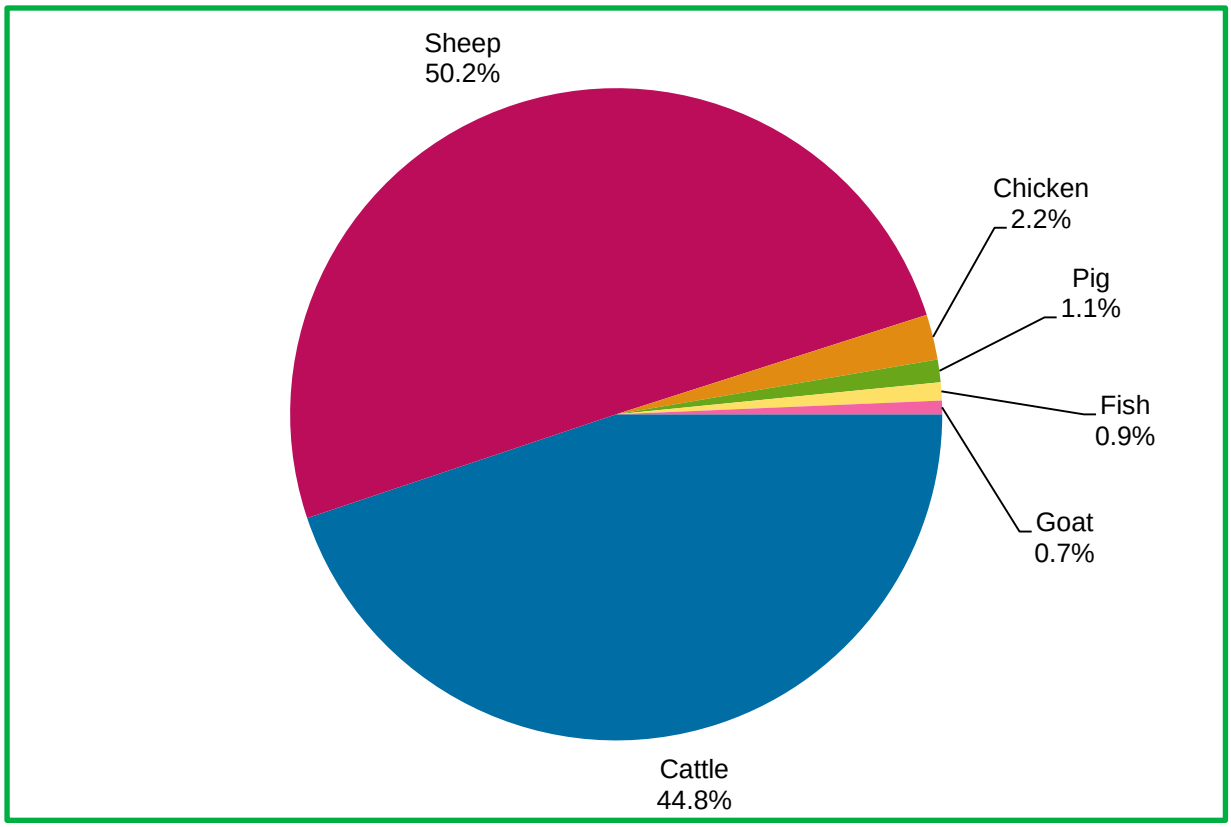


Figure 16 Proportion of SLEE reports per production animal species

As with pet animals, the number of reports with sufficient evidence to support a conclusion of lack of efficacy is significantly lower than the total reported (250/446). Table 3 shows the species and types of product associated with SLEE in these 250 reports.

Product type	Cattle	Sheep	Pig	Chicken	Fish	# of reports
Anti-parasitic	11	60				71
Hormone control	5					5
Infection control	3	1	1		1	6
Vaccine	70	84	3	9	1	167
Euthanasia		1				1
Species total	89	146	4	9	2	250

Table 3 Types of product and number of SLEE reports in different production species

Using figures from Defra's Farming Statistics[30], the number of SLEE reports received for each species was approximately:

- 1 report for every 49,000 cattle, or 1 lack of efficacy was reported in a bovine for every 2,300 bovines
- 1 report for every 119,000 sheep, 1 lack of efficacy was reported in a sheep for every 3,450 sheep
- 1 report for every 900,000 pigs, 1 lack of efficacy was reported in a pig for every 4,400 pigs
- 1 report for every 19 million chickens and other poultry, or 1 lack of efficacy was reported in a chicken for every 14,350 chickens.

The size of the fish population is unknown.

Cattle

We received 200 reports of suspected lack of efficacy in cattle involving 2,400 animals during 2016. For 40% of products there was an alternative explanation for the signs observed other than a lack of efficacy, such as:

[30] Farming statistics: livestock populations at 1 December 2016 – UK, www.gov.uk/government/statistics/farming-statistics-livestock-populations-at-1-december-2016-uk

- another disease, not covered by the medicine, was identified as having caused the signs observed
- the disease for which the vaccine was intended to provide protection, was not isolated
- the programme of treatment was incomplete or was not followed correctly
    - the interval between vaccinations was not as recommended
    - the animals treated were too young
    - the vaccination programme was not completed
- the SLEE occurred before effective immunity of a vaccine could be expected to have developed
- the SLEE occurred beyond the expected duration of immunity of a vaccine
- the medicine was administered by the wrong route
- the medicine was used for an unauthorised indication
- the animals were not healthy at the time of vaccination
- the disease developed too soon after vaccination for immunity to have developed, or may have been pre-existing.

For 49% of the products there was insufficient information to determine the contribution of those products used to the SLEE reported.

For the remaining 11% of products involvement in SLEE was not disproved. These products were of the following types:

- vaccine
- anti-parasitic
- hormone control
- infection control.

Lack of efficacy was most often reported after the use of vaccines against bovine respiratory syncytial virus + parainfluenza virus + *Mannheimia*, bovine viral diarrhoea virus and bovine rhinotracheitis virus.

Sheep

We received 224 reports of suspected lack of efficacy involving 6,900 sheep during 2016. These cases involved the use of 258 different products. For 19% of these products, their involvement in the observed lack of efficacy could be excluded by other explanations.

For vaccines these explanations were:

- the programme of treatment was incomplete or was not followed correctly
- another disease, not covered by the vaccine, was identified as having caused the signs observed,
- lambs would not be expected to be protected for such a long period after the ewes were vaccinated during pregnancy
- the SLEE occurred before effective immunity of the vaccine could be expected to have developed
- the SLEE occurred beyond the expected duration of active or passive immunity of the vaccine.

For treatments against internal and external parasites

- the product was applied incorrectly
- too little product was applied
- too many animals were dipped in the same bath before the solution was replaced
- the product had passed its expiry date.

For 57% of products (mainly bacterial vaccines), insufficient information was provided to determine the contribution of those products to the SLEE reported.

The remaining 23% of products for which the lack of efficacy was not disproved were:

- vaccines, mainly bacterial
- treatments for internal and/or external parasites:
    - pour-on solutions, containing dicyclanil, cypermethrin, alpha-cypermethrin

- oral medicines, containing moxidectin +/- triclabendazole, levamisole +/- triclabendazole, triclabendazole, albendazole, fenbendazole
- injections, containing doramectin, moxidectin.

Pigs

We received five reports of a suspected lack of efficacy involving 1,020 pigs during 2016. Four involved the use of vaccines, the other an antibiotic.

In two of the four vaccine cases, lack of efficacy relating to either of the vaccines used was excluded as a cause of the clinical signs observed for the following reasons:

- another disease, not covered by the vaccine(s), was diagnosed
- the piglets were not healthy at the time of vaccination and it was not certain the vaccinations were done correctly.

In the third vaccine case, Glassers Disease was diagnosed at *post mortem*, but no serovar was isolated to support the lack of efficacy claim.

In the final vaccine case, clinical signs of *Erysipelas* were observed despite vaccination.

In the antibiotic (florfenicol) case, the product was being added to the feed on-farm and the dates and amounts administered were not as recommended, so it was not possible to determine the involvement of the product in the observed lack of efficacy.

Goats

For goats, three cases of a suspected lack of efficacy were reported.

There are only six vaccines authorised for use in goats. Neither of the two vaccines associated with the three cases of lack of efficacy involving 35 goats, are authorised for use in this species. As efficacy of these products has not been tested in goats, lack of efficacy cannot be claimed in this species.

Farmed fish

For trout, one case of suspected lack of efficacy involving over 800 fish was reported during 2016. Traceability of fish movements was poor and evidence of vaccination was missing, so it was not possible to determine the role of the vaccine reported to have been used in this case in the development of the clinical signs observed.

For salmon, three cases of suspected lack of efficacy involving 10,800 fish were reported. In one case another disease, not covered by the vaccine that had been

used, was identified as having caused the signs observed. In another, the cause of the signs observed was not confirmed, so the failed efficacy of the vaccine used was not proven. In the third case, florfenicol antibiotic was suspected of having failed to clear an infection, but no laboratory tests were performed to determine the nature of the infection before treatment commenced.

Chickens

Of the ten reports of a suspected lack of efficacy of vaccination involving over 13,000 chickens, five possibly had alternative explanations for the clinical signs observed other than vaccine failure.

The two cases received following coccidiosis vaccination were found to be due to

- incorrect dosing and another infection was suspected
- *E. necatrix* infection was confirmed, two months after vaccination

In two of five reports received following vaccination against Marek's disease

- Marek's was not isolated after several diagnostic tests
- it was unclear whether the birds that died had actually been vaccinated

In one case reported following vaccination against *Salmonella typhimurium*, the incorrect route of administration (coarse spray, rather than in drinking water) was used, and the second dose was administered at two-weeks of age, instead of between six and eight weeks.

Two cases related to the use of infectious bursal (Gumboro) disease vaccine. In both cases Gumboro disease was suspected, but not confirmed. Birds were being rejected at slaughter because of fatty livers, perihepatitis and small size.

Safety reports

Figure 17 shows how many safety reports we received during 2016 for different groups of animals.

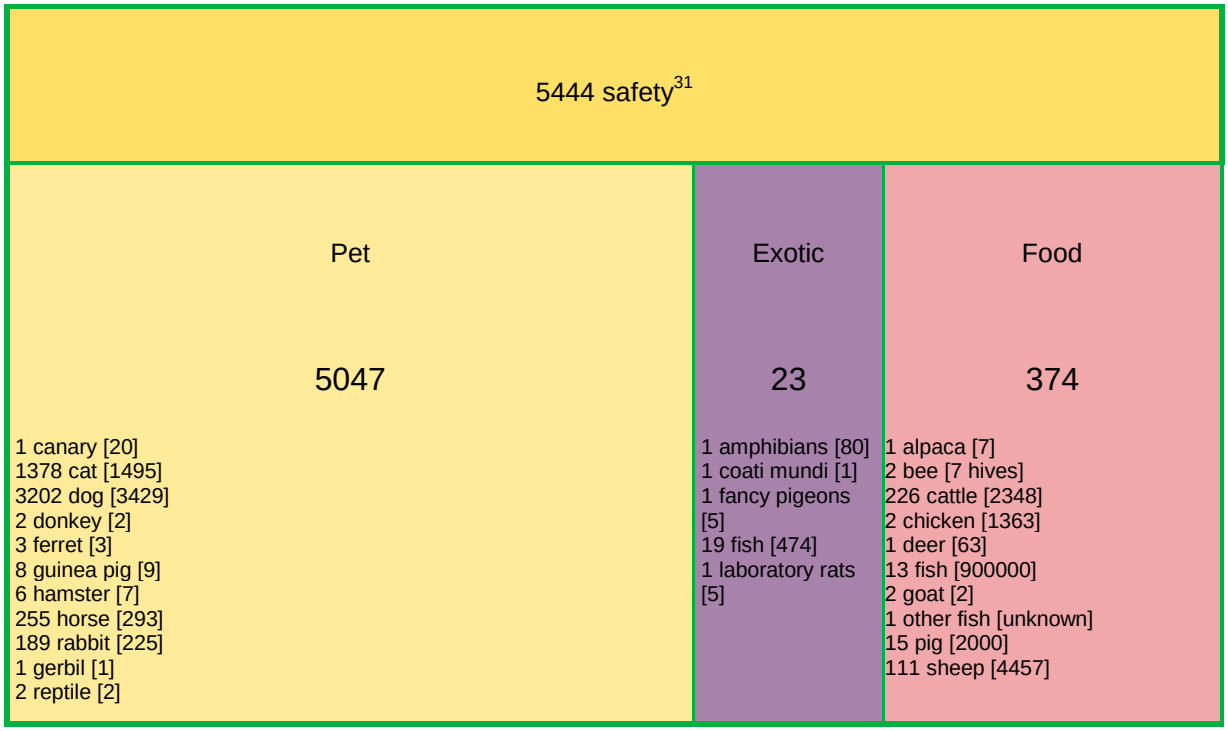


Figure 17 Number of safety reports received for different groups of animals [Number of animals involved]

Pet animals

Of the 5047 pet animal safety reports 3202 (63.4%) involved dogs. Further reports related to:

- cats (27.3%)
- rabbits (3.7%)
- horses (5.1%).

Using the Pet Food Manufacturer's pet animal population figures for 2016[32], we can calculate that we received:

- 1 safety report for every 2,650 dogs, or 1 adverse reaction in a dog was reported for every 2,478 dogs

[31] Some safety reports may involve a lack of efficacy element; in these cases, 'lack of efficacy' is recorded with any other clinical signs observed.
[32] Pet Food Manufacturers' Association, Pet Population - 2016, www.pfma.org.uk/pet-population-2016

- 1 safety report for every 5,450 cats, or 1 adverse reaction in a cat was reported for every 5,017 cats

- 1 safety report for every 4,230 rabbits, or 1 adverse reaction in a rabbit was reported for every 3,555 rabbits.

Using figures from the British Equestrian Trade Association[33], we can calculate that we received 1 safety report for every 3,700 horses, or 1 adverse reaction in a horse for every 3,222 horses.

Dogs

We received 3,202 reports describing adverse reactions involving 3,429 dogs.

A total of 4,645 products of all types were recorded in these 3202 reports associated with adverse reactions in dogs following the use of authorised medicines and various other products.

Table 4 shows a breakdown of the types of products suspected of involvement in adverse reactions in dogs.

[33] British Equestrian Trade Association, National Equestrian Survey 2015, www.beta-uk.org/pages/industry-information/market-information

Product type	Number
Authorised veterinary medicine	4320
Incompletely identified vet medicine	139
Human authorised medicine	138
Other veterinary product	20
Imported medicine	6
Extemporaneous veterinary medicine	9
Non-medicinal product	6
Unidentified product	4
Biocide or disinfectant	3

Table 4 Breakdown of product types thought to be related to adverse reactions in dogs

Authorised veterinary medicines

Vaccines were the largest group (46.2%) of authorised veterinary medicines recorded as potentially being involved in adverse reactions in dogs. Table 5 shows the top 10 groups of authorised veterinary medicines recorded.

Medicine type	Number of product reports	% of all authorised products reported
Vaccine	1995	46.2
Parasites	709	16.4
Inflammation control	634	14.7
Infection control	209	4.8
Hormone control	310	7.2
Anaesthetics & sedatives	141	3.3
Epilepsy control	121	2.8
Heart & circulation	103	2.4
Pain relief	62	1.4
Anti-vomiting	21	0.5

Table 5 The 10 most often recorded groups of authorised veterinary medicines associated with adverse reactions

A further 15 products were authorised medicines for:

- induction of abortion in pregnant bitches
- cancer treatment
- treatment of metabolic acidosis
- behaviour modification
- herbal treatment of various ailments
- vitamin deficiency
- relief of respiratory difficulties.

Vaccines

We received 1285 reports involving the use of vaccines in dogs. Three of these reports recorded the use of four different vaccines. Eighty one reports recorded the use of three vaccines, a further 539 recorded the use of two vaccines, leaving 662 using a single vaccine.

The vaccines most mentioned were inactivated *Leptospira* only vaccines. Live viral vaccines offering combined protection against distemper, adenovirus and parvovirus were the next most often reported group of vaccines. Combined live viral and inactivated bacterial vaccines for protection against distemper, adenovirus, parainfluenza, parvovirus and leptospirosis were the next most often reported vaccine group. The only other vaccine group with a significant number of reports was for vaccines with a live *Bordetella* component and an inactivated parainfluenza component.

During 2016, we became aware of a growing number of social media sites publicising concerns with dog vaccinations, in particular vaccines that contain four inactivated strains of bacteria for the prevention or reduction in *Leptospira* (L4) infections. As a result of this, in March 2017 we wrote a letter[34] to vets reassuring them that we are continuously monitoring these and other vaccines containing only two strains of *Leptospira* (L2). From the reports we had received, we could calculate that fewer than two adverse reactions for L2, and fewer than seven for L4, for every 10,000 doses of the vaccines sold were reported. This indicates that these events are rare following the use of either type of vaccine.

Figure 18 shows the relative distribution of groups of clinical signs associated with the use of *Leptospira*-only vaccines, with either 2 or 4 strains, compared with all *Leptospira*-only vaccines. The frequency of each group of signs is calculated relative to ‘General signs or symptoms’, which was the most commonly recorded sign, usually Lethargy.

It is important to remember that in many cases more than one vaccine and/or other products may be associated with the clinical signs recorded.

[34] Adverse events in dogs given *Leptospira* vaccines, Robbins, H., Ursich, E. (2017) Adverse events in dogs given Leptospira vaccine. Veterinary Record 180, 257

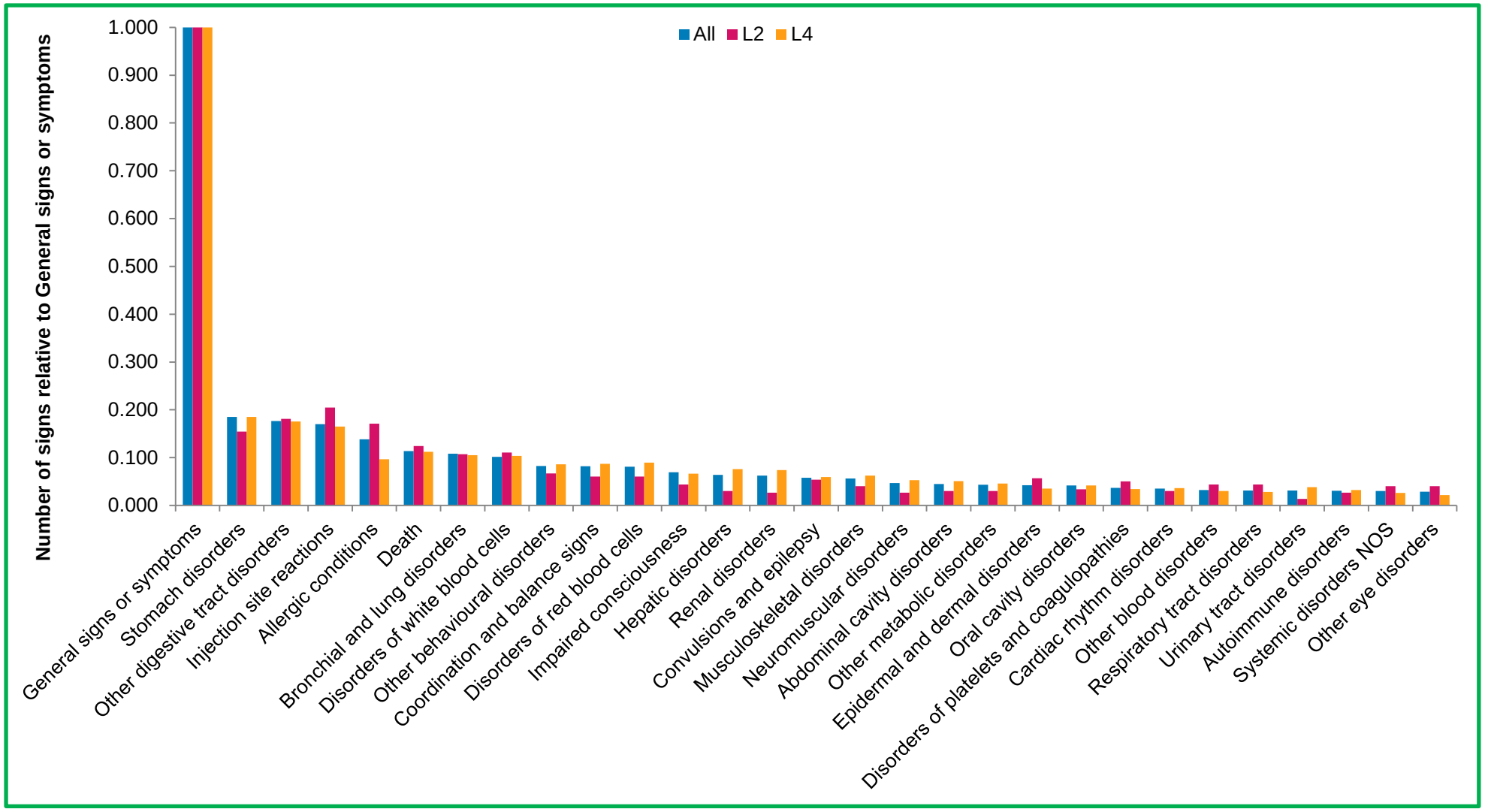


Figure 18 Number of different groups of clinical signs relative to the number of general signs for vaccines containing only either 2 or 4 *Leptospira* strains, compared to all *Leptospira*-only vaccines

Parasites

During 2016, we received 667 adverse reaction reports involving the use of anti-parasitic medicines in dogs.

External parasites

For those products containing fluralaner, the most common clinical signs reported, in the 158 cases received following the administration of tablets, were general signs, such as lethargy and anorexia. Other signs reported were digestive tract disorders, such as vomiting or diarrhoea. The product information lists all of these signs.

Fifty four reports described adverse reactions following the use of spot-on products containing permethrin in combination with other active ingredients. The greatest number of reports described either application site or more generalised pruritus. Reporters also described hyperactivity, other behavioural disorders and lethargy.

We received thirty three reports of adverse reactions following the use of spot-ons containing fipronil. The most often reported clinical sign was convulsion. In one of these cases the owner had administered the product in food, rather than applying it to the dog's skin. These cases involving fipronil illustrate the pattern of reporting we often see with products containing well-established active ingredients. We no longer receive many reports of the signs most commonly expected, meaning that you may perceive a distorted view of the safety of a product due to the few rarer, but more serious signs recorded.

Internal and external parasites

We received 142 reports of adverse reactions that occurred after the use of spot-ons containing moxidectin in combination with other active ingredients. The most commonly reported general signs were lethargy and anorexia. Behavioural disorders, such as hyperactivity and vocalisation, and application site reactions were reported less often.

We received 96 reports of adverse reactions that occurred following the use of tablets containing milbemycin in combination with other active ingredients. Lethargy and anorexia were most commonly reported, followed by digestive tract disorders, such as diarrhoea and vomiting.

Internal parasites

We received 14 reports involving the use of tablets containing febantel in combination with other active ingredients. Vomiting and diarrhoea were most commonly reported, together with anorexia.

Fenbendazole, administered as oral granules, suspension or paste, resulted in general signs and symptoms, such as abnormal test results, or digestive tract disorders, such as vomiting or diarrhoea, in the 16 reports we received.

Clinical signs observed after the use of anti-protozoal tablets, containing metronidazole, were usually general signs, but there were also records of neurological disorders, such as coordination or balance problems, convulsions or epilepsy, or neuromuscular disorders. We received only 13 reports involving this active ingredient.

Inflammation control

We received 630 reports describing the clinical signs observed after the administration of medicines used to control inflammation. Almost 55% of these reactions involved a non-steroidal anti-inflammatory drug (NSAID). 30% of reports involved medicines that suppressed the immune system, either Janus kinase inhibitors or T-cell activity reducers, and the remainder corticosteroids.

Figure 19 shows a comparison of the clinical signs most often observed following the use of the three most commonly reported classes of non-steroidal anti-inflammatory drugs. The occurrence of each sign is given relative to the number of times lethargy was observed and therefore does not provide a direct comparison of relative frequency.

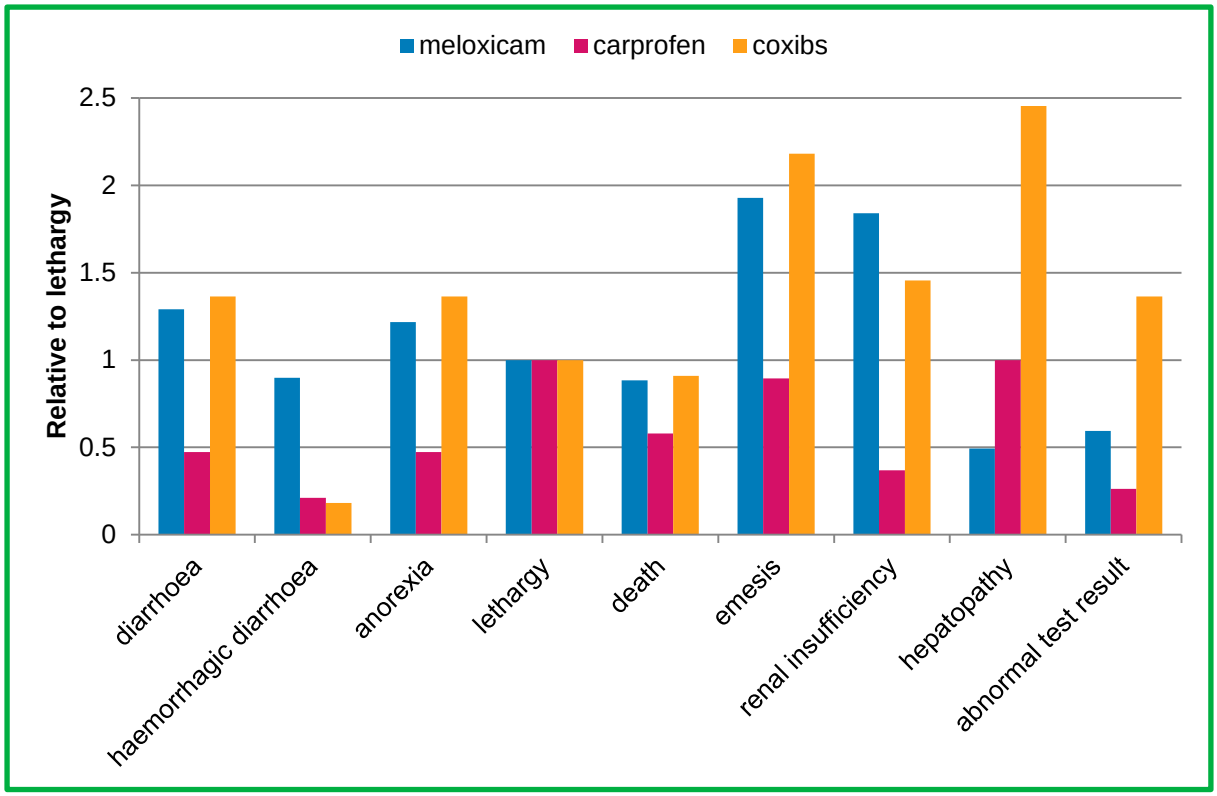


Figure 19 Comparison of clinical signs observed following the use of different types non-steroidal treatment for inflammation

Infection control

During 2016, we received 107 reports involving the use of systemic antibacterials. The substances contained in these medicines included penicillin beta-lactams (47 cases), other beta-lactams (cephalosporins) (26), fluoroquinolones (13), lincosamides (clindamycin and lincomycin) (13), combinations of trimethoprim with various sulfonamides (9), a combination of spiramycin with metronidazole (2) and a tetracycline (1). Some cases involved the use of more than one class of antibiotic.

For beta-lactams, general signs, such as anorexia, and digestive tract disorders, such as vomiting and diarrhoea, were most often reported. For penicillins, renal insufficiency was also often reported.

For the other groups of systemic antibacterials, there were insufficient cases to provide an overview of common clinical signs observed.

We received 31 reports relating to treatments for either eye (7) or ear (24) infections. The most common clinical sign reported was deafness, following the use of eardrops containing dexamethasone or prednisolone in combination with other anti-infective substances.

The clinical signs most often reported after the use of metronidazole, for the treatment of protozoal or anaerobic bacterial (clostridial) infections, were neurological. Signs reported in the 13 cases we received included ataxia, convulsions and neuromuscular disorders.

The three reports of the treatment of minor skin infections with the corticosteroid betamethasone in combination with an antimicrobial did not reveal any common adverse signs.

In three cases the reporter did not specifically identify the antibiotic(s) involved.

Hormone control

We received 15 reports involving the use of insulin as a treatment for diabetes mellitus. Five of those reports related to the use of an intermediate-acting human insulin, authorised for use in cats; the remaining 10 related to the use of an intermediate-acting pork insulin, authorised for use in dogs.

We received 115 reports following the use of desoxycortone for the treatment of Addison's disease. In these reports, an electrolyte disorder was the most commonly reported clinical sign, with associated signs of lethargy, emesis, anorexia, diarrhoea or polydipsia.

Only 15 reports related to the use of thyroxine replacement medicines. Some of the signs observed may have been associated with an overdose, but the majority were too infrequent to make an assessment of their association with the treatment.

Human authorised medicines

The greatest number of adverse events following the administration of medicines authorised only for human use were reported for antimicrobial products. As in previous years, these were almost exclusively associated with a combination of amoxicillin and clavulanic acid. In 70 reports involving this medicine, more than half of all clinical signs recorded were allergic conditions:

- allergic oedema
- urticaria
- peri-orbital oedema

No other human medicines, involved in a total of 61 reports, including

- tramadol
- fludrocortisone
- ranitidine

- omeprazole
- azathioprine

were reported sufficiently to form clear profiles of clinical signs.

Extemporaneous veterinary medicines

Only tetracosactide and trilostane were reported to have been involved in adverse events after the use of individually formulated veterinary medicines.

For both products general signs such as:

- lethargy
- emesis
- anorexia

were reported. But for neither product was there sufficient information to form a clear profile.

Non-medicinal veterinary products

We received three reports relating to the use of contrast media and sutures.

Prescription or dispensing errors[35]

We have identified three reports in which a dog received incorrect medication.

In one case, a dog owner was given an oral syringe intended for the administration of a low strength NSAID solution to a cat. The syringe was graduated by body weight, at the maintenance dose required for a cat. This resulted in the dog receiving a larger volume than intended of the higher strength solution prescribed, resulting in a 1.5 times overdose. The dog had pre-existing elevated renal parameters and became dehydrated with polydipsia. The final outcome is unknown.

A dog that had developed lymphopenia and diarrhoea within 3 weeks of completing a primary course of vaccination against *Leptospira*, was erroneously vaccinated again 5 months after the second vaccination. The diarrhoea that had resolved with a special diet recurred within 3 days of the third vaccination. The dog was referred to a specialist for its ongoing gastro-intestinal issues. The final outcome is unknown.

A dispensing error led to a dog receiving a 4-times overdose of amoxicillin and clavulanic acid tablets. The dog returned to the surgery 3 days after its original visit

[35] Adverse events relating to dispensing errors Veterinary Record (2015) **177**, 360-362

with signs of meningitis. These signs were not thought to be related to the overdose, and the dog was reported to have made a full recovery the following day.

Other administration errors

In the first case, a dog developed pain at the injection site and pyrexia after it was given a kennel cough vaccination subcutaneously.

A large overdose of sulfadiazine and trimethoprim tablets, repeated over 10 days, led to the death of a dog after it became lethargic and was vomiting. The dog was initially treated with maropitant and sent home, but it developed a large haematoma at the injection site. The dog was diagnosed with acute liver failure and died the following day. *Post mortem* examination revealed extensive areas of haemorrhage in both the thoracic and abdominal cavities. The conclusions from this examination are not known.

An owner accidentally administered an underdose of trilostane to a dog that had hyperadrenocorticism. This continued for almost 3 weeks before being corrected. The dog lost weight, developed diabetes and was consequently going to be put on insulin.

Finally, a dog received a 1.8 ml dose of desoxycortone instead of a dose rate of 1.8 mg/kg. This resulted in a dose rate of 3 mg/kg. Ten days later blood potassium was found to be low, so the dog was put on oral supplementation.

Accidental exposure to treatments intended for other species

Treatment for equine Cushing's disease

We received six cases in which dogs reacted to the ingestion of pergolide.

In one case, it is not clear whether the dog stole a half tablet, or the owner administered it instead of the dog's own medicine. The dog vomited and became hypothermic with muscle tremors.

In two linked cases, two dogs each ingested more than 10 tablets that they stole from a table. A 23kg Golden Retriever vomited several times, developed diarrhoea, was lethargic and had ptosis. Blood tests revealed hyperglycaemia, hypokalaemia, raised alkaline phosphatase and alanine aminotransferase. It had recovered by the following day with supportive treatment. The second dog, a 6.2 kg Pinscher, vomited once, became hypothermic with muscle tremors, was hypersalivating and had ptosis. This dog had also recovered by the following day with similar treatment.

A 15kg Springer spaniel was suspected of having taken a tablet from a horse's feed bucket, when it had an episode of diarrhoea, followed by acute onset vomiting,

becoming ataxic, noise sensitive, panting and having muscle tremors. These signs resolved by the following day after treatment with activated charcoal and diazepam.

A whippet and a whippet crossbreed were suspected of ingesting one and a half tablets between them, when they developed vomiting, lethargy and weak femoral pulses later the same day. Both dogs were treated with intravenous fluids, but the final outcome is unknown.

Finally, a Hungarian Vizsla was seen on two occasions, less than 24 hours apart, to ingest the faeces of a horse that was being treated with pergolide. The dog, which had pre-existing epilepsy, collapsed within 24 hours of the first ingestion, with pale mucous membranes, severe vomiting, muscle tremors and ataxia. The signs had resolved the following day.

Oral horse wormers

A young Jack Russell terrier ingested moxidectin from a discarded syringe and later the same day became restless with hyperaesthesia, muscle tremor, dilated pupils and panting. The dog was referred to a specialist. The final outcome is unknown.

Another dog ate horse feed that had moxidectin wormer mixed into it. The dog developed hypersalivation, ataxia, muscle tremors and pyrexia. It showed signs of recovery, after intravenous lipid infusion therapy.

A border collie was seen to have mydriasis, blindness, ataxia and was vomiting some hours after several horses were treated with an ivermectin wormer. The owner would not allow the dog to be hospitalised, but after 5 days of treatment with charcoal and water, the dog was improving, though still unsteady.

Sheep oral suspension

A Border collie was found by a farmer to be very lethargic and barely responsive. It vomited once, so he took it to the vet. During a discussion of the possible routes of exposure to toxins, the farmer recalled that the previous day he had seen the dog lick the face of a sheep that had been dosed with an albendazole drench. Blood tests revealed acute liver damage. The dog became completely comatose, passed haemorrhagic diarrhoea and was euthanased on welfare grounds.

Sheep pour-on

A collie dog was taken to the vet because it had developed a ‘drunken gait’ three days earlier. It is unknown whether the dog had ingested any product, but it was known that it had been exposed to some spilt alpha-cypermethrin product, whilst in a vehicle. The final outcome is unknown.

Dog owners should be aware that they must not allow their pets to ingest anything they may find on the ground in areas where large animals are kept or treated. Even dung can contain medicinal residues that may be harmful to a dog if ingested.

People who administer medicines to large animals should dispose of 'empty' containers, so that they cannot be accessed by dogs or other animals. If any medicine is spilt, it must be dealt with immediately.

Cats

We received 1,378 reports describing adverse reactions involving 1,495 cats.

A total of 2,079 products of all types were recorded in these 1376 reports associated with adverse reactions in cats following the use of authorised medicines and various other products.

Table 6 shows a breakdown of the types of products suspected of involvement in adverse reactions in cats.

Product type	Number
Authorised veterinary medicine	1988
Incompletely identified vet medicine	47
Human authorised medicine	19
Other veterinary product	9
Extemporaneous veterinary medicine	6
Biocide or disinfectant	6
Non-medicinal product	2
Unidentified product	2

Table 6 Breakdown of product types thought to be related to adverse reactions in cats

Authorised veterinary medicines

As with dogs, vaccines were the largest group (41.8%) of the authorised veterinary medicines recorded as being involved in adverse reactions in cats. Table 7 shows the top 10 groups of authorised veterinary medicines recorded.

Medicine type	Number of product reports	% of all authorised products reported
Vaccine	831	41.8
Hormone control	245	12.3
External parasites	237	11.6
Internal & external parasites	200	10.1
Inflammation control	132	6.5
Internal parasites	127	6.2
Anaesthetics and sedatives	109	5.4
Infection control	72	3.5
Pain relief	34	1.7
Heart & circulation	27	1.4

Table 7 The 10 most often recorded groups of authorised veterinary medicines associated with adverse reactions

A further 17 (0.8%) products were authorised medicines including:

- prevention of vomiting
- vitamin supplementation
- sedation reversal
- epilepsy treatment

Vaccines

We received 490 reports involving the use of vaccines in cats. Four of these reports reported the use of four vaccines, five reported the use of three vaccines, 319 reported the use of two vaccines and the remainder (162) reported only one vaccine.

The most commonly reported group of vaccines were those containing live attenuated strains of feline calicivirus, feline rhinotracheitis virus and feline panleucopenia virus.

Slightly fewer reports were received of adverse reactions to inactivated viral vaccines for the reduction of feline leukaemia virus infection. As these two types of vaccine are most often administered at the same time, it is not possible to determine which clinical signs observed relate to which vaccine. In cases where these two vaccines were administered together, the top five signs reported during 2016 were:

- Lethargy
- Anorexia
- Hyperthermia
- Emesis
- Injection site reaction, not described.

Hormone control

We received two hundred reports of adverse events that occurred during treatment of hyperthyroid conditions in cats. Figure 20 compares the clinical signs reported after use of medicines containing carbimazole and thiamazole. Note the data set for thiamazole is much smaller than for carbimazole.

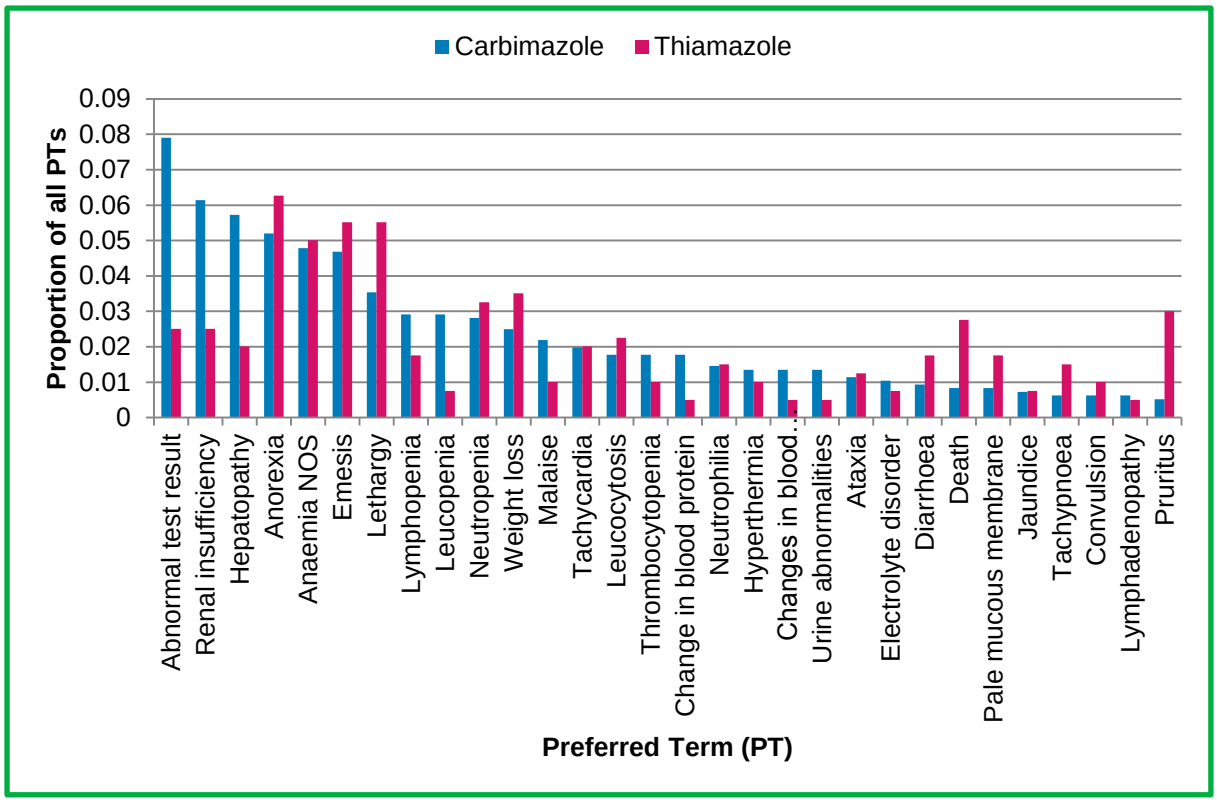


Figure 20 Comparison of clinical signs reported after use of carbimazole- and thiamazole-based medicines for the treatment of hyperthyroidism

External parasites

A variety of active substances are used to prevent the infestation of cats with fleas and other external parasites. For collars containing flumethrin, localised reactions, such as hair change, inflammation, lesions, reddening of the skin and pruritus, were most often reported.

For fipronil spot-ons and sprays, hair changes, convulsions, lethargy, emesis, ataxia, skin reddening and diarrhoea were most often reported. For indoxacarb spot-ons ataxia, was the most common sign reported, together with emesis, mydriasis and other neurological disorders.

For fluralaner spot-ons lethargy was most commonly reported, together with hair changes, emesis and anorexia. We received fewer reports following the use of spinosad chewable tablets; the main sign reported was lethargy.

Internal and external parasites

Treatments for both internal and external parasites contained either an avermectin, selamectin or eprinomectin in combination with other endectocides, or moxidectin in combination with an ectoparasiticide. The most common sign reported following the use of each of these groups of medicines was application site hair changes. Other

signs were lethargy, and other application site disorders, such as reddening of the skin or lesions.

Off-label exposure to treatments intended for other species

A cat, with a pre-existing heart murmur, had an episode of syncope with ataxia, dilated pupils and laboured breathing, on the day its dose was increased from half a small oclacitinib tablet to a whole tablet. The treatment was stopped, but the cat experienced a similar episode the following day.

A cat with a history of chronic paw infection had another broken limb amputated one week before enrofloxacin oral solution was administered by the owner to treat the infected paw. Within two hours of administration, the cat showed respiratory distress and died.

The ears of a cat with chronic bilateral ear disease were cleaned with a standard ear cleaning solution. The vet was unable to check the state of the cat's eardrums due to debris and narrowness of the ear canal. A combination amphenicol antibiotic, steroid and antifungal ear gel was instilled into each ear. Within 10 minutes, the vet noticed the cat's left pupil was myotic; a sign of Horner's syndrome. No other signs were noted, and no other information was received.

In a similar case involving the same medicine, a cat was treated with the product after the vet had confirmed its eardrums were intact. One week later, a second dose was administered, although the vet thought the ears were looking better. When the cat got home, the owner found it was ataxic, its right third eyelid was protruding and the pupil was constricted on that side. Horner's syndrome was diagnosed. Four days later the cat was almost recovered.

In another case, an owner returned to the vet a week after a third cat had been treated with the product, reporting that the cat had been vomiting, was anorexic and was showing signs of Horner's syndrome. The cat's third eyelid was protruding and it had a corneal ulcer. The vet suspected the tympanic membrane was ruptured prior to the product administration. The signs were improving after 7-days treatment with antibiotic, for a middle ear infection, but the signs of Horner's syndrome did not resolve.

Another cat was treated with a combination aminoglycoside antibiotic, steroid and antifungal ear suspension. This was to treat pus in the ear. The cat was treated twice daily for a week. The owner notice the cat had developed head tilt, so the ear treatment was replaced by oral antibiotics. A further week later, the head tilt had resolved. A week after that, the head tilt had returned and a swab revealed a profuse *Staphylococcus* growth.

A vet dispensed milbemycin/praziquantel tablets for cats to an owner one morning. Later that day, the owner returned with four lethargic, twitchy kittens that had collapsed. The owner had given each eight-week-old kitten a whole tablet, appropriate for a cat of over 4 kg. The smallest kitten died overnight, but the other three recovered after two to three days of intravenous fluids and lipid infusion.

An owner treated 4 cats with a permethrin dog spot-on. Two of the cats were taken to the vet, when they started foaming at the mouth and fitting. They were euthanased. The other two that had run off after treatment, returned trembling and wide-eyed. One week later they were reported to have recovered.

An owner split an extra-large dog fipronil/permethrin spot-on between four cats. Within an hour, one of the cats collapsed with tremors and increased heart and respiration rates. It was treated with diazepam. The outcome is unknown.

A cat that was being treated with thiamazole for hyperthyroidism was then treated with phenobarbital drops for seizures. Elevated liver enzymes were detected an unknown time after the phenobarbital treatment. It was decided to stop the phenobarbital treatment, though no interaction between the two medicines is known.

A cat, with inflammatory bowel disease, was treated with an injectable vitamin B12 supplement, intended for use in large animals. A purulent abscess formed close to the injection site within 24 hours. The outcome is unknown.

YOU MUST NOT administer any product to any animal for which it is not intended. Only a vet is able to advise whether it is safe to use an authorised product ‘off-label’, but pharmacists and SQPs can supply a product for use ‘off-label’, providing there is a prescription issued by a vet. Without such advice, you are risking the health of your pet and may end up with a hefty vet bill.

Accidental exposure to treatments intended for other species

In three similar cases, owners accidentally applied a large dog imidacloprid/permethrin spot-on to their cats. In the first case, a cat was exhibiting twitching, muscle tremors and ataxia within six hours of application. These signs persisted for at least two days. The final outcome is unknown.

In the second case, the cat ‘disappeared’ for two hours after the medicine was applied, and was showing signs of twitching and hypersalivation when it returned, The cat also had blood in its urine. It was taken to the vet, who administered fluids, diazepam and other sedative treatment. Nevertheless, by the following day it was seizuring and the decision to euthanase was taken.

In the third case, the cat developed tremors on the day after administration. These progressed to twitching, spasms and seizures. The cat was euthanased, as treatment with diazepam, sedatives and anaesthetics failed to reduce the signs.

A 0.7 kg six-week-old kitten accidentally ingested a 400 mg imepitoin tablet. One hour later it vomited. Half an hour after that it was circling, pacing, sleepy and disorientated, with possible nystagmus and hyperaesthesia. The cat slept for 24 hours and was reported to have fully recovered.

If you have both cats and dogs in your household, you should ensure that when treating your pets with spot-ons, you use the correct medicine for each animal. You should also ensure that your pets are unable to ingest the products, either by grooming themselves, or each other. Keep your pets separate, especially cats from treated dogs, until the product is completely dry.

Human medicinal products

Dantrolene was prescribed for a cat with urethral spams, which were causing blockages. Within 9 days of the start of treatment, the cat had developed liver failure, which resulted in death 6 days later.

In another similar case, oral diazepam was used to treat a cat with a blocked urethra due to spasms. After five days of treatment, blood tests showed raised liver enzymes and the cat died three days later, in spite of fluid therapy.

Another cat was treated for urinary retention with prazosin. Within six hours, the cat appeared profoundly weak, had tachycardia and low blood pressure. It recovered after fluid treatment and withdrawal of prazosin.

Prazosin and meloxicam were also used to treat a cat with a blocked bladder. After six days of treatment, the cat developed haemorrhagic enteritis or colitis. The outcome is unknown.

Prescription or dispensing errors[36]

A cat was accidentally vaccinated with a dog vaccine (adenovirus, distemper virus, parainfluenza virus, parvo virus, Leptospira canicola, Leptospira icterohaemorrhagiae) at the same time as it was given its Feline leukaemia virus vaccination. The following day, the owner reported that it had been inappetent and moderately ataxic.

[36] Adverse events relating to dispensing errors Veterinary Record (2015) **177**, 360-362

A cat died following over-administration of fluids due to an equipment problem. The equipment showed a volume of 32 ml had been infused; the actual volume was 400 ml.

A vet administered atipamezole in error, instead of medetomidine, to a cat before a routine castration. The cat had tremors for five minutes and was then over-reactive to its surroundings. The cat recovered and the castration was postponed until the following week.

In three cases we received during 2016, owners were dispensed meloxicam oral suspension for use in dogs instead of the intended oral suspension for cats. This medicine is three times the strength of the oral suspension for cats.

In all three cases the cat developed out-of-range blood parameters, and in one case the cat also developed facial twitching. In none of the cases was the final outcome known.

Other administration errors

In five cases, all involving meloxicam 0.5 mg/ml oral suspension for cats, owners gave their cats overdoses by mistake. In three of the four cases it is clear that the vet provided appropriate instructions, but the owner still managed to administer the incorrect dose. In two cases whole bottles of medicine were administered; one 3 ml; the other 15 ml. One cat was euthanased, one developed regenerative anaemia, one recovered after a week of supportive treatment, one was still being treated with fluids and for the other the outcome is unknown.

A cat had a hypoglycaemic event, which the owner treated with Glucogel. The owner had been giving the cat 10 times the insulin dose it should have had, but after treatment it was fine, and had been on twice daily doses for several months after that. The signs of diabetes were resolving and the cat had gained weight, so the owner was happy.

Extemporaneous veterinary medicines

Six cases involving the use of a transdermal gel for the treatment of hyperthyroidism were received. Three of the cases described reddening and irritation of the application site, which resulted in self-trauma in one case.

One owner reported that their cat was deaf, during its treatment.

Another owner discovered their cat was seizuring and had bitten its tongue.

In the final case, a cat developed a deep corneal ulcer, seven days after the medicine was administered. It had stroked the application site with its paw, whilst it was still wet, and spread the medicine into its eye. Outcome unknown.

Imported products

No reports relating to imported products for the treatment of cats were received during 2016.

Other veterinary products

We received nine reports involving various unauthorised ear cleaners and liver, kidney or joint supplements.

Biocides

We received two reports of cats being affected by sprays. In one case, a cat died from permethrin poisoning, even though its owner was careful to exclude the cat whilst a rug was being sprayed. In the other, a cat displayed neurological signs after it was sprayed with a product containing methoprene, an insect growth regulator. The owner washed the product off and the cat recovered within 30 minutes.

Three of five cats treated with different products containing margosa oil extract died after developing twitching, convulsions, and vomiting.

Rabbits

189 safety reports were received during 2016 involving 225 pet rabbits.

Authorised veterinary medicines

81% of all authorised medicines reported were for vaccination against myxomatosis and rabbit haemorrhagic disease (RHD). Eleven of the 160 products, involved in vaccination against these diseases, were an imported vaccine, which is given to protect against a variant strain of RHD that appears to be becoming more common in the UK. This vaccine does not cover myxomatosis, so a second vaccine for that has to be given at the same time. Death, skin disorders and lesions, lethargy and eye or eyelid disorders were most often reported in relation to administration of these vaccines.

In only 15 of the 129 cases involving the death of a rabbit following vaccination with a combined myxomatosis/RHD vaccine was a *post mortem* examination carried out. In four of these cases we did not receive the results or they were inconclusive, in two cases (linked) RHD was not detected, in five cases (two linked) the presence of the variant strain of RHD was confirmed and in another the absence of myxomatosis was confirmed. In the remaining three cases, death was attributed to hepatic coccidiosis, pasteurella infection and *E coli* septicaemia.

In only two of the cases involving death following vaccination with the imported RHDV2 vaccine was a *post mortem* examination carried out. In both cases, the rabbit that died had been previously vaccinated against myxomatosis. In one case the *post mortem* results were inconclusive, and in the other the presence of RHDV2 was confirmed, but the rabbit was only vaccinated against this, two days previously.

Other authorised veterinary medicines reported in rabbit safety reports included

- anaesthetics (alfaxalone, ketamine)
- analgesics (buprenorphine)
- sedatives (medetomidine)
- antibiotics (sulfadiazine and trimethoprim, enrofloxacin, marbofloxacin)
- anti-inflammatories (meloxicam)
- wormers (fenbendazole)
- ectoparasiticides (cyromazine, imidacloprid)
- endectocide (selamectin)

Off-label exposure to treatments intended for other species

These included

- anaesthetics (alfaxalone, ketamine)
- analgesics (buprenorphine)
- anti-inflammatories (meloxicam, dexamethasone)
- sedative (dexmedetomidine)
- wormer (fenbendazole)
- endectocide (selamectin)

Prescription or dispensing errors[37]

No prescription or dispensing errors relating to the administration of product to rabbits were received during 2016.

[37] Adverse events relating to dispensing errors Veterinary Record (2015) **177**, 360-362

Horses

In 2016 we received 255 safety reports involving 293 horses, of which 132 involved the use of a vaccine.

A majority of the vaccine cases involved the use of a combined vaccine against equine influenza and clostridium. There are two types of vaccine with these two components; in one, the influenza component is inactivated; in the other the influenza virus is live, but attenuated. In both types of vaccine, the clostridium component is inactivated.

The profile of clinical signs observed after the use of these vaccines is very similar, with oedema at the site of injection being most frequently seen. Stiffness and associated pain are also reported.

Forty two cases involved the use of antimicrobials, with gentamycin being associated with the greatest number of reports (24). Anaphylaxis was the most commonly reported clinical sign, often with excessive sweating, rapid breathing or colic.

Other medicines reported included

- treatments for equine Cushing's disease
- treatments for inflammation
- treatments for parasites.

WARNING

If you treat horses for parasites with oral pastes or gels, you should ensure that used syringes are disposed of quickly and safely. We frequently receive reports of ingestion of either moxidectin or ivermectin and praziquantel by dogs. These dogs often have serious adverse reactions after chewing used horse wormer syringes. Some dogs are euthanased because their symptoms are too severe to treat.

You should also not allow dogs to run free in areas where treated farm animals or horses are kept. Dogs that ingest the faeces of treated cattle or horses may be exposed to toxic levels of veterinary medicines.

Donkey

A donkey, injected with a combination of medetomidine and butorphanol, died three days later, after it developed necrotising fasciitis of the gluteal muscle at the site of injection.

Another donkey developed a large pus-filled abscess, after injection of a combination inactivated equine influenza virus and clostridium vaccine. This is a known potential adverse reaction.

Canary

Twenty of 24 birds in an aviary died within one hour, after utensils were treated with an insecticidal spray containing permethrin and cypermethrin. The product was not sprayed directly onto the birds.

Ferrets

Three safety reports involving ferrets were received during 2016.

In one, a jill ferret developed mammary hyperplasia with malaise approximately six weeks after proligestone administration and 10 days after spaying. She responded to symptomatic treatment, but the final outcome is unknown.

The other two reports were related; two ferrets injected with rabies vaccine showed signs of anaphylaxis with haemorrhagic diarrhoea. One recovered quickly with metoclopramide treatment; the other took longer to recover having become anorexic.

Guinea pigs

We received eight reports involving nine guinea pigs during 2016.

One case involved the use of anaesthetics. In the first case, the animal died suddenly within 48 hours of surgery to remove a burst abscess. It was anaesthetised with medetomidine, butorphanol and ketamine.

A guinea pig was reported to have shown neurological signs, including ataxia, after being injected with an ivermectin product intended for use in cattle, pigs and sheep. The vet assumed it had recovered, but the final outcome is unknown.

Another case involved an exempt ivermectin spot-on. A guinea pig had four 50 µg pipettes applied (the correct dose for the weight of the animal), before it was returned to its cage with another guinea pig. The following day the untreated animal was found dead. No investigations were reported.

Two cases involved the use of exempt spot-ons containing permethrin. In both cases, the treated animals became hyperactive. In one case, the application site was erythematous and pruritic for a short time. In the other, anxiety, ataxia and hyperaesthesia were evident within 12 hours of product application, and persisted for several days.

Three cases involved combined trimethoprim and sulfamethoxalone. One guinea pig developed abnormal breathing within 24 hours of administration and died the following day. Another was treated with a variety of other medicines, including meloxicam and ranitidine. It developed mammary masses, which were removed, but eventually died eight weeks after treatment started. In the third case, two guinea pigs treated developed diarrhoea within six hours. Both recovered with supportive treatment; the diarrhoea resolved 2 days after the medicine was withdrawn.

Hamsters

A hamster was treated with oral enrofloxacin solution for a respiratory tract infection. It was accidentally given a 10 times overdose on three successive days. Three days after that it had developed swelling of its cheeks and mouth ulcers. The role of the product in the death of the animal a week later is unclear.

Another hamster was treated for mites with a fusidic acid gel and an unknown spot-on. Five days later it became lethargic and listless, with death occurring 3 days after that.

Use of a permethrin-based insecticidal spray resulted in a hamster developing swollen eyes, lethargy, skin inflammation and hair loss. It was treated with steroids and antihistamines.

A hamster was treated for suspected endometriosis with enrofloxacin oral suspension for 8 days. A month later it collapsed and had an exploratory laparotomy, during which blood was discovered in the abdomen. Liver neoplasia was suspected.

A hamster that had been treated with a chloramine T wound powder was found dead 24 hours after treatment. Its cage companion, which had not been treated, was found dead at the same time. No investigations were carried out.

A hamster treated with an exempt permethrin-based spot-on, developed muscle tremors, ataxia and other more general signs, such as anorexia, hypothermia and lethargy. It improved when treated with Diazepam, but it went on to develop ‘wet tail’ and was euthanased.

Gerbil

A gerbil that had been previously treated with enrofloxacin and meloxicam for an inner ear infection, was prescribed a course of amoxicillin and clavulanic acid drops when the infection recurred, two months later. The animal developed diarrhoea, was subdued, had a reduced appetite and was breathing quickly. Seven days after starting the treatment, it was found dead.

Reptiles

A Royal python was treated for mites with an exempt antimicrobial spray that contained cypermethrin. The snake exhibited neurological signs and open mouth breathing. Two other snakes, a Western Hognose and a Lavender Corn snake, treated at the same time, were unaffected. The final outcome is unknown.

A Veiled chameleon died suddenly, shortly after its owner administered enrofloxacin oral suspension at the same time as a calcium supplement. The animal was not well before treatment. *Post mortem* examination revealed underlying intestinal problems, which were probably responsible for the death of the animal.

Exotic animals

We received twenty three safety reports describing adverse reactions in exotic species during 2016, nineteen of which related to fish.

Fish

Apart from one report that related to the use of some fish food, all fish reports were received following the use of exempt veterinary products. Various treatments for fungus, fin rot, white spot, ulcers and internal or external parasites were reported to have resulted in similar clinical signs, usually death. It is often unclear what the active ingredients of these products are, and information about the conditions of use is often, at best, brief. A total of 474 fish were mentioned in 19 reports.

Amphibians

One hundred frogs of an unknown species were treated with chorionic gonadotrophin, normally used in dogs, horses and cattle, to induce super-ovulation. Most of the frogs developed redness of the skin and limb weakness. Ten of the frogs died. The outcome for the remaining frogs is not known.

Coati mundi

A Coati mundi was injected with meloxicam at 5pm one evening, as it was in poor condition, suffering from vomiting, diarrhoea and abdominal pain. Later the same evening it died during surgery, due to a ruptured stomach.

Laboratory rats

An unknown number of animals were anaesthetised with ketamine before a procedure. All recovered uneventfully, but within an hour, some had developed tachypnoea and ultimately five died.

Fancy pigeons

Five female fantail pigeons were treated for internal parasites with an exempt oral solution containing levamisole at the recommended dose. The following day, they were shaking and vomiting. No veterinary advice was sought, but the birds were euthanased.

Food-producing animals

During 2016, 374 food animal safety reports were received. These reports involved the following food producing species:

- cattle (60.4%)
- sheep (29.7%)
- pigs (4.0%)
- farmed fish (3.5%)
- bee (0.5%)
- chickens (0.5%).
- goats (0.5%).

The remaining reports involved alpacas, deer and lumpsucker fish.

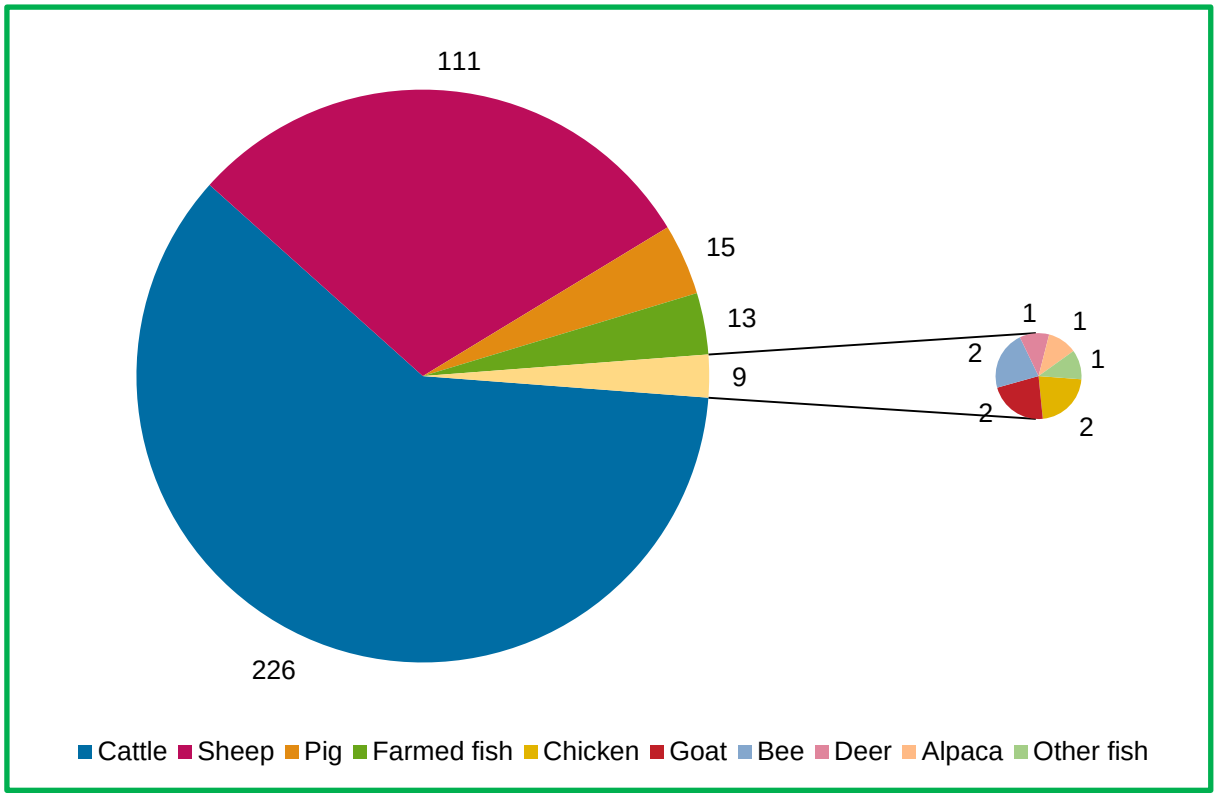


Figure 21 Number of reports received per species of production animal in safety reports during 2016

Using figures from Defra's Farming Statistics[38], the number of safety reports received for each species was approximately:

- 1 report for every 43,400 cattle, or 1 adverse reaction in a bovine for every 4200 cattle
- 1 report for every 214,400 sheep, or 1 adverse reaction in a sheep for every 5,300 sheep
- 1 report for every 300,000 pigs, or 1 adverse reaction in a pig for every 2,250 pigs.

[38] Farming statistics: livestock populations at 1 December 2016 – UK, https://www.gov.uk/government/statistics/farming-statistics-livestock-populations-at-1-december-2016-uk

Cattle

A total of 226 safety reports involving 2,348 cattle were received during 2016.

Authorised veterinary medicines

Vaccines

We received 108 reports that involved the use of vaccines in cattle during 2016.

Almost 57% of the inactivated viral vaccines associated with these adverse events were Pregsure BVD. This product was withdrawn from the market in September 2011, but reports of death, haemorrhage and bone marrow abnormalities in the calves of vaccinated dams still predominate. There were several reports associated with calves, which although born to unvaccinated dams were known or were thought to be have been given colostrum from Pregsure vaccinated cows.

There were insufficient reports relating to other inactivated BVD vaccines to reveal any common signs.

There were insufficient reports relating to other vaccine types

- Live viral
- Inactivated bacterial
- Inactivated viral and bacterial
- Live and inactivated viral
- Live parasitic

Internal and external parasites

Of the 37 reports associated with treatments for internal and external parasites, 18 involved the use products containing ivermectin with other active ingredients. Blindness was most often described in these reports. In only two of these cases was an overdose reported to have been administered. Death occurred in eight cases, four of which involved overdosing. Two other clinical signs of note were vitamin and trace element deficiency.

A further 13 reports involved the use of products containing moxidectin. In these cases, the common signs were all neurological. These may either have been due to overdosing or inadvertent misadministration via an intravascular route. It is important that these products are only injected subcutaneously.

Teat seals

Acute mastitis was reported in more than half of the 13 cases involving the use of teat seals at the start of the drying-off period. In most of these cases the infective organism was not identified. Also, there was insufficient information to determine whether the organism was introduced at the time of administration, or was already present at low levels before the teat canal was sealed.

Other veterinary medicines

Other veterinary medicines mentioned in adverse event reports were various antimicrobials, an immuno-stimulant, treatments for internal parasites (including anti-protozoals), mineral supplements, corticosteroids and treatments for external parasites.

Off-label use of veterinary medicines

We received twenty five safety reports following off-label use of medicines in cattle.

The types of incorrect use reported were:

- overdose (5 cases involving antiparasitics)
- inaccurate dosing (1 case involving an anti-parasitic, animals not weighed)
- disregarding warnings or contraindications (3 cases involving a teat seal, a vaccine or a pour-on anti-parasitic)
- treatment program not respected (13 cases involving anti-parasitics(6), corticosteroid anti-inflammatories(2), vaccines(2), a non-steroidal inti-inflammatory, an immuno-stimulant or a mineral supplement)
- use of a product intended for another species (anti-parasitics(2)
- maladministration of a bolus wormer (1 case)
- incorrect route of administration (antimicrobial (1 case), intra-arterial instead of subcutaneous)
- use of a non-steroidal anti-inflammatory product for an indication not listed.

Other products

Other products mentioned in adverse event reports involving cattle were a calcium and vitamin D3 supplement, which does not require a marketing authorisation, and an unidentified antimicrobial.

Sheep

We received a total of 111 safety reports involving 4,457 sheep during 2016.

Vaccines

Forty nine of the reports involved the use of a vaccine.

The most often reported vaccines were inactivated bacterial vaccines for protection against clostridium and pasteurella. In these cases, death was most often reported, but there were often other factors, such as the condition of the treated animals, contributing to the outcome. In many cases, no investigations were carried out to determine the cause of the deaths.

A further 11 cases involved live chlamydia vaccines. All cases reported abortions. In very rare cases the vaccine strains have been associated with abortion.

Antimicrobials

In seven cases reporting deaths after the use of the antimicrobial tilmicosin, the cause of the deaths remained unexplained. In only one case did a *post mortem* provide evidence of product involvement.

Anti-parasiticides

Cases received relating to the use of medicines for the control of internal and external parasites were evenly split between products containing ivermectin, doramectin and either moxidectin or ivermectin in combination with another active substance. Most cases involved the deaths of one or more animals.

Off-label use of authorised veterinary medicines

Twenty seven of the 111safety reports received indicated that off-label use of medicines had occurred.

For anti-parasitic medicines, dosage errors were most often reported. Failure to accurately weigh stock before dosing led to seven cases involving overdosing and three involving under dosing. In one case, the interval between doses was longer than recommended. In two cases the route of administration was incorrect; intramuscular rather than subcutaneously, and inadvertent injection into the spinal column. In two cases, warnings or contraindications were ignored.

For all other medicines, use was off-label because

- sheep were not an indicated species (6 cases)
- warnings or contraindications were ignored (8 cases)

- the administration route was incorrect (1 case)
- the treatment program was not respected (2 cases).

Pigs

Fifteen safety reports describing adverse events in 2,000 pigs were received during 2016.

All products involved in these cases were authorised veterinary medicines.

Seven of the eleven vaccines, reported to have been used prior to an adverse reaction, were intended to reduce the effects of porcine reproductive and respiratory syndrome virus. In most cases other factors were identified to explain the clinical signs observed. In two cases, the treatment program for the vaccine used was not respected. In another, the vaccine was not administered by the recommended route.

Other products identified in reports were antibiotics, a non-steroidal anti-inflammatory medicine and an iron supplement.

Farmed fish

Salmon

All thirteen reports of adverse reactions, involving a total of approximately 0.9 million fish produced for food use, described the use of vaccines in Atlantic Salmon. In ten cases, the vaccine used was an inactivated viral and bacterial vaccine with a UK marketing authorisation. In two of those cases, use was off-label; in one case the fish were smaller than recommended for vaccination; in the other, it was believed that the fish had been overcrowded during transportation post-vaccination, resulting in a higher than expected rate of mortality. In eight cases, the fungal skin infections and other signs observed post-vaccination may have been triggered by temporary impairment of the immune system, or may have been due to poor husbandry.

Three cases related to the use of an imported inactivated viral and bacterial vaccine. Increased mortality was reported in one case, with ulceration and decreased appetite in the other two.

Lumpsucker fish

Whilst not actually being a fish farmed for meat, this species is becoming associated with the production of Atlantic Salmon, as a natural method of reducing the incidence of sea lice. We received one case, in which salmon had been treated with emamectin, and a higher mortality was found in the lumpsucker fish that were in the same cage, than in a cage that had not been treated. The number of fish involved in this report is not known.

Bees

A total of two reports involving seven honey bee hives were received. Both reports occurred after treatment of hives for Varroa mite with formic acid.

Death of bees occurred overnight, after treatment. The ambient temperature at the time of treatment in both cases was within the recommended limits. In one case the hives were adequately ventilated, but the mite load was unknown. There was insufficient information to assess the involvement of the product in the deaths of the bees. In the other case, there was photographic evidence that the hive was not sufficiently ventilated during treatment, which could have led to the deaths of the bees.

Goats

Two safety reports involving two goats were received during 2016.

A three to four week-old goat was treated, off-label, by its owner with a cypermethrin pour-on indicated for use on sheep. The owner reported that it had developed neurological signs, was lethargic and had profuse diarrhoea. A vet treated it for dehydration, and it is assumed to have recovered.

In another case, a goat developed convulsions and died on the same day epinephrine was used for an unknown reason. Epinephrine is not indicated for use in goats.

Chickens

Two safety reports involving fewer than 1,400 chickens were received during 2016.

One case appeared to be more of a product problem, in which the user reported that a human cefuroxime antibiotic had turned a milky white when reconstituted.

In the other case, an owner mistakenly gave a group of 20 birds a solution to drink that contained a 50 times overdose of the tylosin medicine. One bird was found dead, but it was disposed of, so no *post mortem* could be performed. Nevertheless, the vet thought it most likely to have succumbed to the mycoplasma infection it was being treated for.

Alpacas

One alpaca case was reported during 2016.

In this case, seven crias died following treatment over three days with the antiprotozoal medicine, toltrazuril. The owner accidentally gave a dose that was up

to double that recommended. The animals died from eight to thirty days post-treatment.

Deer

A group of 63 of an unspecified species of deer were treated off-label with a combination closantel and mebendazole wormer. They were dosed at the recommended rate for sheep. Within 3 days all of the deer had become ataxic. The attending vet thought the dose should have been reduced for the deer, and they had therefore received an overdose. One animal died and two more were shot because of limb damage caused by the ataxia.

Withdrawal period issues

Two cases of the detection of veterinary medicine residues in animal produce intended for human consumption were reported. One case involved a cow, the other a sheep.

The first case involved the detection of residues of the antibiotic cephalonium in milk. The cow had aborted an unknown time after being treated with an intramammary suspension as it was dried off. The product information indicates that if calving occurs earlier than 54 days post-treatment, the milk should be tested for the absence of antibiotic before it is used for human consumption. The withdrawal period for this product is 54 days, plus 96 hours, with the milk from at least 7 complete milkings being discarded. It is not clear whether the correct withdrawal period was observed in this case.

In the second case, residues of oxytetracycline were found in meat at slaughter, 13 days after a lamb had received an appropriate dose. The withdrawal period for meat is 9 days. The farmer's records did not identify each individual sheep treated, but otherwise appeared compliant. Possible explanations for the residue violation were an unrecorded dose or a pharmacokinetic problem.

Environmental incidents

Six reports of adverse effects from possible exposure to a veterinary medicine in the environment were received during 2016, four of which affected wild birds, the other two involving bee hives.

Three of the cases that affected wild birds occurred in the south west of Wales. In one case, a dead female red kite was handed into a visitor centre. Laboratory analysis revealed a background level of difenacoum, an anti-coagulant rodenticide, and a level of fenthion, an organophosphate insecticide, which was likely to have caused the death of the bird. Fenthion has not been available for veterinary use since 1999. It is likely that this bird died as a result of illegal use of this substance.

In a second case, laboratory tests revealed diazinon (dimpylate) residues in the gizzard contents of a dead peregrine falcon. There were also low levels in the liver of anticoagulant rodenticides, brodifacoum and bromadiolone, consistent with exposure. Diazinon is currently authorised for use in sheep dips, but it is possible that its use in this case was illegal.

In a third case, the remains of six ravens were analysed for residues of pesticides. They had been found near the leg of a lamb and appeared to have died around the same time, as the maggots found on them were all the same size. The local farmer stated that he had last dipped his sheep three weeks previously. He was unaware of the dead birds or that one of his animals may have died. Diazinon was detected in

the raven remains and a surface wash of the lamb leg. It appeared the birds had been poisoned following exposure to the veterinary use of diazinon on sheep.

The final bird case occurred in 2015. It involved another peregrine falcon that was found dead at an RSPB monitored nest. Low levels of three different rodenticides were detected in the liver. These were insufficient to have caused the death of the bird. Further analysis of the gizzard contents revealed levels of diazinon likely to have been the cause of death. Given the amount found, it is likely that this bird was deliberately poisoned.

The two bee cases both involved fipronil. In the first case, four bee colonies, of a group of sixteen, failed with no obvious signs of disease. The bees were showing unusual behaviour followed by rapid death. This is consistent with pesticide poisoning. The hives were located adjacent to a dog rehoming centre, which could have been a source of fipronil from flea treatments. However, an agricultural insecticide and a fungicide were also detected in the dead bees, in addition to fipronil. There was an oilseed rape crop nearby. The levels of fipronil detected were consistent with this substance being the cause of death.

In the other case, which occurred in 2015, fipronil was again implicated in the deaths of thousands of bees from 14 hives. These hives were located between fields of beans and oilseed rape. These crops had been sprayed with various substances before the bee mortality occurred. Laboratory analysis revealed the presence of various agricultural pesticides, but the levels of these were mostly only indicative of exposure. The results, however, were consistent with some of the bees having died of pesticide poisoning, specifically fipronil. Fipronil has biocidal (ant control) and veterinary (pet flea control) uses, but the source of the fipronil in this case is unclear.

Conclusions

The number of reports received in 2016 increased by 15.6% compared with that received in 2015. The sub-group of animal reports with the greatest increase in numbers was safety reports (16.2%), with pet animal safety reports increasing by 16.7%. Lack of efficacy reports, across all animal species, only increased by 7.4% during the year. But these reports for food animals alone increased by 26.3%.

The number of cases involving people that were reported to us increased by 45.2% compared to 2015.

No new major pharmacovigilance issues arose during the year.

Things to remember

- Vets, vet nurses, large animal handlers and pet owners should be particularly careful when administering injectable or pour-on/spot-on products, to avoid needle-stick and eye injuries.
- If you accidentally self-inject with a mineral oil-adjuvanted vaccine, you must get immediate medical treatment, even if you think only a small amount may have been injected.
- Social media may be an easy way to share experiences with other pet owners. But it is not an effective means of communicating concerns about specific veterinary medicines to us. If you are aware of any adverse event occurring after the use of an authorised veterinary medicine, please use the online reporting form[39] to tell us about it
- Full product information (including brand, strength and how it was used) will improve our ability to detect problems with specific medicines
- Vets are reminded[40] that they should always check the VMD's product information database[41] to ensure that they are aware of recent changes to product information.
- Owners are reminded that they should always obtain medicines for their animals from reputable sources, such as their vet or pet shops. If you want to buy medicines online,

[39] Report a problem with an animal medicine, www.gov.uk/report-veterinary-medicine-problem
[40] Using the VMD's product information database, Veterinary Record (2015) **177**, 448
[41] Product information database, www.vmd.defra.gov.uk/ProductInformationDatabase/

you should check that the website you are using is based in the UK. If the website is registered with the accredited internet retailer scheme[42] (AIRS), you can be sure that the medicines you are buying are genuine.

- You are breaking the law, if you import prescription medicines from another country into the UK, unless you have a prescription from a vet and a suitable import certificate[43].

- Do not give medicines to an animal unless you are qualified to do so, or have been instructed how to by a vet, pharmacist or SQP

- Vets are further reminded to ensure they have given animal owners sufficient instruction in how to give their animals the medicines you handover to them, including extemporaneous veterinary medicines.

- If you want to send medicinal products through the post, you must check that you are permitted to do this. You must then make sure the medicine is adequately protected to prevent postal workers or the recipient being exposed to noxious substances, if the container leaks

- Vet practices should have adequate ventilation, or gas scavenging systems, in rooms where anaesthetic gas are used. This will minimise exposure of staff to these gases. Pregnant staff should be particularly careful.

- Adverse events involving microchips should be reported via the appropriate online reporting form[44]

[42] List of Accredited Internet Retailers, www.vmd.defra.gov.uk/InternetRetailers/accredited-retailers.aspx
[43] Apply for a certificate to import a veterinary medicine into the UK, www.gov.uk/guidance/apply-for-a-certificate-to-import-a-veterinary-medicine-into-the-uk
[44] Report a microchip, www.vmd.defra.gov.uk/microchipeventreporting/

Annex

Trends

Reports received per year

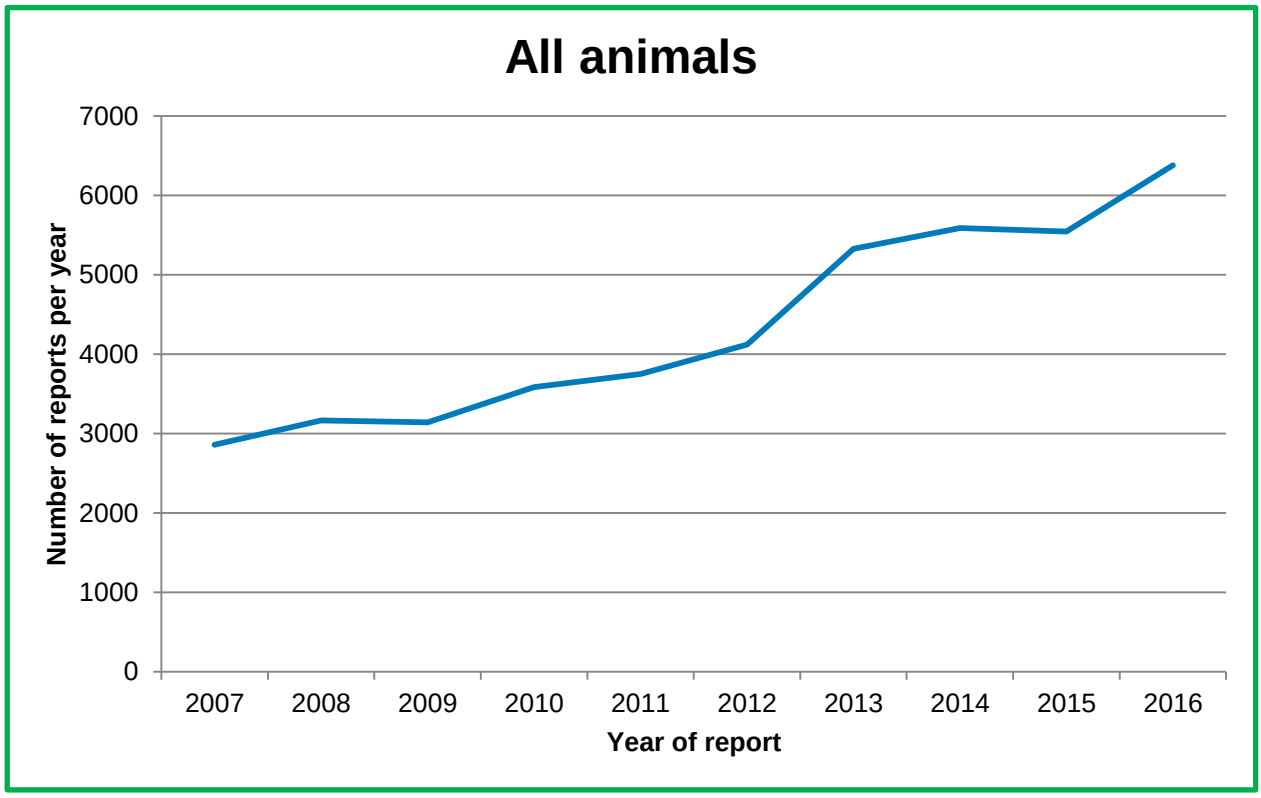


Figure 22 Number of animal reports received since 2007

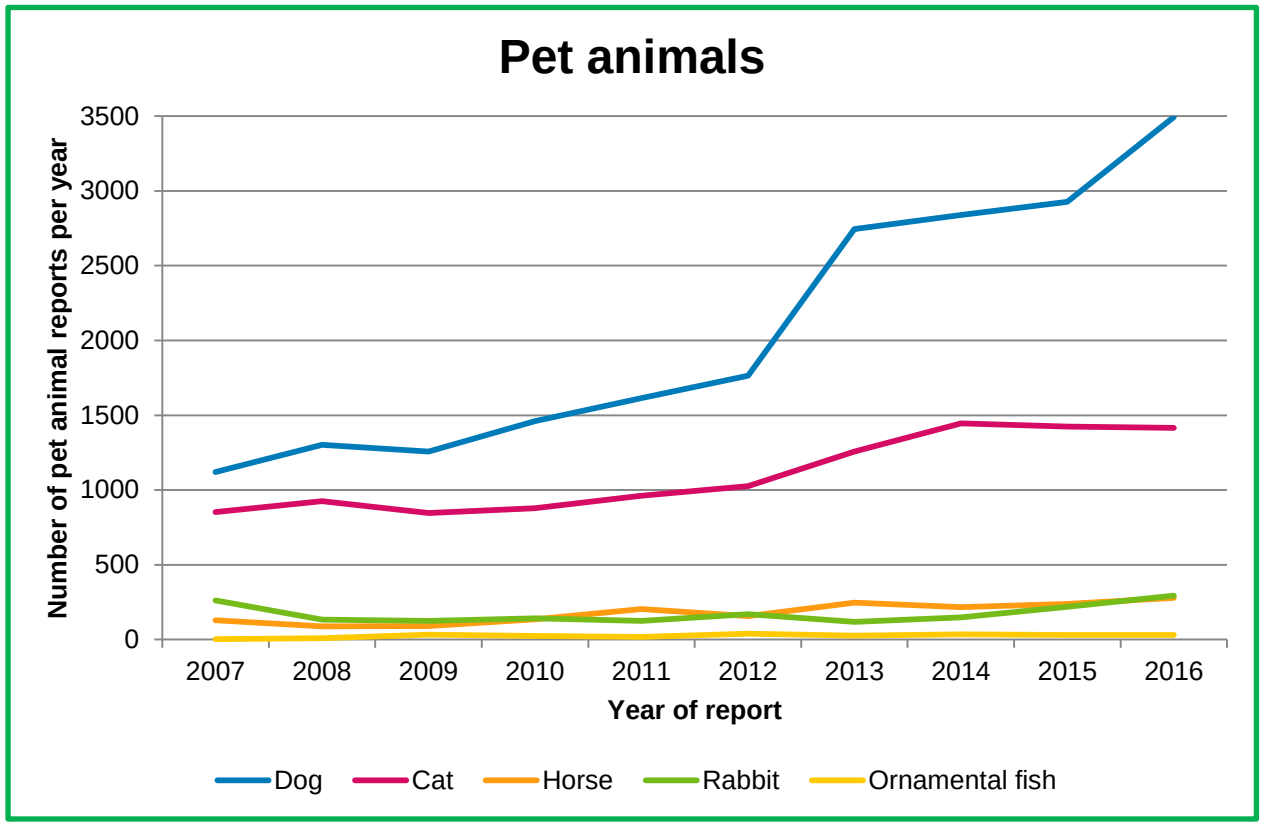


Figure 23 Number of pet animal reports received since 2007

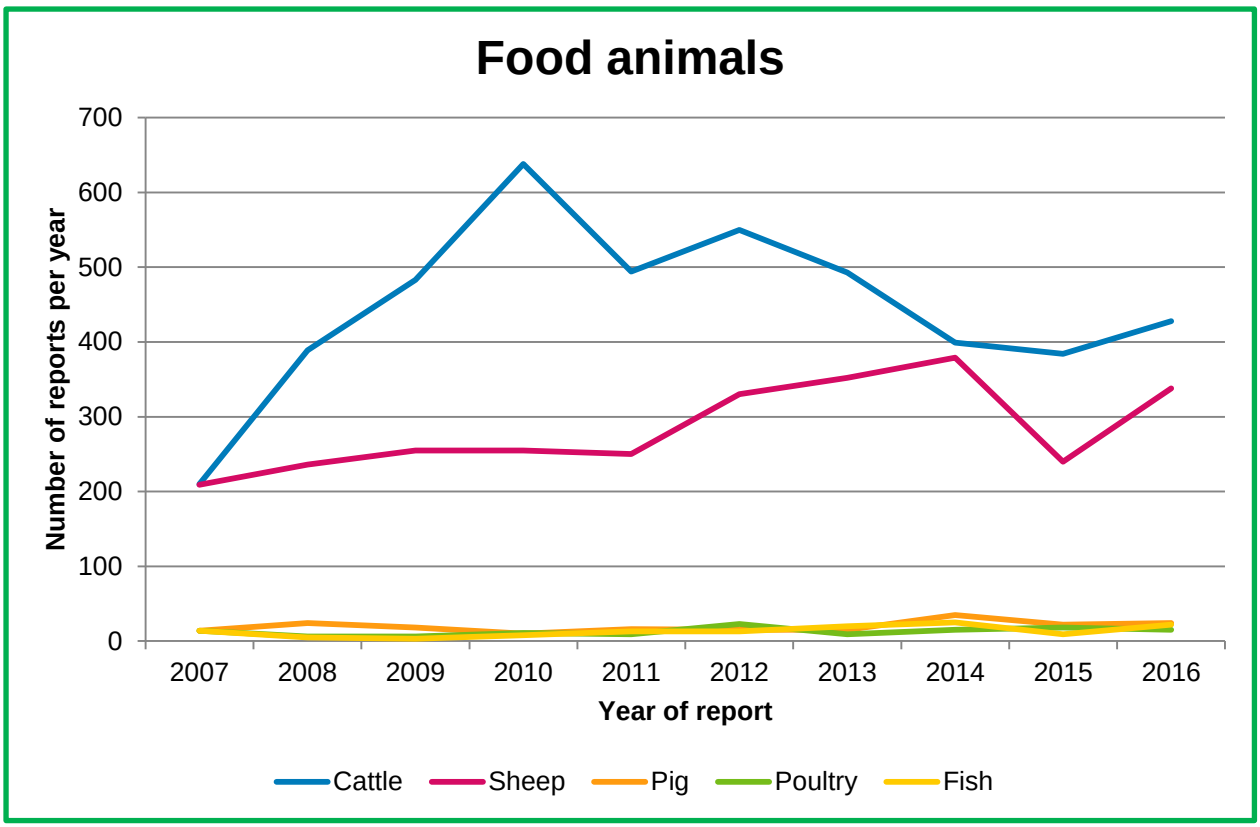


Figure 24 Number of food animal reports received since 2007

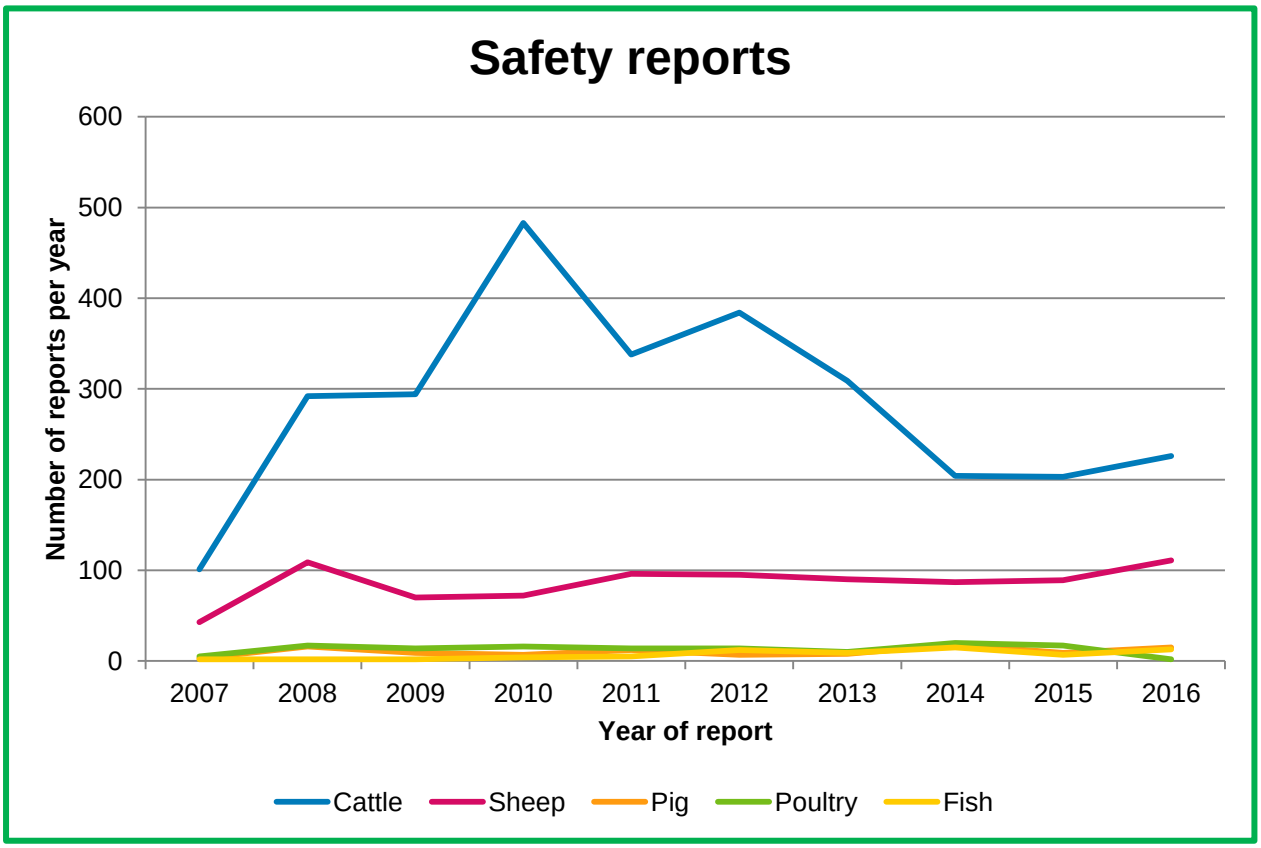


Figure 25 Number of food animal safety reports received since 2007

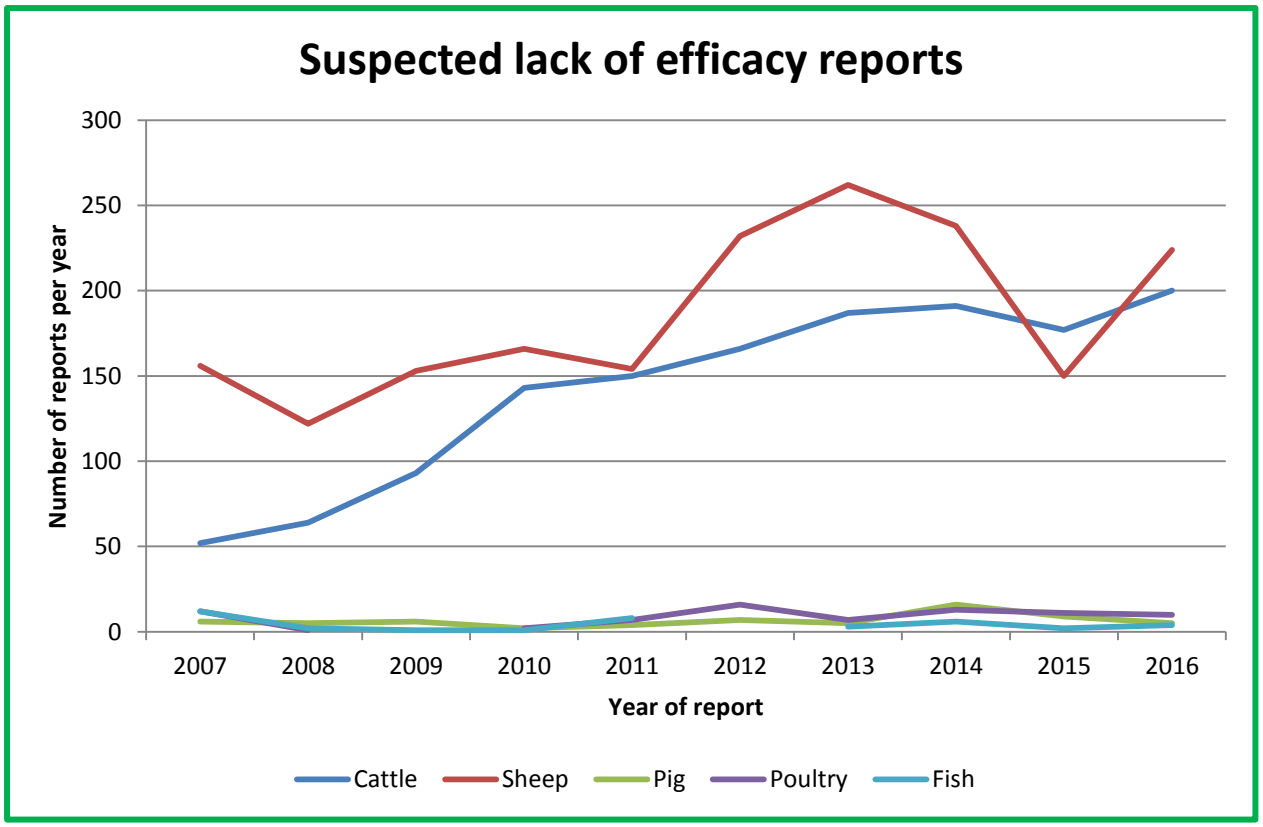


Figure 26 Number of food animal suspected lack of efficacy reports received since 2007

We have tried to make reporting easier and quicker, but accept that there is still room for improvement. We are actively trying to address this, but would welcome any feedback, so that we can identify what we could do to improve the rate of reporting from this sector.

Lack of efficacy of antimicrobials in animals

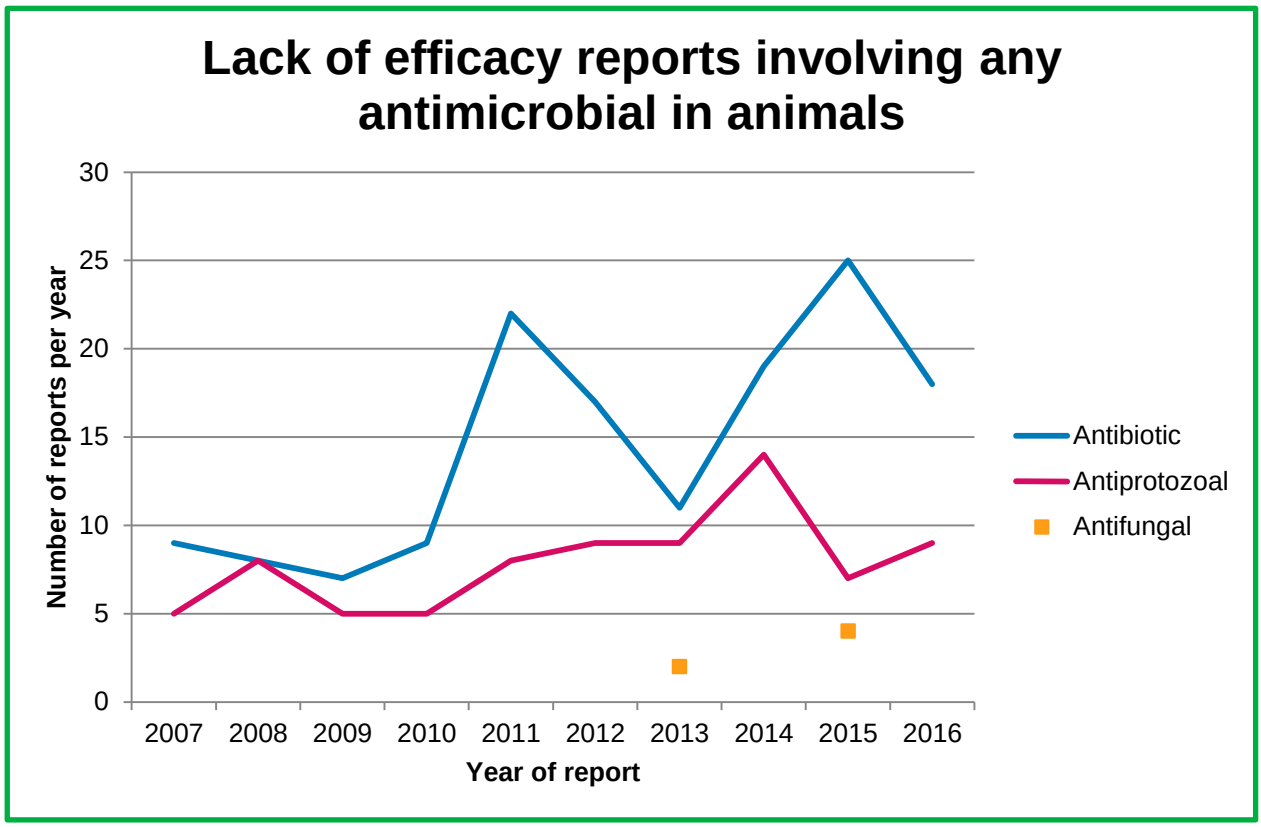


Figure 27 Number of reports of lack of efficacy for different groups of antimicrobial products used in animals since 2007

Number of suspected lack of efficacy reports received per year for different groups of antimicrobials

Note: These are NOT confirmed cases of lack of efficacy.

Year Active	07	08	09	10	11	12	13	14	15	16
Amprolium								1		
Decoquinate				1			1	2		1
Diclazuril		4	4	4	5	3	3	2	1	2
Halofuginone	3	3	1		3	5	5	7	3	6
Imidocarb								1	2	
Lasalocid		1						2		
Maduramicin									1	
Toltrazuril	2	1				1		1		

Table 8 Number of reports of lack of efficacy for antiprotozoal ingredients used in animals since 2007

Year Active	07	08	09	10	11	12	13	14	15	16
Bronopol						1	1			
Itraconazole									1	
Miconazole							1		1	
Nystatin							1			
Terbinafine									2	

Table 9 Number of reports of lack of efficacy for antifungal ingredients used in animals since 2007

Tetracyclines (QJ01A)

Year / Active	07	08	09	10	11	12	13	14	15	16
Chlortetracycline						1				
Oxytetracycline									2	3

Amphenicols (QJ01B)

Year / Active	07	08	09	10	11	12	13	14	15	16
Florfenicol	4		2	1	4		1		2	3

Table 10 Number of reports of lack of efficacy for tetracycline and amphenicol antibiotics used in animals since 2007

Penicillins and clavulanic acid (QJ01C)

Year / Active	07	08	09	10	11	12	13	14	15	16
Amoxicillin			1			2		2	1	1
Ampicillin						1				
Cloxacillin					1	2	2	1	1	
Penethamate		1			1			1	1	
Procaine Benzylpenicillin		1	1		1			1	1	2
Clavulanic acid			1			2		2	1	

Cephalosporins (QJ01D)

Year / Active	07	08	09	10	11	12	13	14	15	16
Cefovecin	1	2					2		2	
Cefquinome	1	1		1	5			1	2	
Ceftiofur						1				
Cefalonium					1			1	2	

Sulfonamides and trimethoprim (QJ01E)

Year / Active	07	08	09	10	11	12	13	14	15	16
Sulfaquinoxaline										
Trimethoprim										

Table 11 Number of reports of lack of efficacy for penicillin, clavulanic acid, cephalosporin and sulfonamide and trimethoprim antibiotics used in animals since 2007

Macrolides (QJ01F)

Year / Active	07	08	09	10	11	12	13	14	15	16
Gamithromycin						1				
Tildipirosin					1	3	1	3	1	
Tilmicosin		1						1		1
Tulathromycin	3		1	5	1	1			1	5
Tylosin					2	1	1	1		
Tylvalosin					1					

Aminoglycosides (QJ01G)

Year / Active	07	08	09	10	11	12	13	14	15	16
Dihydrostreptomycin			1							
Framycetin		1			1		1	1	1	
Gentamicin					3					
Neomycin									1	1
Streptomycin									1	1

Quinolones (QJ01M)

Year / Active	07	08	09	10	11	12	13	14	15	16
Enrofloxacin						1			1	
Marbofloxacin									1	

Table 12 Number of reports of lack of efficacy for macrolide, aminoglycoside and quinolone antibiotics used in animals since 2007

Others (QJ01X)

Year / Active	07	08	09	10	11	12	13	14	15	16
Fusidic acid										1
Polymyxin B							1		1	
Spectinomycin				1					2	
Tiamulin				1			1	2		

Table 13 Number of reports of lack of efficacy for other antibiotics used in animals since 2007

Cat injection site sarcomas

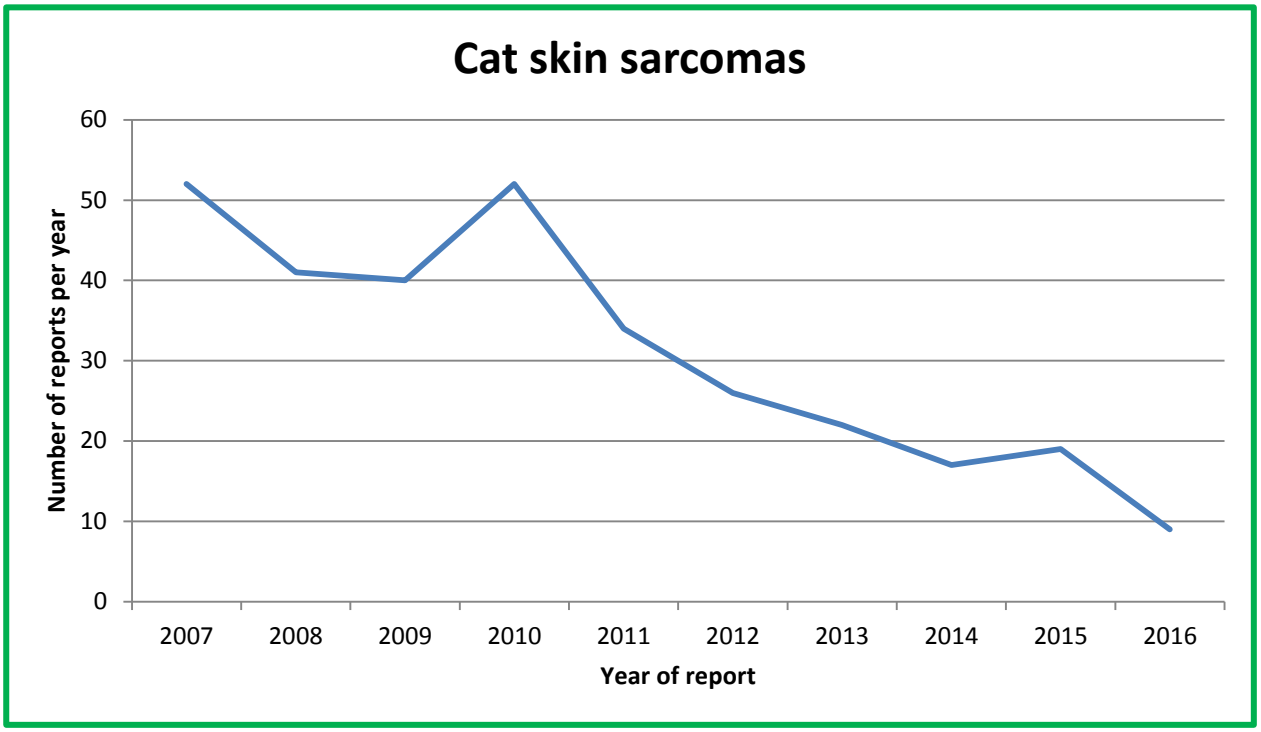


Figure 28 Number of cat injection site sarcoma reports received since 2007

Additional information

Injectable products containing mineral oil[45]

Aftopur DOE	Evalon (PB-134)	Nobilis E.coli inac	Porcilis PCV Emulsion for Injection for Pigs
Aftovaxpur DOE Emulsion for Injection for Cattle, Sheep and Pigs	Footvax	Nobilis IB + ND + EDS	Porcilis PCV ID
Alpha Ject 2-2 Emulsion for Injection	Gallimune 302 ND + IB + EDS	Nobilis IBmulti + ND + EDS	Porcilis PCV M Hyo Emulsion for Injection for Pigs
ALPHA JECT micro 1 PD Emulsion for Injection, Vaccine for Atlantic Salmon	Gallimune 303 ND + IB + ART	Nobilis Influenza	Porcilis Pesti Emulsion for Injection
AquaVac FNM Plus Emulsion for Injection for Fish	Gallimune 407 ND + IB + EDS + ART	Nobilis Influenza H5N2 Emulsion for Injection for Chickens	Porcilis Porcoli Diluvac Forte
Aquavac PD Emulsion for Injection for Atlantic Salmon	Gallimune Se + St, Water-in Oil Emulsion for Injection	Nobilis OR Inac Emulsion for Injection for Chickens	Rispoval Pasteurella
AquaVac PD3 Emulsion for Injection, for Atlantic Salmon	Gudair Emulsion for Injection for Sheep and Goats	Nobilis Paramyxo P201	Rotavec Corona Emulsion for Injection for Cattle
Bovalto Ibraxion Emulsion for Injection	Hiprabovis Somni/Lkt Emulsion for Injection for Cattle	Nobilis Reo + IB + G + ND	Startvac Emulsion for Injection for Cattle
Bovigen Scour Emulsion for Injection for Cattle	Hyogen Emulsion for Injection for Pigs	Nobilis REO Inac	Stellamune Mycoplasma
CattleMarker IBR Inactivated Emulsion for Injection for Cattle	Inactivated Oil-adjuvanted Furunculosis, Winter Ulcer and IPN Vaccine "Novartis"	Nobilis RT + IBmulti + G + ND	Stellamune Once
Circogen Emulsion for Injection for Pigs	Ingelvac M Hyo Emulsion for Injection for Pigs	Nobilis RT + IBmulti + ND + EDS	Suvaxyn Aujeszky 783 + o/w, Powder and Solvent for Emulsion for Injection
Circovac, Emulsion and Suspension for Emulsion for Injection for Pigs	Lapinject VHD	Nobilis TRT Inac	Suvaxyn Parvo/E
Entericolix, Emulsion for Injection for Pigs	Louping-Ill Vaccine	Norvax Compact PD Emulsion for Injection	Tur-3
Enteroporc AC	M+PAC	Parvovax	VIMCO Emulsion for Injection for Ewe and Goat
ERAVAC Emulsion for Injection for Rabbits	Mydiavac	Porcilis M Hyo ID Once Emulsion for Injection for Pigs	Winvil 3 Micro Emulsion for Injection for Atlantic Salmon

[45] This list was correct on 15 Apr 2018. Check the Product Information Database for other products.

Glossary of clinical and other terms

A clinical term is a word or phrase used by a veterinary or medical professional to describe symptoms observed in, or experienced by, an animal or human patient. Whilst not exhaustive, this glossary explains some of the more obscure expressions in layman's terms.

Term	Meaning
Addison's disease	Hypo-adrenalism or adrenal insufficiency
Adjuvant	Immune system stimulant
Anaphylaxis	Severe allergic reaction
Ataxia	Lack of muscle co-ordination
Bronchial	To do with the main airways to the lungs
Bolus (plural boli)	Large tablet
Cellulitis	Bacterial infection of inner skin layers
Coagulopathy	Bleeding disorder
Cushing's disease	Hyperadrenocorticism
Ectoparasiticide	Treatment for external parasites
Emesis	Vomiting
Endectocide	Treatment for both internal and external parasites
Erythema	Reddening
Euthanasia	Put to sleep (end of life)
Fibrosarcoma	Connective tissue tumour
Glässer's disease	Bacterial disease of young pigs

Term	Meaning
Haematuria	Blood in urine
Haemorrhagic	Bloody
Hepatic	To do with the liver
Hepatopathy	Liver disease or disorder
Hyperthermia	Raised temperature
Hyperthyroidism	Over active thyroid
Lethargy	Lack of energy, inactivity
Liver fluke	Parasitic flatworm
Mast cell tumour	Type of skin cancer
Malaise	Discomfort, illness
Melaena	Dark (digested) blood in faeces
Melanisation	Excessive pigmentation due to tissue damage in fish
MRI	Magnetic resonance imaging
Mydriasis	Dilated pupils
Necrosis	Death of body tissue
Nematode	Roundworm
Oedema	Swelling
Paraesthesia	Pins and needles
Polydipsia	Excessive drinking

Term	Meaning
Pruritus	Severe itching
Pyrexia	Raised temperature
Recumbency	Lying down
Renal	To do with the kidney
Scour	Diarrhoea
Spasmolytic	Relieves muscle spasms

Term	Meaning
Suppurative meningitis	Bacterial infection of the membranes surrounding the brain and spinal chord
Tachycardia	Fast heart rate
Tachypnoea	Breathing quickly
Urticaria	Nettle rash, raised and itchy

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Veterinary Medicines Directorate