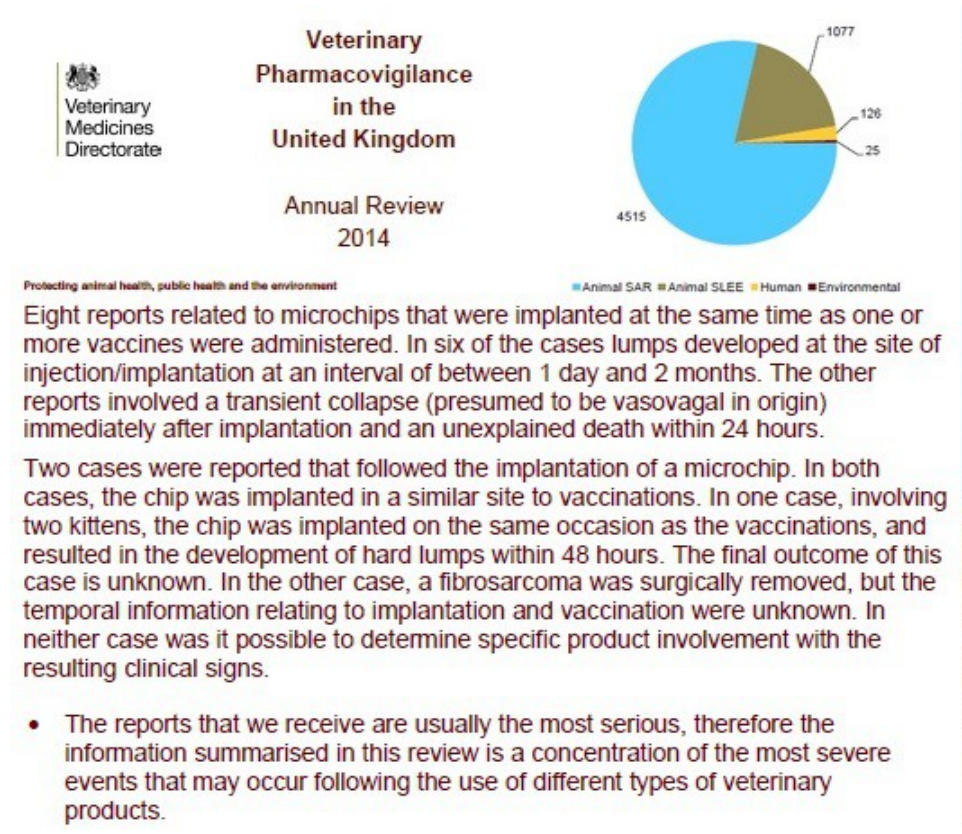


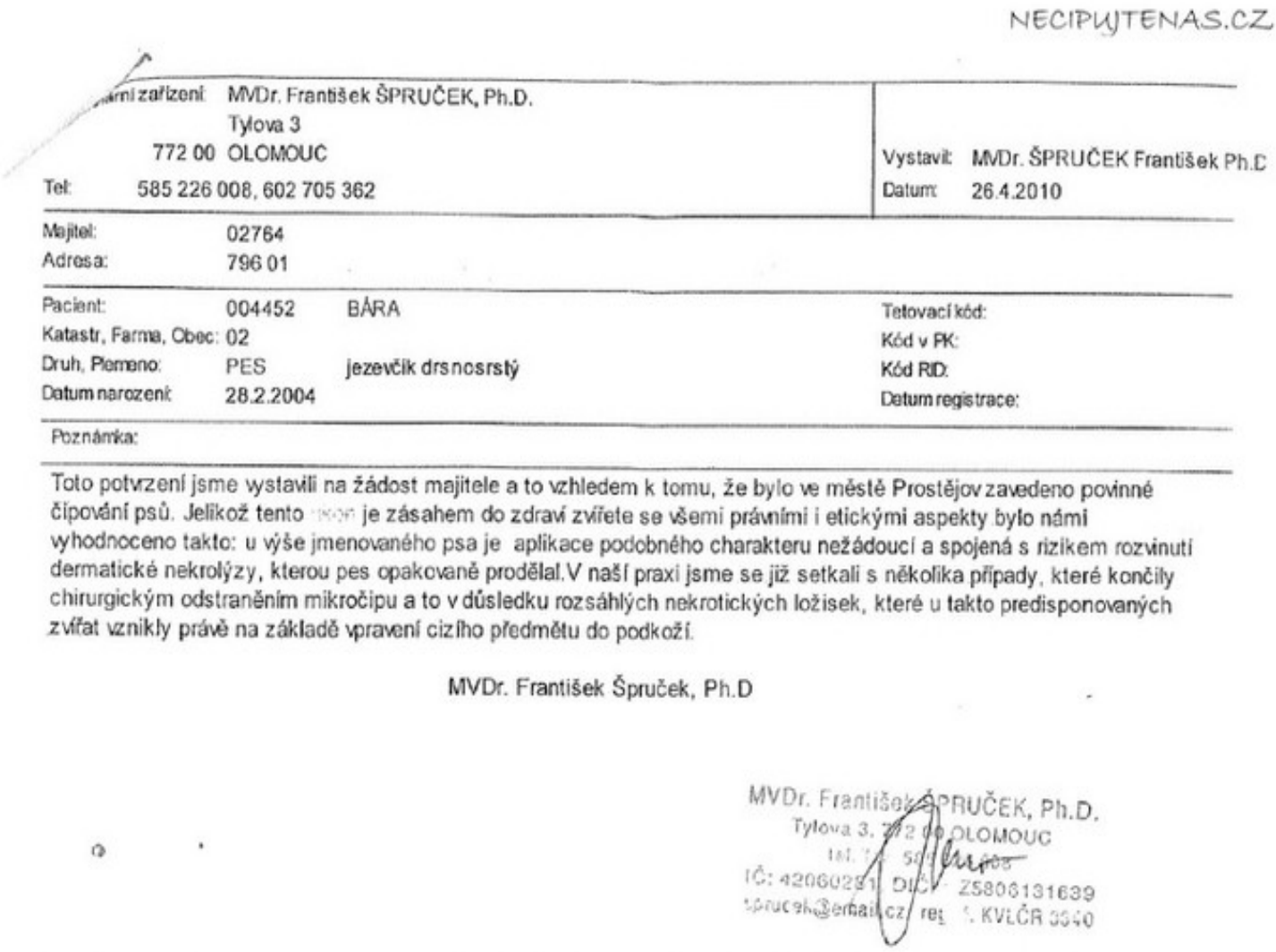
Ukázka z odborné/oficiální publikace britské státní Vrchní správy pro kontrolu veterinárních léčiv („The Veterinary Medicines Directorate“; VMD; vládní agentura spadající pod britské Ministerstvo životního prostředí, výživy a záležitostí venkova; „Department for Environment, Food and Rural Affairs“, DEFRA) z února 2016 s názvem „Veterinary Pharmacovigilance in the United Kingdom. Annual Review 2014“; doplněná obrázkem Katedrály svatého Pavla v Londýně. – Zdroje obrázků: VMD, „Veterinary Pharmacovigilance in the United Kingdom. Annual Review 2014“, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/501782/PhV_Annual_Review_2014_Final_Version_v3.pdf; https://en.wikipedia.org/wiki/London#/media/File:South_facade_of_St_Paul%27s_Cathedral_2011_1.jpg

Oficiální publikace britské státní Vrchní správy pro kontrolu veterinárních léčiv z února roku 2016 potvrdila na konkrétních případech nebezpečí čipování zvířat! Další odborníci z České republiky a mnoha zemí světa již také zveřejnili svá varování! Ostravští politici však všechny faktické argumenty sveřepě odmítají! Zachování nefunkčního a v konkrétních kauzách nebezpečného systému identifikace psů je prý důležitější než jednotlivé tragické situace RFID transpondérem označených zvířat! Pořádek musí být: výjimky nepřipustíme i kdyby trakaře padaly! Vzhůru ke světlým zítřkům totalitního uspořádání společenských vztahů, kde životy konkrétních občanů a jejich nejlepších čtyřnohých přátel nemají pro kruté papaláše posedlé mocí a jedinou egoistickou (ne)pravdou vůbec žádný význam! – Společenství webu Necipujtenas.CZ publikuje v důsledku závažného veřejného zájmu v originálním znění (viz níže) původní/oficiální dokument z února 2016 nazvaný „*Veterinary Pharmacovigilance in the United Kingdom. Annual Review 2014*“ s tématikou nebezpečných veterinárních preparátů a jejich zjištěných nežádoucích účinků, který byl k dispozici každému občanovi z celého našeho globálně propojeného světa prostřednictvím Internetu na vládním webu britské státní Vrchní správy pro kontrolu veterinárních léčiv („The Veterinary Medicines Directorate“; VMD; vládní agentura spadající pod britské Ministerstvo životního prostředí, výživy a záležitostí venkova; „Department for Environment, Food and Rural Affairs“, DEFRA). **Výše uvedená publikace popisuje případy šesti zvířat, kdy došlo v důsledku čipování a zřejmě také vakcinace k vývinu nádorů, další čtyřnohý živý tvor po nastřelení RFID transpondéru zkolaboval a jeden dokonce zemřel!** Nutno podotknout, že **VMD shromažďuje každý rok taková fakta prostřednictvím svého systému pečlivě zpracovaných úředních hlášení.** – Ostatně již na jaře roku 2014 vydala VMD oficiální prohlášení, ve kterém upozornila, že existují možná zdravotní rizika implantovaných RFID mikročipů. Právě v této souvislosti a také s ohledem na povinné/plošné čipování psů účinné ve Velké Británii od 6. dubna 2016 zavedla VMD včas pro širokou veřejnost ve čtvrtém měsíci roku 2014 zcela nový systém online monitoringu a zasílání hlášení všech vzniklých komplikací, nemocí, problémů, technických obtíží, systémových selhání apod. záležitostí spojených s podkožními RFID identifikačními transpondéry mj. domácích čtyřnohých mazlíčků (viz formuláře a informace o podávání hlášení zde). Výsledky sběru dat jsou průběžně analyzovány a provázány s již v předchozích letech zjištěnými údaji. Budou každým rokem zpětně publikovány. Zároveň jsou také získané informace předávány k řešení zodpovědným výrobcům čipů, veterinářům, organizacím zajišťujícím ochranu přírody apod. **Britská vláda se tím zároveň jistí před možnými budoucími žalobami rozzlobených chovatelů domácích zvířat, kteří museli své čtyřnohé přátele nechat označit mikročipy pod hrozbami legislativního násilí a značných pokut.** – Není jistě bez

zajímavosti, že výše uvedený projekt zasílání negativních zkušeností s čipy velmi rychle podpořili i samotní distributoři RFID transpondérů. – Britští veterinární odborníci tedy už před dvěma roky správně očekávali přísun nových dat o třech základních dosud známých a již z minulosti velmi dobře potvrzených negativních dopadech čipování: **1/ přímá onemocnění**: nežádoucí reakce zvířat na implantaci cizího tělesa – mikročipu. K nejčastěji hlášeným zdravotním komplikacím v souvislosti s čipováním patřil v Británii např. hematom, infekce, záněty, celkové odmítnutí mikročipu živým organismem aj. **2/ migrace RFID transpondéru v těle domácího mazlíčka**. Stále jsou také přiznávány problémy se samovolným pohybem mikročipů pod kůží jednotlivých živočichů v celém jejich těle včetně nemožnosti takový transpondér správně detekovat čtečkou dat. Mj. vyjma vlastního pohybu zvířete k tomu dochází v důsledku neodborného nebo nepřesného operačního úkonu při vlastním čipování. V takových případech je posléze nutné podrobně zkoumat organismus třeba očipovaného psa/kočky pohmatem nebo využít pro zajištění správné lokalizace čipu až dokonce rentgen či ultrazvuk. **3/ úplné nebo částečné selhání samotného čipu** (viz třeba případy hlášené z vícero států včetně České republiky ve věci vadných transpondérů distributora „BackHome Biotec Microchips"). – **V českém prostředí** již např. upozorňoval na podobná rizika čipování **posudek Váženého pana profesora MVDr. Miroslava Svobody, CSc. („Veterinární a farmaceutická univerzita Brno", VFU)** vypracovaný na žádost presidenta „Komory veterinárních lékařů České republiky". Dále třeba soudní znalec Vážený pan MVDr. František Špruček, Ph.D., MBA z Olomouce: V oficiální zprávě popsal, že **čipování způsobuje v některých případech rozvinutí dermatické nekrolýzy; ve své praxi se již Vážený pan doktor Špruček a jeho tým setkali s několika kauzami, kdy bylo nutné odstranit z těla implantované RFID transpondéry právě v důsledku rozsáhlých nekrotických ložisek; ta vznikla na základě vpravení cizího předmětu – identifikačního mikročipu – do živé tkáně zvířat.** – Z desítek dalších veterinárních specialistů v ČR a stovek odborníků na celém světě, jejichž vyjádření již Společenství webu Necipujtenas.CZ publikovalo, vyberme např. praktické zkušenosti veterinární lékařky Barbary Royalové, DVM, CVA (absolventka jedné z nejlépe hodnocených vysokých škol pro zvěrolékaře v rámci celého našeho globálního světa – „University of Illinois College of Veterinary Medicine"), která je zakladatelkou/majitelkou veterinárního centra „The Royal Treatment Veterinary Center" v Chicagu a zastávala krom jiných vysoce uznávaných odborných pozic také místo presidentky Americké holistické veterinární asociace („American Holistic Veterinary Medical Association"; organizace začleněná do struktury prestižní veterinární komory USA – „American Veterinary Medical Association"). Doktorka Royalová vysvětlila široké veřejnosti jednoznačná rizika označování domácích zvířat formou RFID invazivních mikročipů a to i přes to, že sama je zastánkyní čipování – uvědomuje si také jeho výhody. Avšak její svědomí, přísaha chránit zdraví svých pacientů a vědecké poznatky obsažené v odborné literatuře jí nedovolily zamlčet fakta o nebezpečích implantací cizích těles do živých těl zvířat. Uvedla, že: „***Existuje vždy riziko v případě jakékoliv aplikace čehokoliv do těla, že na to bude organismus odpovídat nějakou nežádoucí reakcí a nakonec to skončí rakovinou nebo podobnou zánětlivou nemocí. Je to možné.***" **Obzvláště dále také upozornila na známý zdravotní hazard: kombinaci vakcinace/čipování do stejného místa na těle zvířete. Vědecké studie (viz seznam a citace zde) již totiž prokázaly karcinogenitu některých typů očkování a související problémy s čipováním zvířat. Pokud umístíte RFID transpondér do oblasti vpichu vakcíny, tak dochází ke značnému posílení nebezpečí vzniku vážných chorob**. Navíc samotná aplikační jehla s mikročipem „*je pořádně velká*", vysvětlila navíc veterinářka. Díky tomu se malým zvířatům provádí lokální anestezie, aby u nich nedošlo k poměrně značné bolesti. Dr. Royalová doporučila všem chovatelům činit pohmatem pravidelné kontroly svých očipovaných domácích čtyřnohých mazlíčků, zda je podkožní identifikátor stále na stejném místě a jestli nedošlo k zánětu tkáně nebo jiným nežádoucím reakcím organismu. Závěrem vyzdvihla nutnost udržování aktuálních údajů v chovatelských registrech: jinak by bylo celé slavné čipování úplně zbytečné. – A opět na to navazuje v českém prostředí: Ministerstvo zemědělství ČR skutečně potvrdilo v listopadu 2015, že se „***v literatuře uvádějí důvody k vyjmutí nebo neaplikování čipu z důvodu vzniku neoplazma nebo posunu mikročipu***". – **České úřady také poskytly Společenství webu Necipujtenas.CZ roku 2015 ve spolupráci se Stranou svobodných občanů (Svobodní) a dalšími význačnými osobnostmi napříč společenským spektrem oficiální dokumenty k více než 212 zdravotním/etickým výjimkám z vynucování čipování, které musely být uděleny proto, aby se zabránilo závažnému týrání psů, jejich utrpení a fyzické i psychické újmě dotčených občanů/chovatelů**. – Ministerstvo vnitra České republiky dokonce uznalo v březnu 2016 legalitu zdravotních výjimek z povinného čipování zvířat a již dříve roku 2015 shledalo jako souladnou se zákonem městskou vyhlášku sestavenou ostravským občanem za účelem osvobození chovatelů psů z čipovacího útlaku. – Zdravotní/etické výjimky do svých podzákonných předpisů zavedla nebo jiným způsobem je již realizovala například níže uvedená města, městyse, obce v ČR: **Karlovy Vary, Prostějov, Přerov, Česká Lípa, Litoměřice, Desná, Vodňany, Litoměřice, Brandýs nad Labem-Stará Boleslav, Roudnice, Jeseník, Litvínov, Smržovka, Tanvald, městys Zásada, Albrechtice v Jizerských Horách, Kořenov aj. V zahraničí se to krom jiného týká například Texasu, Kalifornie, Anglie, Skotska, Irska, Austrálie, Nového Zélandu aj. států.** – Nejvyšší správní soud ČR navíc podobně jako Ústavní soud uznal na základě expertních stanovisek existenci zdravotních rizik povinného čipování mj. ve své argumentaci z roku 2013 (viz 4 As 79/2013 – 44) a to „***ve výjimečných případech nezbytných z důvodu ochrany těchto jedinců (pokud by implantování čipu ohrozilo zdravotní stav exempláře)***". – A takto bychom mohli pokračovat dále a dále. Viz další dokumentace a tisíce stran argumentů z celého světa na webu Necipujtenas.CZ. – Přesto je špatný čipovací moloch dále s umíněnou urputností mnohde plošně vynucován: obzvláště v Ostravě. Toto město představuje typickou ukázku zlého a

přirozeně také krutého přístupu veřejné moci v některých státech Evropské unie, kde dochází pod hrozbou likvidačních pokut, zásahů speciálních/úředních tzv. „čipovacích komand“ a mnohdy ještě za pomoci lokálních/městských policejních jednotek k plošnému/bezvýjimečnému vymáhání tzv. trvalého označení např. psů, koček nebo fretek i v případě ohrožení jejich zdraví nebo rovnou života. – Nezbývá než poděkovat Pánu Bohu za to, že jsou zde ještě stále čestní veterináři s vysokými etickými principy a s desítkami let praktických zkušeností, kteří se proti takovému vyloženě totalitnímu systému oprávněně bouří a zastávají se svých čtyřnohých pacientů i lidských vlastníků zvířat. – Společenství webu Necipujtenas.CZ dodává: Nefunkční a dokonce životu nebezpečný systém čipování/identifikace zvířat nelze občanům vnucovat a tlačit je k tomu, aby se na něm navíc nedobrovolně finančně podíleli, jestliže přirozeně existují daleko úspěšnější, méně stresující nebo dokonce zcela neinvazivní metody označování/navracení zatoulaných zvířat zpět domů. Patří k nim především policejní foto-identifikační metoda rozpoznávání tváří v návaznosti na mobilní/internetové aplikace a sociální sítě/média, DNA značení/vzorkování, klasické i elektronické známky, adresáře, GPS moduly a v neposlední řadě osvěta včetně propagace dobrých příkladů soužití mezi zvířaty a lidmi obzvláště ve městech. Vždy však musí být na svobodném zvážení majitele zvířete: jak a zda vůbec provede označení svého psa, kočky aj. živých tvorů.

Zdroj:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/501782/PhV_Annual_Review_2014_Final_Version_v3.pdf; http://www.necipujtenas.cz/Files/necipujtenas/czech-ministry-of-interior-accepts-legality-of-exceptions-from-mandatory-microchipping-animals-ostrava-city-prepares-amendment-to-its-regulation-czech-republic-2016.pdf; http://www.necipujtenas.cz/fakta/dokumenty-ke-stazeni/; http://www.raingoddess.com/vetmed/microchips.s.html; http://www.necipujtenas.cz/fakta/rizika-cipovani/; http://www.necipujtenas.cz/fakta/tragicke-pripady/; http://www.necipujtenas.cz/fakta/legislativa/; http://www.necipujtenas.cz/media/



NECIPUJTENAS.CZ

MVDr. František ŠPRUČEK, Ph.D.
Tylova 3
772 00 OLOMOUC
Tel: 585 226 008, 602 705 362

Vystavil: MVDr. ŠPRUČEK František Ph.D
Datum: 26.4.2010

Majitel: 02764
Adresa: 796 01

Pacient: 004452 BÁRA
Katastr, Farma, Obec: 02
Druh, Plemeno: PES jezevčík drsnosrstý
Datum narození: 28.2.2004

Tetovací kód:
Kód v PK:
Kód RD:
Datum registrace:

Poznámka:

Toto potvrzení jsme vystavili na žádost majitele a to vzhledem k tomu, že bylo ve městě Prostějov zavedeno povinné čipování psů. Jelikož tento [illegible] je zásahem do zdraví zvířete se všemi právními i etickými aspekty bylo námi vyhodnoceno takto: u výše jmenovaného psa je aplikace podobného charakteru nežádoucí a spojená s rizikem rozvinutí dermatické nekrolýzy, kterou pes opakovaně prodělal. V naší praxi jsme se již setkali s několika případy, které končily chirurgickým odstraněním mikročipu a to v důsledku rozsáhlých nekrotických ložisek, které u takto predisponovaných zvířat vznikly právě na základě vpravení cizího předmětu do podkoží.

MVDr. František Špruček, Ph.D

MVDr. František ŠPRUČEK, Ph.D.
Tylova 3, 772 00 OLOMOUC
tel.: [illegible]
IČ: 42060281 DIČ: CZ5806131639
spurcek@email.cz reg. č. KVLČR 3940

Ukázka ze souboru veterinárních zpráv čtrnácti medicínských specialistů z Olomouce, Brna, Kojetína, Prostějova, Hvozdu, Kostelce na Hané v České republice, které popsaly závažná zdravotní nebezpečí a mohutná etická rizika spojená se státním/městským vynucováním invazivního čipování zvířat. – Zdroj obrázku: Magistrát Statutárního města Prostějova.

Veterinary Medicines Directorate

Veterinary Pharmacovigilance in the United Kingdom

Annual Review 2014

Protecting animal health, public health and the environment

Word cloud – a visual representation composed of the words used in this review, in which the size of each word indicates its frequency of use

[Produced using Tagxedo.com]

Contents

Introduction

Thousands of millions of doses of different types of veterinary medicine are manufactured, sold and used annually within the UK. In a relatively small number of cases, an adverse event (AE) occurs during or sometime after the use of a medicine. AEs can be reported by veterinary professionals, animal owners (including farmers) or anyone else who has reliable knowledge of the incident, either to the company marketing the medicine or to the VMD.

An **adverse event** is any observation in animals, humans or the environment whether or not considered to be product-related, that is unfavourable and unintended and that occurs after any use of a veterinary medicine.

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

A **suspected lack of expected efficacy** (SLEE) is when a product is not thought to have worked as well as expected.

During 2014, the VMD's Pharmacovigilance team received and assessed a total of 5743 AE and environmental incident reports. Most of these reports describe events that occurred in animals during or after the use of authorised veterinary or human medicines. Fewer reports were associated with other types of products.

A **serious adverse event** is one which ends in death, is life-threatening, ends in significant disability or incapacity, a congenital anomaly or birth defect, or which results in permanent or prolonged signs in treated animals.

Some reports describe reactions experienced by humans, who have been exposed to products used to treat animals or the household environment.

A small number of the reports we receive describe environmental incidents, in which active ingredients suspected of originating from veterinary medicines have been detected.

All types of report are considered in this review.

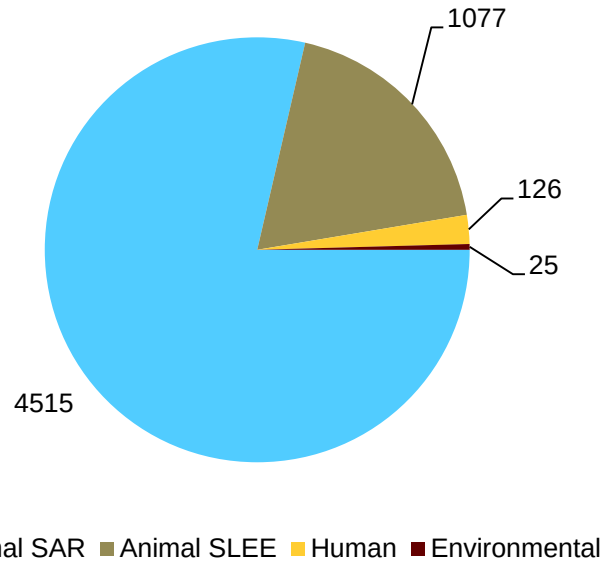


Figure 1. Number and type of adverse event reports received during 2014

Important points to note

The purpose of this review is to give a summary of the reports received by the VMD's Pharmacovigilance team during 2014. The information provided may provoke interest or discussion, but must not be used in isolation to make judgements on the safety of authorised veterinary products. Any decision on the choice of product to be used in a particular instance is a matter for an animal owner and the appropriate veterinary professional to discuss and agree.

At the end of this report you will find a glossary explaining some of the more technical clinical terms used.

Remember:

- Companies that own or market authorised veterinary medicines (known as Marketing Authorisation Holders or MAHs) are obliged to send all serious animal and human AE reports to the VMD's Pharmacovigilance database within 15 days of becoming aware of the incident. Non-serious reports are submitted by MAHs by a different means at intervals of between 6 months and 3 years, depending on the time since authorisation. Sales information for each product are also received at these intervals, but this means that the most recent figures we have for specific products may be up to 3 years old.
- 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.
- No reports have been excluded from this review, even if it was considered unlikely that the products were in fact responsible for the signs observed.
- The reports that we receive are usually the most serious, therefore the information summarised in this review is a concentration of 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.
- A single report involving multiple products will be included in the data review of each product type for the species involved.
- Interpretation of the information summarised in this review may therefore be confounded by the use, in any one case, of multiple medicinal and/or non-medicinal products that could have contributed to additional clinical signs.
- It is assumed that each of the products involved in individual cases has been used as it is intended to be used, unless it is obvious from the report that this was not the case.
- When death is reported, it is not always directly associated with the use of the product(s) involved. Euthanasia is frequently reported simply as death, and there are often other factors involved in a decision to euthanase an animal.

Using sales data from 2012, the most recent year for which we have full information, we estimate that we receive 1 AE report for every 2.1 million doses of authorised veterinary medicines sold.

It is acknowledged that there is a large amount of under-reporting; however, the UK receives by the far the highest number of reports in Europe.

Who sends reports

Most of the AE reports that we receive come from MAHs (65% in 2014). The majority of reporters contact the MAH of the product involved as this is the best way to get immediate advice and initiate rapid investigations into the AE.

We receive many reports (35%) directly from those who witnessed an event, or are reporting for someone else. Only about 15% of reporters, who reported directly to us, told us that they had also informed the MAH. A further 24% of the reports received from vets and others were later also received from the MAH.

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

Three routes are used to send AE reports to the VMD. MAHs report directly into our pharmacovigilance database. Other reporters use the online reporting form[1], which transfers information directly to our database, or post a handwritten 'yellow' paper form. The information from paper forms is manually entered, but is often very difficult to read.

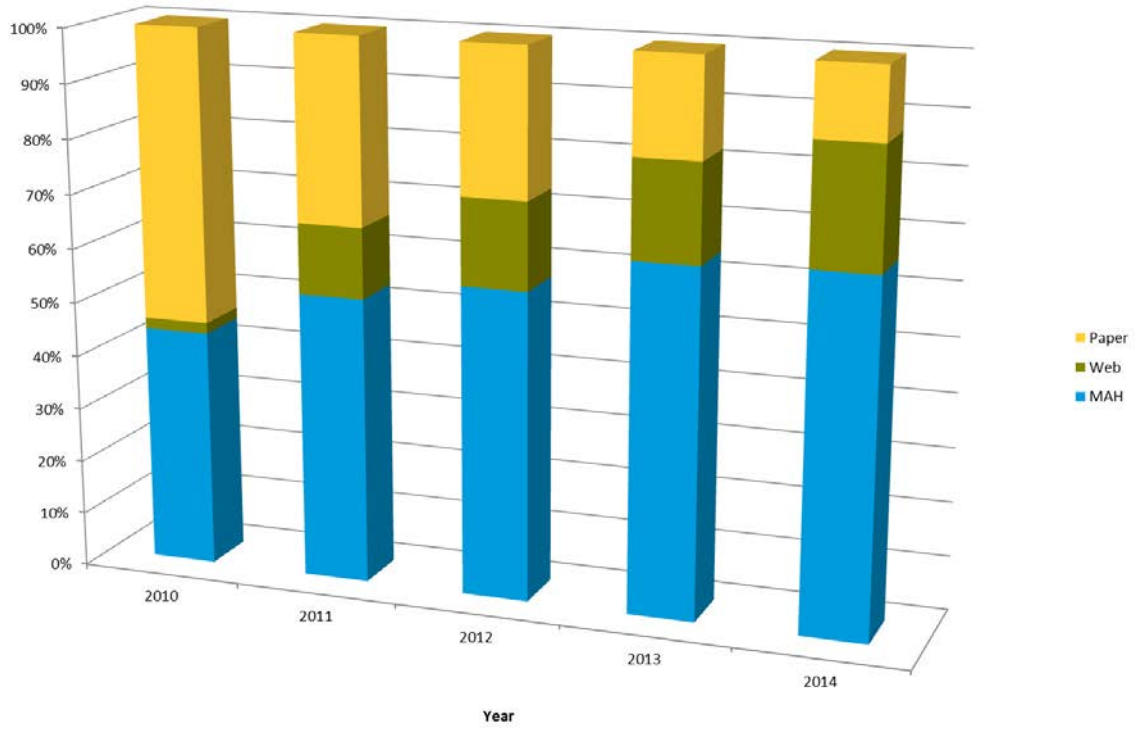


Figure 2. Proportion of reports received by different methods since 2010

Figure 2 shows that since the introduction of the online form late in 2010, there has been a significant decrease in the proportion of reports received as yellow forms.

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

We recommend that vets, animal owners and other members of the general public use the online reporting form[2]. It is quicker and easier to send than a paper form and you get an automatic acknowledgement summarising the report for your records.

Please note: As of January 2016 we are no longer accepting reports sent via fax, so please do not use this method of contacting us, even if the yellow form you have still has a fax number on it.

Figure 3 shows how many reports are received from which groups of people, and how many are received as online or paper forms.

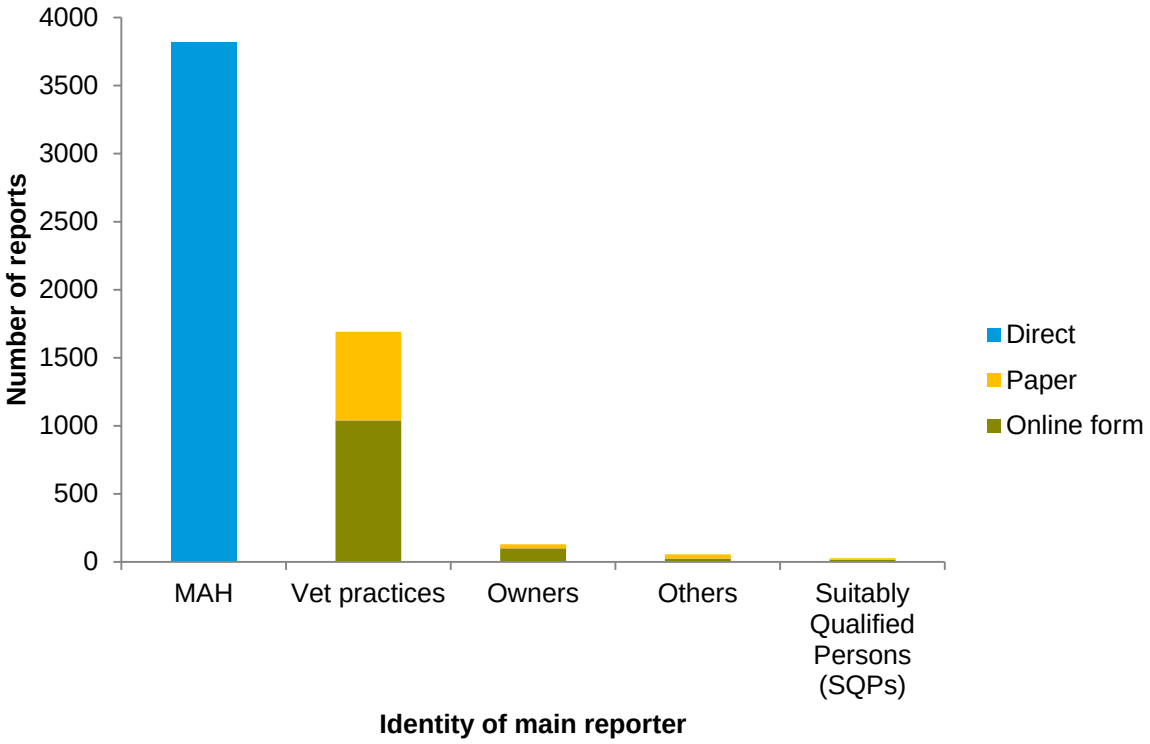


Figure 3. Number of reports received from different reporters by different means in 2014

A suitably qualified person (SQP) is someone who has undertaken a course or courses of study to give them the knowledge to advise farmers and pet owners about specific types of veterinary medicines. You may meet an SQP at the agricultural or equine merchants, in the local pet shop or at a vet surgery. As they can prescribe some types of medicines, they are an important potential source of AE reports.

We also received reports from other people connected with animals, including agricultural merchants, vets working for the Animal and Plant Health Agency, and a pharmacist.

For human adverse events, almost all cases were reported by the MAH of the product(s) involved, although important additional information was often provided to us by the patients themselves, or by other health professionals.

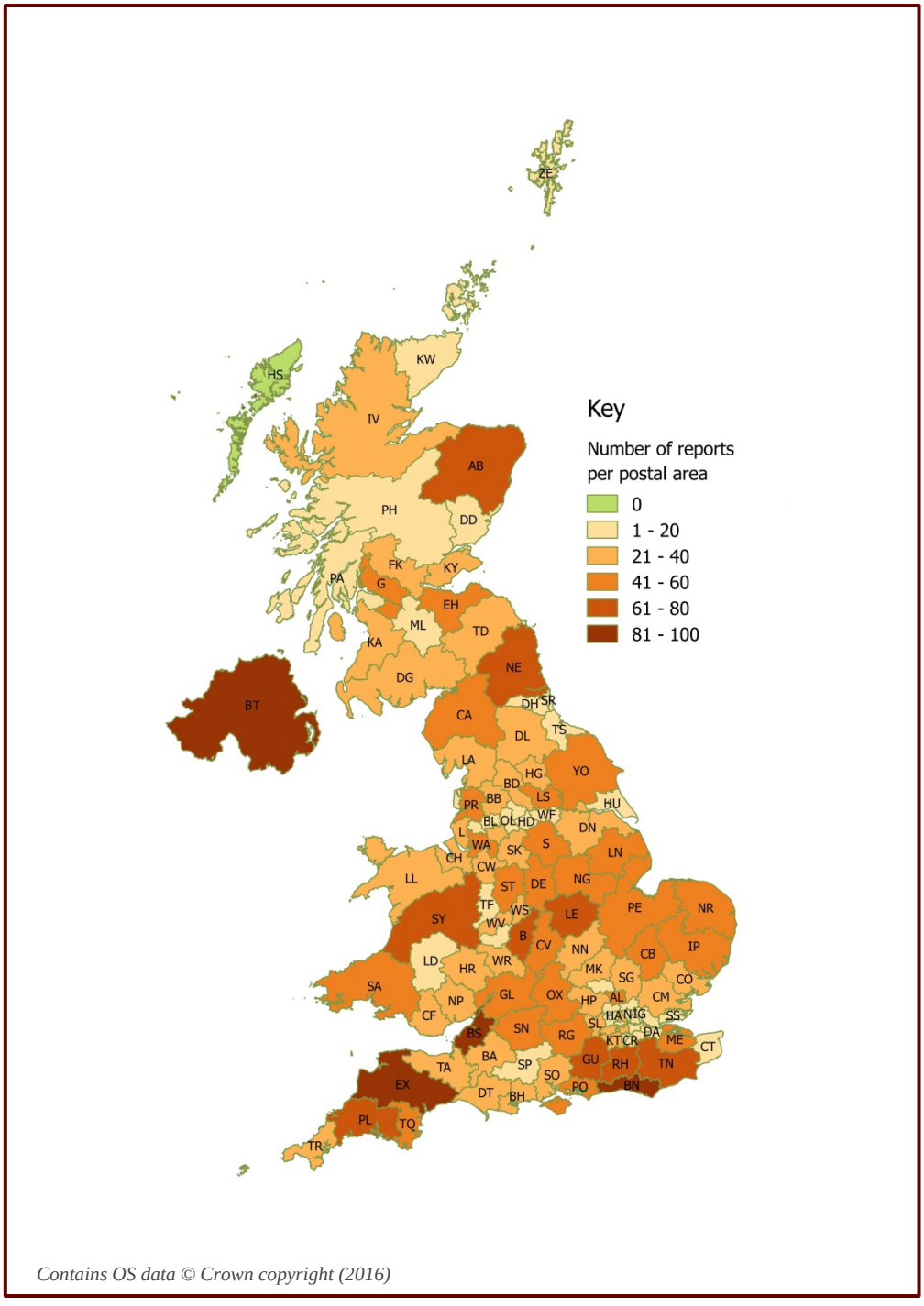
We also received reports involving the environment or wildlife from the Wildlife

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

Incident Investigation Scheme (WIIS), when there was a suspicion of veterinary medicine involvement. This collates reports from various UK organisations including:

- Science and Advice for Scottish Agriculture (SASA), who investigate suspected pesticide poisoning incidents in Scotland
- the Wildlife Incident Unit of Fera Science Ltd, who carry out chemical analysis on samples from England and Wales, obtained during WIIS investigations

Figure 4 shows the number of animal reports received from each postcode area, but only for those reports (3969) for which the location of the initial reporter was recorded. It is worth noting that we received reports from all areas, except the Outer Hebrides.



Contains OS data © Crown copyright (2016)

Figure 4. Number of reports received per postcode area in 2014

Types of products mentioned in Adverse Event reports

Most products mentioned in AE reports are fully identified by the reporter, but a significant number are not.

The complete identification of products ensures that a full assessment of the involvement of products used in each case can be made.

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 try to make an educated guess as to the identity of the product used, using whatever evidence is provided in the description of the AE as a guide.

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

Authorised veterinary medicines

There are currently over 2,500 veterinary medicines[3] 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. A new medicine is only authorised for use when these experts are satisfied that the benefits gained by using the medicine outweigh the risks that may be incurred.

All aspects of medicines are checked, including

- 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. A copy of the SPC for every authorised product can be accessed using the VMD's Product Information Database[3].

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
- user safety precautions (eg whether protective gloves should be used whilst handling it)

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

If an authorised medicine is used following the instructions provided in the SPC, this is known as '**authorised use**'.

If an authorised medicine is used in a way that is not described 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 known as '**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[4].

Therapeutic groups

A therapeutic group is a group of medicines that may be based on different active ingredients (drugs), but can all be used to treat a specific type of disease or condition.

Vaccines

Vaccines comprise a very wide range of products. Each vaccine is designed to protect 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 either contain a killed or weakened form of whole bacteria or viruses, or just a small part of them. They may prevent an animal catching a specific infection, or just reduce the severity of infection.

Ectoparasiticides

Ectoparasiticides are medicines that kill the parasites that live on the skin of animals, e.g. fleas, ticks, mites and lice; they treat external parasites.

Endectocides

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; they treat both internal and external parasites.

Anthelmintics

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

[4] The Cascade: Prescribing unauthorised medicines, www.gov.uk/guidance/the-cascade-prescribing-unauthorised-medicines

Anti-inflammatories

These products are used to treat inflammation. They are divided into sub-groups depending on the type of drug that makes them work. Different types used in animals include

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

Antimicrobials

- 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
- Spasmolytics (to treat scour and equine colic)

Hormones and hormone regulators

These drugs may replace hormones that are no longer being produced, for example insulin to control the symptoms diabetes mellitus. They may also stimulate or suppress the production of hormones that are being under or over produced respectively. Examples of these are thyroid suppressants for cats with overactive thyroids, and synthetic thyroid hormone replacements for dogs with underactive thyroids.

Authorised human medicines (including extemporaneous ‘vet specials’)

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. In exceptional circumstances, a vet or pharmacist can prepare a suitable medicinal product for veterinary use.

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[5] 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.

Exempt veterinary medicines

Some medicines, which are intended for use in minor pet species, are exempt[6] from the need to be authorised like other more widely-used veterinary medicines. These products contain a restricted range of ingredients. Although these medicines are not individually assessed in the same way as authorised veterinary medicines, they are manufactured to the same standards. Many of their ingredients have been used to treat animals for a long time, and they have been found to be safe to use. Nevertheless, it is still important that the instructions that come with the medicine are carefully followed. These types of products are intended to be used to treat

- 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

Veterinary non-medicinal 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
- behaviour-modifying pheromones

These products are not medicines and cannot claim to have medicinal properties.

Other non-medicinal products

These are generally products that are made for human use, and although legally they may be authorised human medicines[7] or medical devices[8], they are not in themselves medicinal in the true sense of the word as they do not treat or prevent

[5] 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
[6] Exemption from authorisation for medicines for small pet animals, www.gov.uk/guidance/exemption-from-authorisation-for-medicines-for-small-pet-animals
[7] Article 1 of Directive 2001/83/EC (as amended), http://ec.europa.eu/health/documents/eudralex/vol-1/
[8] Article 1.2 of Directive 93/42/EEC (as amended), http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/index_en.htm

disease. Examples include suture materials (stitches) and contrast agents, which are used to highlight certain organs or tissues for diagnostic imaging (eg x-rays and MRI scans).

We have also included microchips used for animal identification in this category.

Pesticides

Pesticides are used to control flea and other insect infestations. They are not authorised veterinary medicines. Some are meant to be applied to your animal and repel insects. Others are for treating where your animals live, including farm buildings, furniture, carpets and pet beds; these products will either repel or kill fleas and other insects. The Health and Safety Executive[9] (HSE) have a database[10] listing pesticide products containing substances regulated under the Control of Pesticide Regulations.

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

Products used in clinical/field trials

In the latter stages of development of new veterinary medicines (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 the best treatment options for a particular disease.

In order for such trials to be conducted in animals owned by the general public, MAHs and veterinary researchers must apply[11] to the VMD for an Animal Test Certificate[12] (ATC) which authorises the study. One of the conditions of an ATC is that all serious adverse events occurring following use of any product involved in the trial (even control products) must be reported to the VMD within 15 days.

Due to the confidential nature of these studies, in this review, we will not discuss the findings of any adverse events reported to us originating from trials carried out under ATCs.

[9] Reporting incidents of exposure http://www.hse.gov.uk/biocides/reporting.htm
[10] HSE COPR registered products, webcommunities.hse.gov.uk/connect.ti/pesticides/viewdatastore?dsid=2308&showAdvancedSearch=Y
[11] Apply for an animal test certificate, https://www.gov.uk/government/collections/apply-for-an-animal-test-certificate
[12] Animal Test Certificates, https://www.gov.uk/guidance/animal-test-certificates

Overview of Animal Adverse Event Reports

A total of 5592 animal-related reports were received during 2014. Of these 4684 were associated with companion (pet) animals, 872 with production (food-producing) animals and 36 with exotic animals. Figure 5 shows a breakdown of the species for which reports have been received.

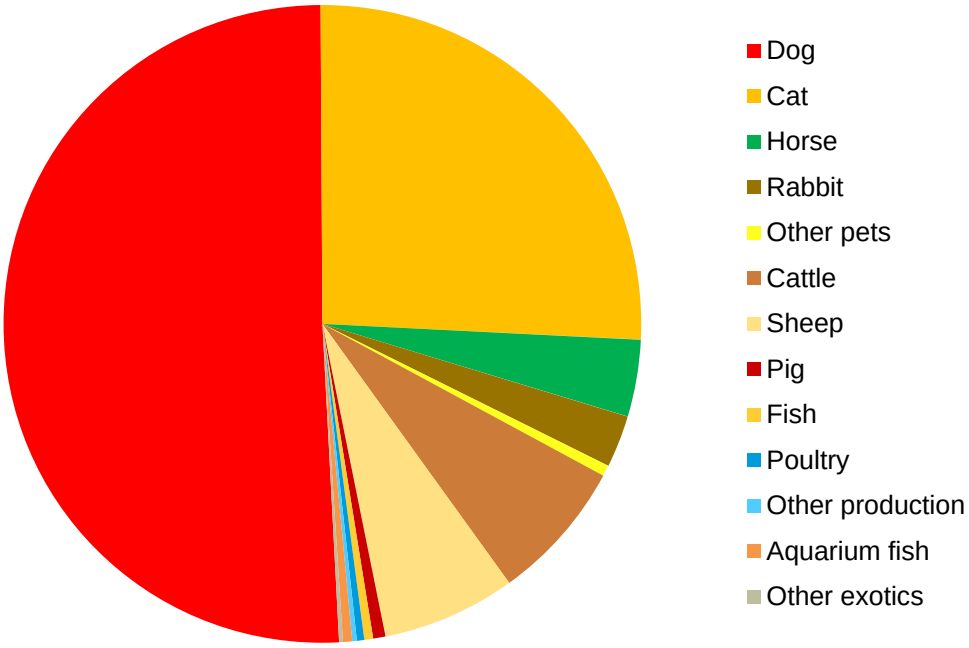


Figure 5. Proportion of reports received for different animal groups during 2014

For the purposes of this review;

- Companion animals include cats, dogs, horses, donkeys, small mammals kept as pets and single caged birds, which may be exotic in the true sense of the word, but live in close proximity to their owners.
- Food-producing animals include cattle, sheep, pigs, poultry, farmed fish etc.
- Exotic animals are taken to be all other non-food producing animals, including native wild animals, aquarium fish, zoo animals, aviary or racing/ornamental birds and laboratory animals.

These 5592 reports involved 7480 product usages, with between one and nine products used per report. Figure 6 shows the broad therapeutic groups of those products.

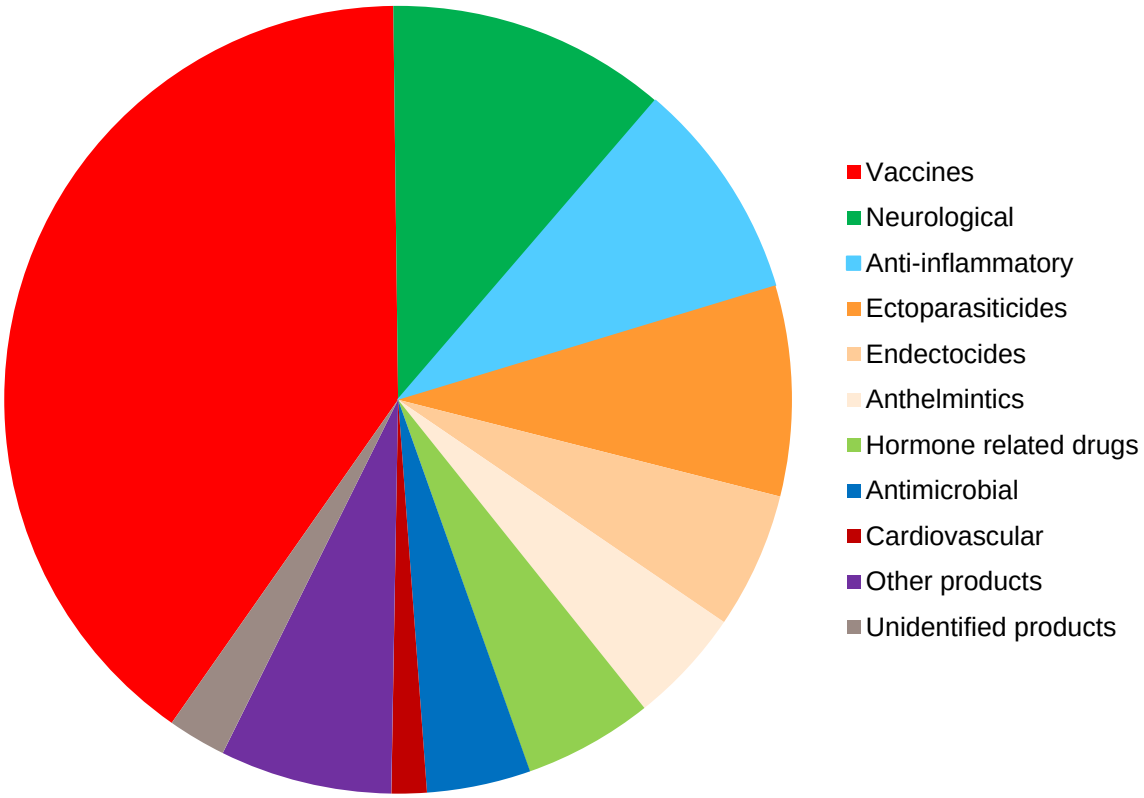


Figure 6. Therapeutic groups of products reported in animal AE reports

'Other products' include

- Cancer treatments
- Anti-vomiting treatments
- Teat sealants
- Anti-fungal treatments
- Vitamins and minerals

Companion Animals (Pets)

Figure 7 shows the proportion of different species that were involved in the 4,684 reports linked to animals kept at pets.

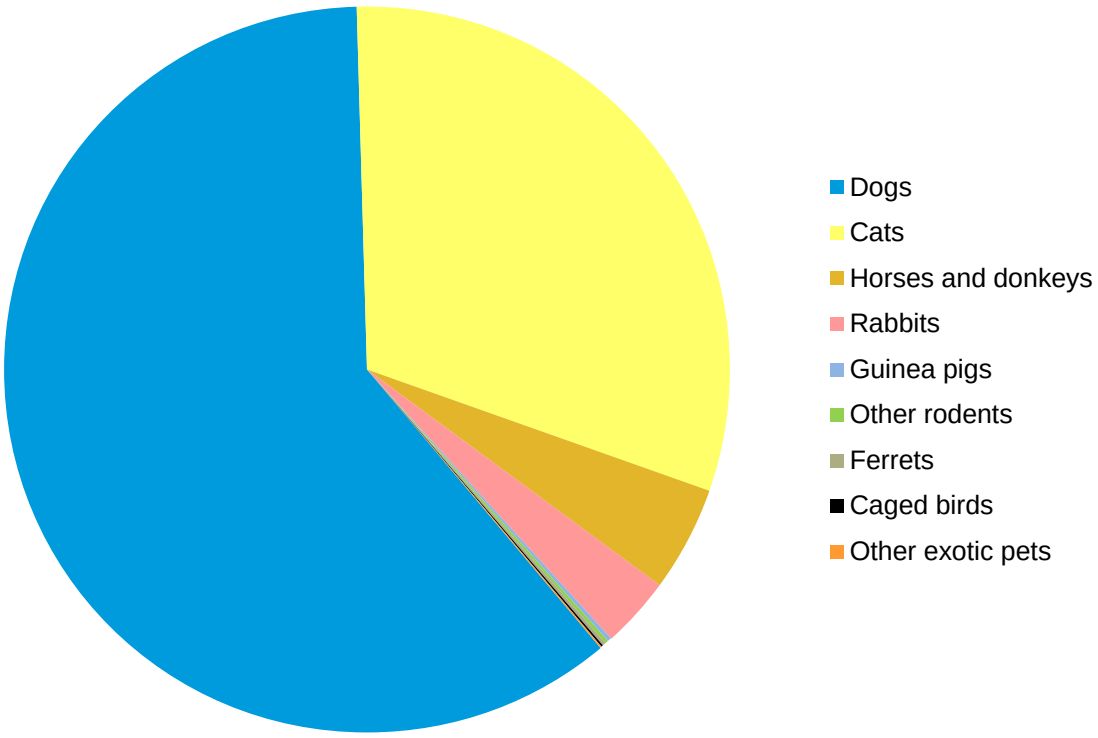


Figure 7. Pet animal species involved in AE reports received in 2014

Dogs and cats accounted for over 90% of reports; the remaining 8.5% involved horses and donkeys (4.5%), rabbits (3%), guinea pigs, rats, hamsters, ferrets, caged birds, and other exotic species that have recently become popular as pets; African pigmy hedgehog, Vietnamese pot-bellied pig and micro pig.

Almost 13% of companion animal AE reports related to SLEEs. Of these, 80% related to either anti-epileptic drug or vaccine use. Another 10% related to products for the treatment of parasites.

It is important that when you treat your pet for external parasites, you also treat your home with a suitable household pesticide, unless the product you use on your pet also claims to treat the environment. This will ensure that any parasite eggs or larvae that may be present are killed, and will reduce the likelihood of immediate re-infestation.

There were no reports of adverse events involving reptiles or amphibians in 2014.

Dogs

Table 1 shows the breeds of dog most commonly identified in the 2,841 AE reports received involving dogs in 2014.

Breed	Proportion of reports (%)
Crossbreed	12.8
Breed not reported	10.8
Labrador Retriever	9.5
Jack Russell Terrier	4.7
Border Collie	4.5
West Highland White Terrier	3.1
Staffordshire Bull Terrier	2.9
Yorkshire Terrier	2.8
Cavalier King Charles Spaniel	2.7
Chihuahua	2.6
German Shepherd Dog	2.5
English Cocker Spaniel	2.4
English Springer Spaniel	2.4
Golden Retriever	2.4
Shih Tzu	2.4
Pug	2.3
Border Terrier	1.6
Miniature Schnauzer	1.4
Boxer (German Boxer)	1.4
Bulldog	1.3
Beagle	1.3
Rottweiler	1.1
Lhasa Apso	1.1

Table 1. Dog breeds identified in AE reports received during 2014, in descending order

The remaining 20% are accounted for by over 100 other breeds, each of which amounted to less than 1% of the dogs involved. Although this may just be representative of the distribution of dog breeds in the UK, for individual products there can sometimes be differences in the reporting patterns for different breeds.

The identification of the breed of animals involved in adverse events is useful for identifying previously unknown, or monitoring known, breed-specific reactions.

Adverse reactions following authorised use

2,013 reports, excluding SLEEs, occurred following the authorised use of veterinary medicines. In these reports, a total of 2,749 products were mentioned, with up to six different products in each report.

Figure 8 shows the therapeutic groups most commonly reported.

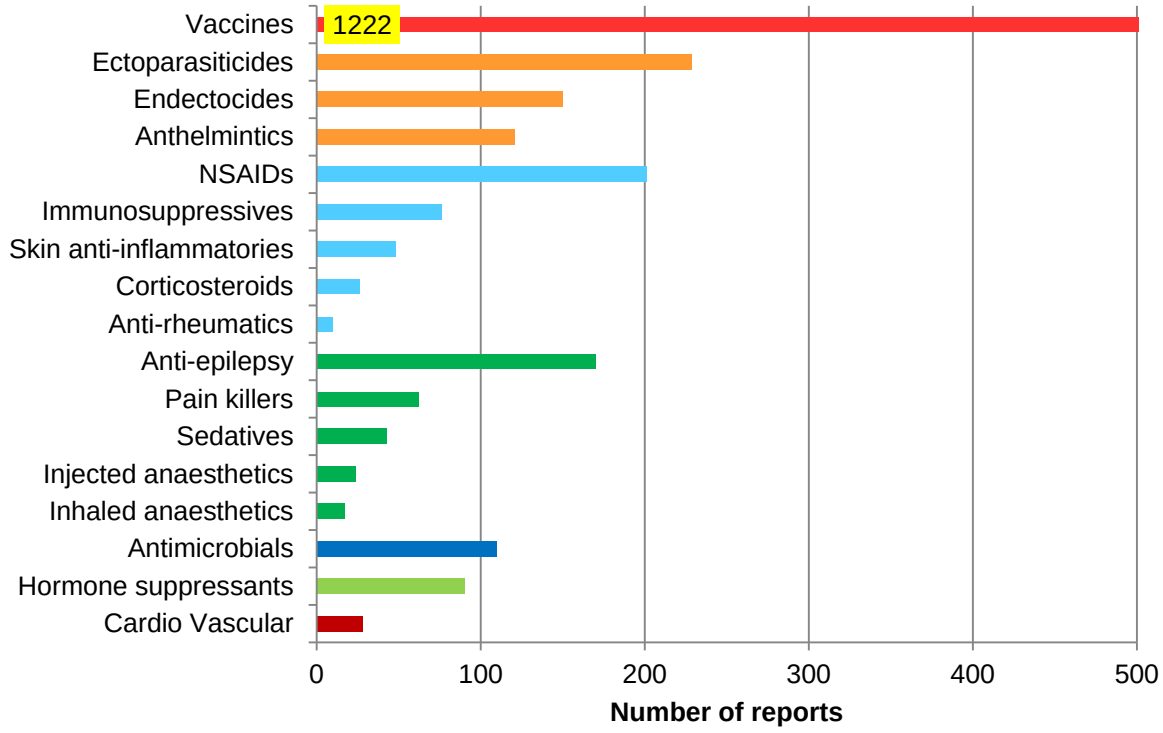


Figure 8. Therapeutic groups associated with SARs after authorised use of veterinary medicines in dogs

Vaccines

Vaccines can be divided into groups that provide protection against the core[13] infectious diseases found in dogs or against kennel cough, rabies virus, *Leishmania*, herpesvirus or Lyme disease alone.

The following figures (9-11) show the most common clinical signs reported in cases that have occurred after the use of products from different groups of vaccines. In some cases vaccines from different groups will have been used at the same time.

It should be noted that the different maximum value for the number of reports for the following three figures is likely to reflect the relative level of use for the three product groups. Very many more dogs receive the core vaccinations than receive a kennel cough vaccination, and relatively few receive vaccination against rabies.

[13] The World Small Animal Veterinary Association (WSAVA) defines core dog vaccines as distemper, parvovirus and adenovirus (www.wsava.org/guidelines/vaccination-guidelines). However, for the purposes of this report, we have classified core vaccines as those giving protection against any combination of distemper, parvovirus, adenovirus, parainfluenza and/or leptospirosis. We have done this, as in the UK dogs are almost invariably vaccinated against leptospirosis at the same time as the other diseases, which makes it very difficult to determine which vaccine component is responsible for the signs observed. Similarly, as there are so many different combinations of the various antigens available, it would not be possible to provide meaningful analysis for each permutation.

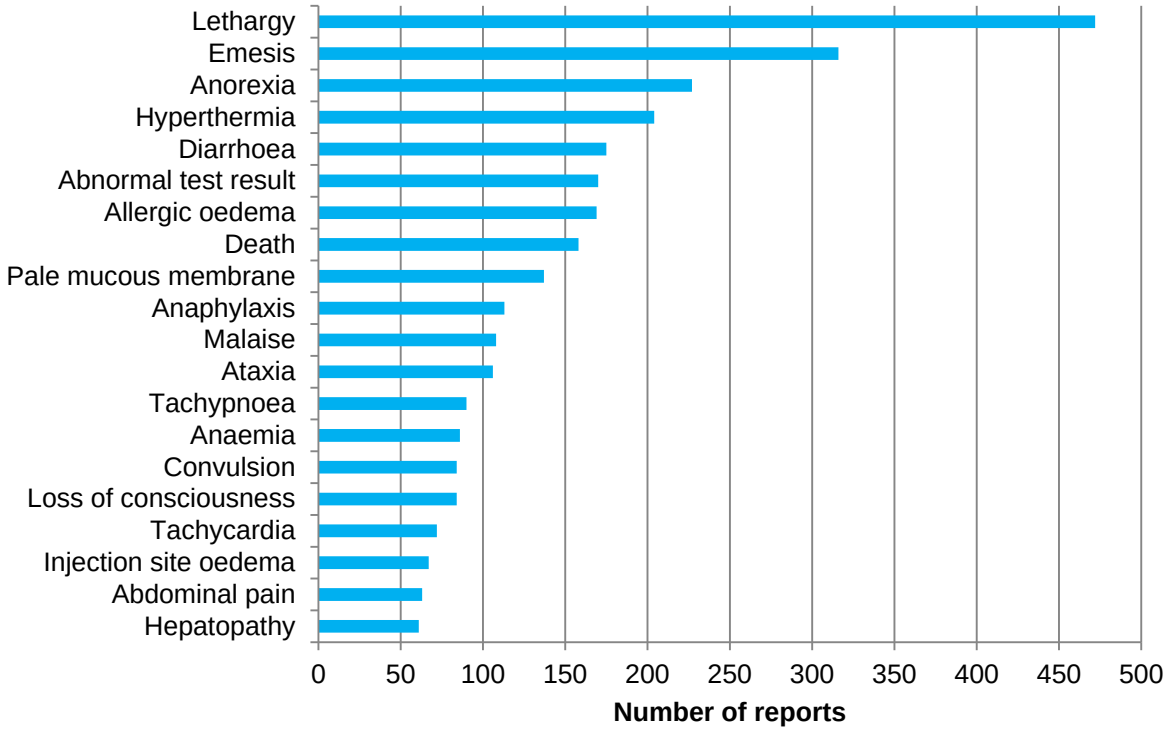


Figure 9. Clinical signs associated with the use of one or more core vaccines in dogs

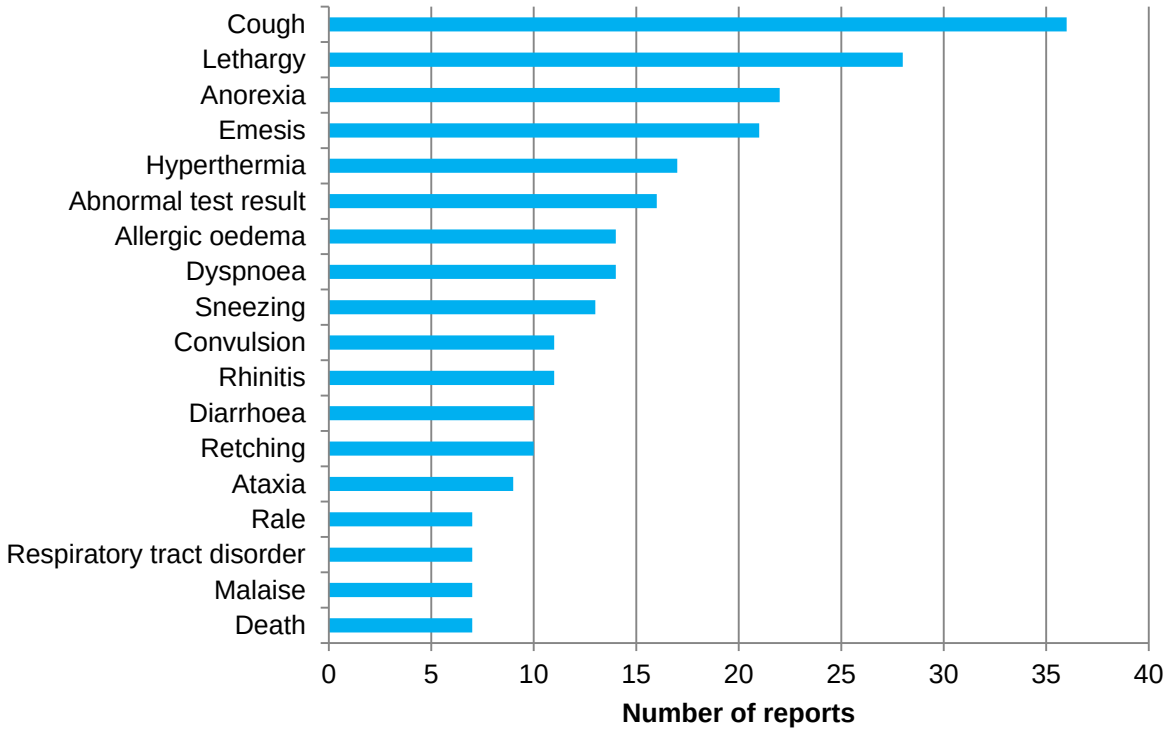


Figure 10. Clinical signs associated with the use of kennel cough vaccines in dogs

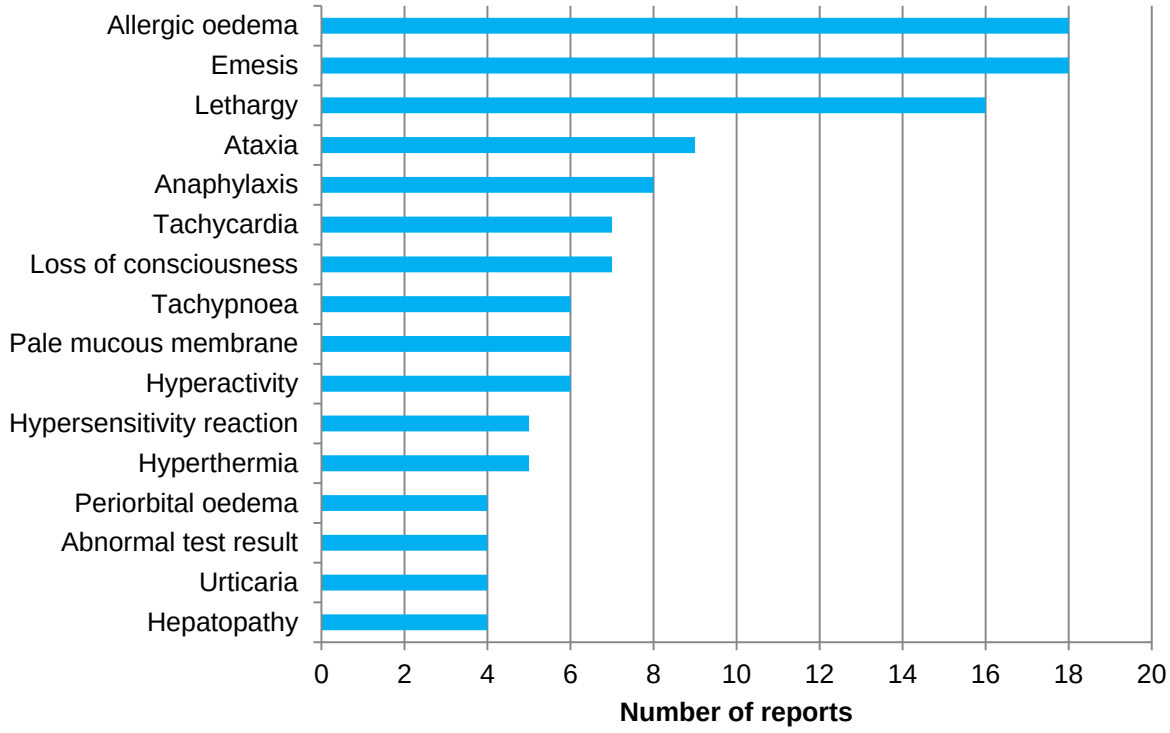


Figure 11. Clinical signs associated with the use of rabies vaccines in dogs

Very few reports were received linked to the use of vaccines against *Leishmania*, herpesvirus and Lyme disease which is probably related to the relatively uncommon use of these products. However, generalised signs, such as anorexia, lethargy or emesis, were observed; after vaccination against Lyme disease, bone or joint disorders were also observed, which may have been due to pre-existing disease.

Ectoparasiticides

Lethargy, pruritus and ataxia were the most commonly reported signs for ectoparasiticides applied as spot-on solutions. For chewable tablets, the most common signs were lethargy, emesis and convulsion. Figure 12 compares the occurrence of the most common signs for the two pharmaceutical forms. Occurrence is expressed as a percentage of the total number of signs reported in all cases involving each pharmaceutical form.

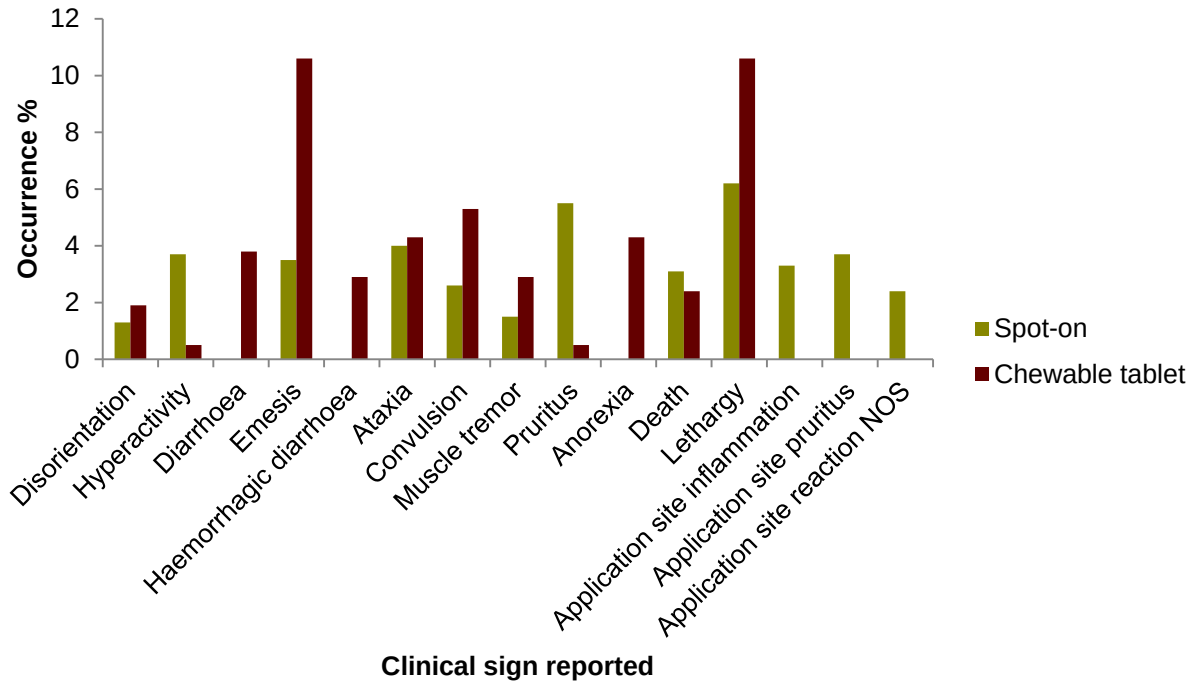


Figure 12. Comparison of the occurrence of the most commonly reported clinical signs for spot-on and chewable tablet products for the treatment of external parasites in dogs [NOS – not otherwise specified (not described)]

Endectocides

For endectocides, the reports received were almost exclusively related to the use of spot-on products. The most commonly reported signs were (in decreasing order) lethargy, emesis, diarrhoea, anorexia, hyperactivity and convulsion.

Anthelmintics

The most commonly reported clinical signs were, in decreasing order: emesis, lethargy, death, diarrhoea, anorexia, convulsion, ataxia, hyperthermia, hepatopathy and hyperactivity. Interpretation of these signs is not easy as, for example, many animals are wormed around the time of vaccination, so signs reported could be linked to either product.

Anti-inflammatory drugs

Emesis was the most commonly reported clinical sign after the use of NSAIDs. These drugs are known to produce gastric symptoms, particularly after prolonged use. Other clinical signs commonly reported were anorexia, diarrhoea, renal insufficiency, haemorrhagic diarrhoea, lethargy and hepatopathy. Death is often reported, but the animals being treated are commonly old or already very ill, and are frequently treated with multiple products to alleviate their clinical signs. During 2015, in collaboration with researchers from Bristol University, we published an in-depth analysis of all adverse events reported following use of NSAIDs in dogs and cats, which yielded similar findings[14].

After the use of immunosuppressants, diabetes mellitus was most commonly reported. Less commonly reported, and probably associated with diabetes mellitus itself, were emesis, lethargy, polydipsia, hyperglycaemia, polyuria and urine

[14] An analysis of the relative frequencies of reported adverse events associated with NSAID administration in dogs and cats in the United Kingdom, *The Veterinary Journal* 2015, 206(2): 183-190

abnormalities. Other signs reported were diarrhoea, hepatopathy, skin neoplasm and death.

Antimicrobials

Deafness and impaired hearing accounted for most signs reported after the use of antimicrobial eardrops, although it was not always clear whether this was related to the underlying disease being treated or the product administered. For antimicrobials administered as tablets, emesis, lethargy and death were most commonly reported. It is possible that anaphylactic reactions to certain antibiotics (especially beta-lactams) may account for some deaths, but this was not specifically reported.

For injectable antimicrobials, AEs reported to have occurred after authorised use were few, but death, diarrhoea and emesis were most often reported.

Neurological agents

For all types of neurological agent, death was the most commonly reported clinical sign, followed by emesis, lethargy and ataxia. The high incidence of death probably reflects the inherent risk associated with surgery and the accompanying use of anaesthetics.

Lack of expected efficacy following authorised use

374 cases of lack of efficacy following authorised use of one or more products were reported. A total of 418 products were mentioned in those reports. Figure 13 shows the different types of products that were involved in cases of SLEE in dogs.

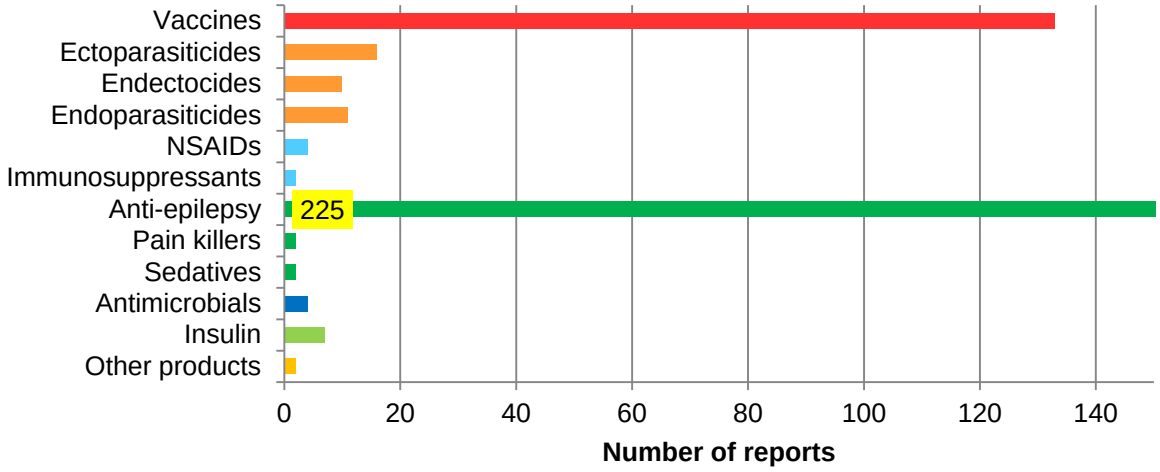


Figure 13. Therapeutic groups associated with SLEE after authorised use of veterinary medicines in dogs

More than half of the cases reported related to the treatment of epilepsy. A letter[15] was published in the Veterinary Record in September 2014 reminding veterinary surgeons to refer to the SPC, in particular to the very specific indications for use.

Over a third of products mentioned were vaccines. The majority of these reports related to cases of suspected parvovirus infection, however, a small number of reports of distemper, canine adenovirus, kennel cough and leptospirosis were also received. In many of these reports, full diagnostic investigations were not carried out and in some multiple infections were detected. We have published a position paper

[15] Use of Pexion tablets for dogs, *Veterinary Record* 2014, 175(9): 232

on the authorised vaccination schedules[16] for dogs which may help vets and owners to agree the most appropriate vaccination programme for individual dogs.

More than a tenth of products reported were anti-parasite products. Reports describing treatment for external parasites often did not make it clear whether the household environment was treated at the same time as the animal.

Off-label use of authorised veterinary medicines

336 of the 2841 dog reports involved the off-label use of between one and five authorised veterinary medicines. Of these 336 reports, 77 resulted in SLEE.

Table 2 lists the five therapeutic groups most commonly identified and a description of the most common types of unauthorised use for each group.

Therapeutic group (% of unauthorised use products)	**Unauthorised use description** (% of group)
Anti-epileptics (25%)	Overdose (39%)
	Underdose (27%)
	Warnings or contraindications ignored (27%)
Vaccines (20%)	Warnings or contraindications ignored (79%)
NSAIDs (14%)	Warnings or contraindications ignored (38%)
	Overdose (27%)
Immunosuppressants (9%)	Unauthorised indication (35%)
	Warnings or contraindications ignored (19%)
	Underdose (19%)
Endectocides (8%)	Underdose (36%)
	Unauthorised route of administration (32%)

Table 2. Therapeutic groups associated with AEs following off-label use in dogs, including the type and proportion of unauthorised use per group

For antiepileptics, overdose was associated with SLEE in 35 of 36 cases. The remaining case resulted in lethargy and inappetence. Other signs observed in conjunction with SLEE were sleepiness, sedation, ataxia and lethargy, but these were only reported in a minority of cases. Conversely, underdosing also gave rise to SLEE, in 14 of 23 cases. Seven of these cases also resulted in death by euthanasia. Other signs observed were sedation, sleepiness and ataxia. In the 24 cases in which warnings or contraindications were ignored (mostly due to an inappropriate loading dose), SLEE was most commonly reported, with lethargy, ataxia and death by euthanasia reported less frequently.

[16] VMD position paper on authorised vaccination schedules for dogs, www.gov.uk/government/publications/vaccination-of-dogs

For vaccines, use was most commonly determined to be off-label due to:

- concurrent use with another vaccine
- the animal being unwell at the time of vaccination
- vaccination intervals being incorrect or
- different brands of vaccine being used for primary and secondary vaccinations.

SLEE and death by euthanasia were frequently reported outcomes.

Off-label use of NSAIDs was usually due to the treatment program not being respected because the product was:

- administered too frequently
- administered in combination with another NSAID product or
- given again despite having been withdrawn due to a previous suspected AE

Although the last bullet above has been classified as off label use, the practice of "dechallenge and rechallenge" is one of the best ways of confirming whether a particular product is truly responsible for the signs observed. However, vets and animal owners should carefully consider the benefits and risks of reintroducing a product that is thought to have caused adverse effects previously.

These cases most often resulted in vomiting and death, along with other gastrointestinal signs, renal insufficiency or hepatopathy.

Ciclosporin A (immunosuppressive) products were sometimes used to treat conditions for which they are not specifically recommended, such as anal furunculosis. In some cases, immunosuppression was such that secondary infections became established, sometimes with severe results.

Underdosing of endectocides did not result in any signs different to those commonly observed for these products (application site disorders, such as erythema, lesions and pruritus). In eight cases, a spot-on product was incorrectly administered by mouth or in food. Seven of these cases resulted in muscle tremors, ataxia, convulsions, collapse and hyperthermia, and ultimately recovery after treatment. The final case was the most extreme. The owner attempted to administer the product orally, but her dog inhaled most of it resulting in coughing, emesis and rale, progressing to tachypnoea, cyanosis, cardiac arrest and death.

These cases highlight the need to follow instructions carefully; the consequences of accidental misuse are often unpleasant and sometimes fatal.

Imported medicines

There were 11 reports associated with products legally imported under SICs or STCs.

Nine of these reports were related to the use of immunotherapy products, four of which gave rise to generalised hypersensitivity reactions within minutes of administration; the other five reports had no common signs.

One case occurred following the administration of an acepromazine injection, which

was administered concurrently with an authorised opioid sedative. The dog became unresponsive, but recovered with symptomatic treatment.

A Canadian mexiletine product was being used to treat heart arrhythmia. The treated dog began to suffer convulsions when the source changed from Canada to Japan.

There was also a report associated with the use of a spot-on product which is available in the UK but had been illegally purchased from a German website. Several days after the product was applied, the dog had two short seizures and died. No PME was performed.

The purchase of this product from a German website was illegal. However, we do not wish to discourage reporting of AEs involving any authorised products (even if obtained illegally). We do not take formal action against isolated cases of illegal purchasing, which are more often due to ignorance rather than a deliberate intention to break the law. If buying medicines online we recommend that you look for a website that we have approved through the Accredited Internet Retailer Scheme.

Authorised human medicines (including extemporaneous 'vet specials')

We received 40 reports of adverse reactions following the use of products authorised for human use, but used in animals under the 'Cascade'. In a majority of cases, the human product was reported to have been used concurrently with one or more authorised veterinary medicines. Table 3 summarises 26 of these reports.

Human drug	Number of cases	Clinical signs included:
Co-amoxiclav/Augmentin[17]	7	Facial oedema, urticaria, periorbital oedema. Death in one case when lincomycin was infused through the same line 5 minutes after amoxicillin and clavulanic acid.
Tramadol	6	Urinary retention, lymphoplasmacytic gastritis. These cases were often complex and protracted, involving the use of multiple authorised and other products. 3 resulted in death.
Omeprazole	3	Diarrhoea, vomiting, lethargy, hyperactivity
Cefuroxime	2	Tachycardia, dyspnoea, cyanosis and haemorrhagic diarrhoea
Tetracosactide	2	Ataxia, adrenal tumour, polydipsia, vomiting, dehydration, lethargy, tachypnoea, heart murmur, pale mucous membranes
Metronidazole	2	Acute hypotension, periorbital oedema, lethargy, death
Ranitidine	2	Erythema, emesis, diarrhoea
Levetiracetam	2	Epilepsy control not improved, other neurological signs, euthanasia

Table 3. Ingredients and clinical signs associated with AEs following the use of human medicines in dogs

A letter[17] was published in the Veterinary Record in June 2015 highlighting the rise in

[17] Adverse event reports relating to Augmentin, *Veterinary Record* 2015, 176(23): 602

the number of adverse event reports following the use of Augmentin specifically, and referring to an earlier letter[18] relating to Co-amoxiclav.

The remaining 14 cases involved the use of alprazolam, chlorpheniramine, dexamethasone/neomycin/polymixin b, diazepam, diphenoxylate/atropine, dorzolamide, erythromycin, heparin, methadone, midazolam, norethisterone, penicillin, piroxicam and ursodeoxycholic acid.

In many of the cases there was insufficient information to determine the role of these human or extemporaneous medicines in the development of the clinical signs observed.

Veterinary non-medicinal products

Eighteen reports involving products intended for veterinary use, but without medicinal claims, were received.

- Four reports involving ear cleaners resulted in deafness, ataxia, ear erythema and irritation, and an allergic reaction.
- Two reports followed the use of a probiotic product and resulted in urticaria.
- Two reports followed the use of joint supplements; in one case, a dog developed itchy feet, and in the other, the resulting gastrointestinal signs were more likely to have been due to the concurrent NSAID treatment.
- One of two reports after the use of potassium bromide (authorised products are now available), as an adjunct to imepitoin, resulted in continued seizure activity and eventually death, in spite of attempts to use different combinations of medication. The second report resulted in ataxia, probably due to overdosing; a dispensing error was suspected.

Other reports were linked to:

- a pheromone collar
- a ‘detox’ tablet
- a coal tar shampoo
- a bladder supplement
- a ‘pesticide-free’ flea spot-on
- a drinking water additive
- a liver function supplement
- a dog attack deterrent spray

Other non-medicinal products

Fourteen reports involving non-medicinal products were received.

Eight reports related to microchips that were implanted at the same time as one or more vaccines were administered. In six of the cases lumps developed at the site of injection/implantation at an interval of between 1 day and 2 months. The other reports involved a transient collapse (presumed to be vasovagal in origin) immediately after implantation and an unexplained death within 24 hours.

[18] Co-amoxiclav powder for solution for injection or infusion, *Veterinary Record* 2011, 169(17): 450

Six other reports involving non-medicinal products were received, five of which related to the use of gadolinium–based contrast agents. Symptoms observed in these cases included anaphylaxis, allergic oedema, tachycardia, hypotension, bronchospasm, bradypnoea and dyspnoea. The final report involved wound healing problems after the use of synthetic suture material (stitches).

Since April 2014, when the VMD formally took on responsibility for monitoring reports of adverse events following microchipping, a separate means of reporting these has been available. Due to the different way these reports are handled, if you submit a report for a microchip problem, such as migration or not working, via the report form intended for veterinary medicines, you will be asked to resubmit the report via the correct online form. For further details on this scheme please see this leaflet. A separate review will discuss the findings from the microchip adverse event reporting scheme.

Reports from studies

Eight reports were received from clinical trials authorised through ATCs.

Cats

The breed of cat was not identified in 566 (39%) of the 1,446 adverse event reports received that involved one or more cats. The largest group of breed type identified was mixed breed (47%), which includes all Domestic Short- and Long-haired cats. Of specific breeds, British, Siamese, Ragdoll and Bengal each accounted for 2% of the reports, Persian, Maine Coon, Burmese and Birman each accounting for 1%, with the remaining 2% split between another 18 breeds.

Adverse reactions following authorised use

1,153 reports, excluding SLEEs, occurred following the authorised use of veterinary medicines. In these reports, a total of 1,670 products were mentioned, with up to six different products in each report.

Figure 14 shows the medicine groups most commonly reported.

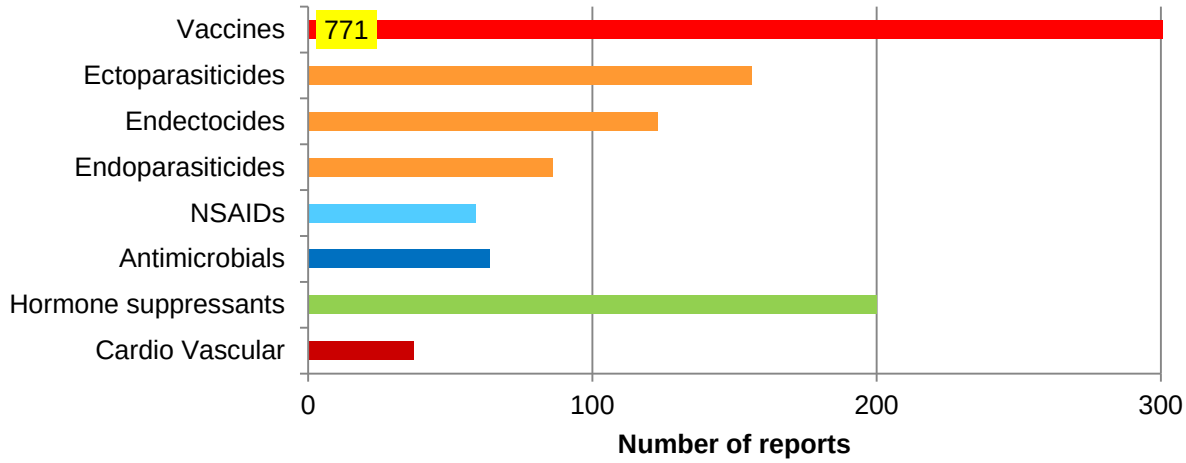


Figure 14. Therapeutic groups associated with SARs after authorised use of veterinary medicines in cats

Vaccines

Cat vaccines can be divided into groups that provide protection against the core[19] feline infectious diseases or against rabies alone.

Figure 15 shows the most common clinical signs reported in cases that have occurred after the use of core vaccines. There were too few cases (6) following the use of a rabies vaccine to show graphically but the most commonly reported signs were lethargy and emesis.

[19] The World Small Animal Veterinary Association (WSAVA) defines core cat vaccines as panleucopenia, herpesvirus and calicivirus (www.wsava.org/guidelines/vaccination-guidelines). However, for the purposes of this report, we have classified core vaccines as those giving protection against any combination of panleucopenia, herpesvirus and calicivirus, chlamydia and/or leukaemia. We have done this, as in the UK most cats are also vaccinated against leukaemia at the same time, which makes it very difficult to determine which vaccine component is responsible for the signs observed. Similarly, as there are so many different combinations of the various antigens available, it would not be possible to provide meaningful analysis for each permutation.

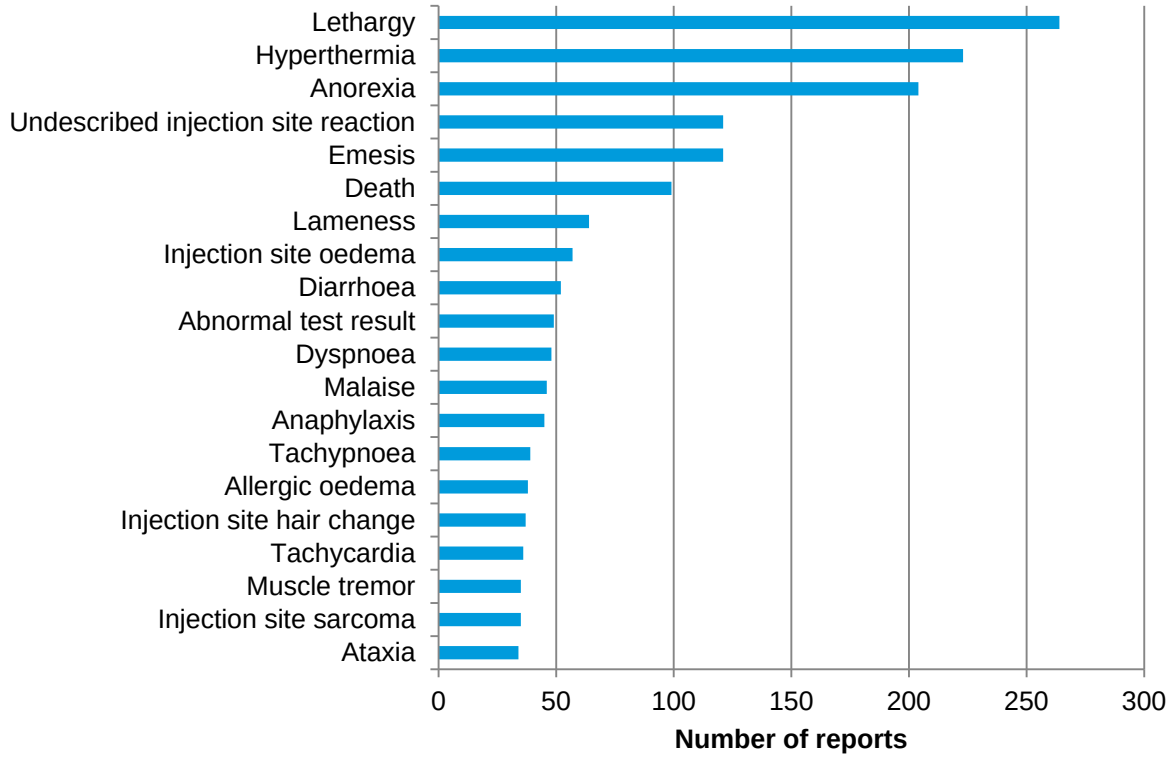


Figure 15. Clinical signs associated with the use of one or more core vaccines in cats

Ectoparasiticides

The most common clinical signs observed were lethargy, application site hair changes, ataxia, muscle tremor and death. The products associated with these signs were collars, chewable tablets and cutaneous spot-ons or sprays.

Endectocides

Hair change at the site of application was the clinical sign most often reported, following the use of endectocide spot-ons. Lethargy and other application site reactions such as pruritus, inflammation and lesions were also reported, together with death.

Anthelmintics

The most commonly reported clinical signs following treatment for internal parasites were ataxia, muscle tremor, anorexia, hyperthermia and death. The products involved were either oral formulations or cutaneous spot-ons.

NSAIDs

The most common clinical signs reported were anorexia, renal insufficiency, death, lethargy, emesis, ataxia and unspecified oedema. These findings are generally in line with the in paper published in collaboration with researchers from Bristol University in 2015[20].

Antimicrobials

Most cases related to the use of an injectable cephalosporin product. For cephalosporins as a whole, the most common clinical signs observed were death,

[20] An analysis of the relative frequencies of reported adverse events associated with NSAID administration in dogs and cats in the United Kingdom, *The Veterinary Journal* 2015, 206(2): 183-190

anorexia, ataxia, emesis, convulsions and lethargy. Some of these signs are indicative of anaphylaxis which was also reported but less commonly.

For other antibiotic groups there were fewer cases, but together the most common signs were emesis, anorexia, lethargy and convulsions.

Hormone suppressants

Hyperthyroidism is common in cats. The most common clinical signs observed during treatment are shown in Figure 16. Several of these signs are more likely to be related to the disease being treated than to the product given.

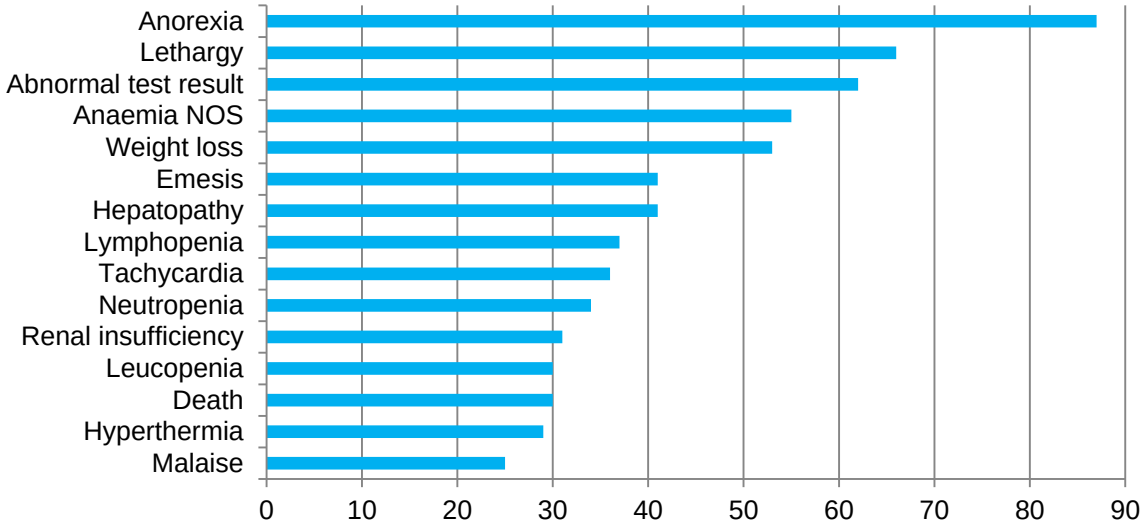


Figure 16. Clinical signs associated with hyperthyroid treatment in cats

Cardiovascular

Following treatment for cardiovascular problems, the most common clinical signs observed were death, renal insufficiency, emesis, anorexia, lethargy and electrolyte imbalances.

Lack of expected efficacy following authorised use

53 cases of lack of efficacy following authorised use of one or more products were reported. Figure 17 shows which types of product were associated with SLEE in cats.

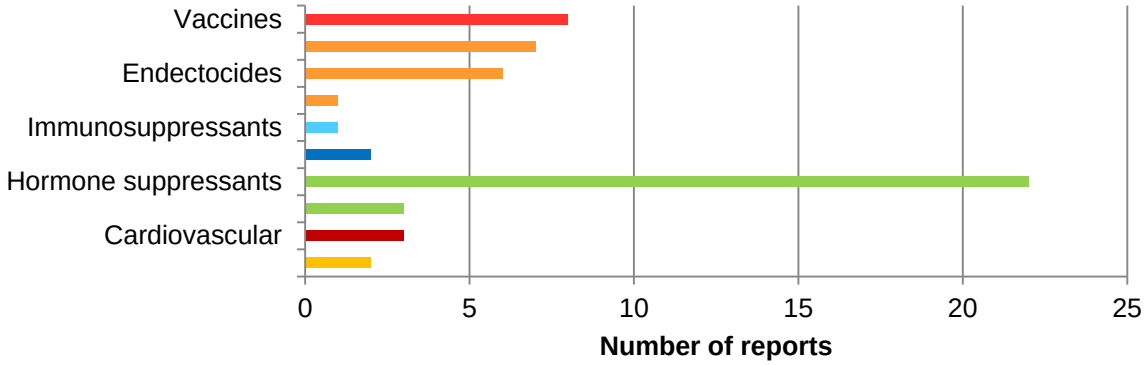


Figure 17. Therapeutic groups associated with SLEE after authorised use of veterinary medicines in cats

In eight cases, involving six different vaccine combinations, three each resulted in the development of panleucopenia or calicivirus infection, with rhinotracheitis and another unrelated disease developing in the final two.

For hyperthyroid treatments, in all but one report, SLEE was confirmed by blood tests. Owner compliance in administering the treatment was noted as good in four reports, but unsure in one and 'not good' in another. It most cases it was not clear whether the lack of efficacy was due to ineffective treatment, either because the animal involved resisted administration, or because it managed to subsequently regurgitate the treatment.

Off-label use of authorised veterinary medicines

225 (16%) of the 1446 cat reports, involved off-label use of one or more authorised veterinary medicines in a manner that was not in accordance with the product labelling. Table 4 lists the five therapeutic groups most commonly identified and a description of the most common types of unauthorised use for each group.

Therapeutic group (% of unauthorised use reports)	**Unauthorised use description** (% of group)
Ectoparasiticides (33%)	Warnings or contraindications ignored (58%)
	Unauthorised species (29%)
Anti-inflammatories (24%)	Warnings or contraindications ignored (36%)
	Unauthorised indication (23%)
	Overdose (15%)
Anthelmintics (13%)	Overdose (79%)
Antimicrobials (10%)	Unauthorised indication (24%)
	Treatment program not respected (24%)
	Overdose (19%)
	Warnings or contraindications ignored (19%)
Hormone suppressants (8%)	Warnings or contraindications ignored (56%)
	Treatment program not respected (39%)

Table 4. Therapeutic groups associated with AEs following off-label use in cats, including the type and proportion of unauthorised use per group

The most common reason for the unauthorised use of ectoparasiticides was a failure to observe the warnings or contra-indications.

In 22 cases, cats were the unauthorised species treated with products only intended for use on dogs; 19 of these cases involved products containing permethrin (18 spot-ons and one shampoo), and the others involved imidacloprid or fipronil.

Typical signs of permethrin toxicity in cats are convulsions, muscle tremor (twitching)

and death.

Table 5 shows the approximate incidence of reactions and deaths in cats, following exposure to dog products containing permethrin, in relation to the number of doses of these products sold per year since 2006.

Year	Ratio of no. of cats reacting to no. of dog doses sold	Ratio of no. of cat deaths to no. of dog doses sold
2006	1:48,500	1:416,000
2007	1:65,000	1:269,000
2008	1:79,000	1:475,000
2009	1:75,500	1:216,500
2010	1:107,000	1:589,000
2011	1:119,000	1:302,000
2012	1:162,000	1:287,500
2013	1:135,000	1:473,500
2014	1:106,500	1:274,000

Table 5. Incidence of adverse events in cats involving permethrin spot-ons authorised for use in dogs

From this table it can be seen that there was a general decline in the incidence of reported reactions (but not necessarily deaths) until 2012, which has to some extent reversed in more recent years.

During 2014, the topic of permethrin reactions in cats received increased media attention due to a campaign involving several pet charities, which crossed over into online fora for pet owners, which may explain the increased level of reporting.

In response to this campaign we published online guidance[21] aimed at cat owners to explain the risks of using the wrong product and highlight the need for care when using any spot-on product on cats. Hopefully, increased owner knowledge will reduce the number of future permethrin poisoning incidents but this will remain hard to measure with passive surveillance.

With regards to spot-ons authorised for use in cats, overdose was also an issue. Four of the five cases relating to the use of spot-on pipettes that were too large for the weight of the cat, resulted in neurological, digestive tract or behavioural disorders. The fifth resulted in an application site lesion.

In the majority of remaining cases, when the warnings or contraindications were ignored, the product was applied to the animal on the back of the neck or between the shoulder blades, not at the base of the skull as indicated. This enabled the cat to ingest the product during grooming, with expected resultant clinical signs.

For anti-inflammatory drugs, most reports related to cases where an underlying condition made use of the product unwise, or where concurrent administration of another product was contrary to the instructions. There were also a number of cases where the product was

- used to treat a condition for which it is not indicated
- given at too high a dose or

[21] Permethrin: don't put your cat at risk, www.gov.uk/government/publications/permethrin-dont-put-your-cat-at-risk

- not intended for use in cats.

In these cases the most common signs observed were death, anorexia, renal insufficiency and lethargy.

For cases associated with anthelmintic overdose, the most commonly observed clinical signs were lethargy, muscle tremor, ataxia, anorexia and death. In two separate cases, a kitten died following the administration of a tablet intended for an adult cat.

For antimicrobials, the most commonly seen signs were death, ataxia, anorexia, dyspnoea, emesis, lethargy, renal insufficiency and convulsion.

Products for the treatment of hyperthyroidism were often used in multiple ways that were contrary to the instructions. Often, the reports received provided no evidence of pre-treatment blood analysis or monitoring during treatment, or overdosing occurred. In other cases, the treatment program was not respected, and in a couple of cases the owners crushed the tablets to ease administration, destroying the sustained release properties of the drug. The most common signs reported were blood disorders, weight loss, SLEE, abnormal test result and anorexia.

Authorised human products (including extemporaneous 'vet specials')

Table 6 summarises the 12 cases we received involving the use of authorised human medicinal products. These products were used under the cascade, as the active ingredients were either not authorised for use in animals in the UK at all, or not in the required pharmaceutical form at the time.

Human drug	Number of cases	Clinical signs included:
Midazolam	1	Thrombocytopenia, ataxia, mydriasis
Chlorphenamine (Piriton)	1	Anxiety, tachypnoea, haemorrhagic gastritis, anorexia, collapse, euthanasia
Tramadol	1	Hypersalivation
Chlorambucil	1	Lymphosarcoma, anaemia, leucocytosis, neutrophilia, erythema, alopecia, skin lesion, weight loss
Buprenorphine (sub-lingual tablet)	1	Euthanasia
Liquid paraffin (Lacrilube)	1	Corneal ulcer
Mirtazipine (appetite stimulant)	3	Vocalisation, urinary incontinence, faecal incontinence, convulsion, death
Amlodipine	3	Hepatopathy, emesis, anorexia, weight loss, renal insufficiency, hypertension, lymphopenia, sudden death

Table 6. Ingredients and clinical signs associated with AEs following the use of human medicines in cats

Prior to May 2015, there were no amlodipine products available for veterinary use in the UK, but since that date two products have been authorised.

Exempt veterinary medicines

There was one report involving a cat following the use of an exempt veterinary medicine. In this case, a cat was accidentally injected with an oral fenbendazole product, instead of an anaesthetic agent. The cat developed respiratory problems

and low blood pressure, and blood tests revealed neutropenia. The final outcome remains unknown, but the cat appeared to be recovering.

If you are contacted by the VMD or an MAH to provide further information, please do so. This helps us determine the final outcome which can aid the assessment of product involvement. This is especially important for serious cases.

Veterinary non-medicinal products

Nine AEs were reported after the use of unauthorised veterinary products. Seven of these cases related to spot-on flea and tick products, one concerned a shampoo and the other a collar.

The signs observed in association with the use of these flea and tick products included muscle tremor, hyperaesthesia, convulsions, mydriasis, ataxia, alopecia, rash, erythema, pruritus and self-trauma. The more serious signs are generally associated with the use of products containing permethrin or fipronil, so it is possible that the identity of the products involved in these cases has been misreported.

The use of the shampoo gave rise to hypersalivation, blindness and convulsions. The kitten involved was finally euthanased. This case was more serious than would be expected for one linked to the use of a non-medicinal product.

The use of the collar resulted in impaired vision, ataxia and paresis.

Other non-medicinal products

Two cases were reported that followed the implantation of a microchip. In both cases, the chip was implanted in a similar site to vaccinations. In one case, involving two kittens, the chip was implanted on the same occasion as the vaccinations, and resulted in the development of hard lumps within 48 hours. The final outcome of this case is unknown. In the other case, a fibrosarcoma was surgically removed, but the temporal information relating to implantation and vaccination were unknown. In neither case was it possible to determine specific product involvement with the resulting clinical signs.

Since April 2014, when the VMD formally took on responsibility for monitoring reports of adverse events following microchipping, a separate means of reporting these has been available. Due to the different way these reports are handled, if you submit a report for a microchip problem, such as migration or not working, via the report form intended for veterinary medicines, you will be asked to resubmit the report via the correct online form. For further details on this scheme please see this leaflet. A separate review will discuss the findings from the microchip adverse event reporting scheme.

Reports from studies

Two reports were received from clinical trials authorised through ATCs.

Horses and donkeys

We received 218 horse and two donkey adverse event reports during 2014.

The breed of horse was not identified in 40% of cases, with 9% being crossbred. Thoroughbred (14%), Welsh Cob (5%) and Shetland pony (4.5%) were the most commonly identified breeds. Other breeds included Dutch Warmblood, Arab, Irish Hunter, Welsh pony, Miniature pony and Irish Draught horse.

Adverse reactions following authorised use

During 2014, we received a total of 180 reports, describing adverse reactions in horses, in which there was no evidence that products were used other than according to the instructions.

Figure 18 shows the medicine groups most often reported.

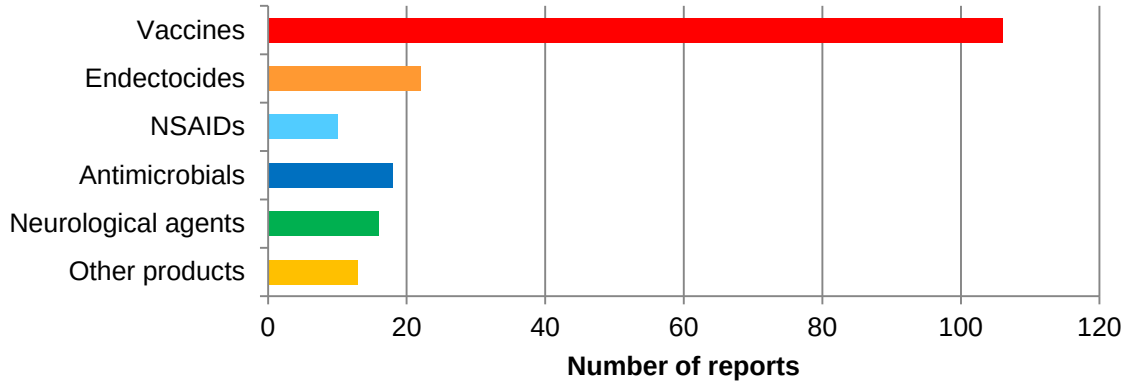


Figure 18. Therapeutic groups associated with SARs following authorised use of veterinary medicines in horses and donkeys

For vaccines the vast majority of clinical signs were directly associated with the site of injection. The most commonly described injection site signs were, in descending order, oedema, pain, stiffness, infection and inflammation.

Endectocides, administered as oral pastes, gels or tablets, were associated with application site oedema, hypersalivation, anorexia, mouth inflammation, lethargy, abdominal pain, ataxia and death.

Clinical signs reported following treatment with NSAIDs included tachycardia, tachypnoea, death, gastric perforation or ulcer, hyperthermia and urticaria.

For antimicrobials, anaphylaxis, tachycardia, death, tachypnoea and hyperhidrosis were most often reported. Oxytetracycline was involved on most occasions involving anaphylaxis and/or death, followed by sulfadiazine/trimethoprim and penicillin/streptomycin, with one case each associated with penicillin or gentamicin use.

Sedatives were most often associated with tachypnoea, loss of consciousness, muscle tremor, ataxia and convulsion; analgesics were associated with tachypnoea, and a spasmolytic product was associated with ataxia, death, anorexia and convulsion.

Other products included anthelmintics, corticosteroids, an immunosuppressant, an immunomodulator, hormones, vitamins and a treatment for lameness.

Lack of expected efficacy following authorised use

Thirteen reports of SLEE, after use according to the instructions, were received.

In one case, colic in a horse did not resolve as expected, but the horse had other medical conditions that may have made the administration of the spasmolytic product inappropriate.

Seven reports related to the use of one or more anthelmintics and ectoparasiticides. In addition to SLEE, other clinical signs observed in five of the reports involving use of an endectocide, were diarrhoea and weight loss, with death in three cases.

There were two cases involving a euthanasia product; in the first case, a horse exhibited hyperactivity as the product was administered, in spite of prior administration of a sedative. In the other, an extra dose of product was administered, as it was taking longer than expected for the heart and breathing to stop. This horse had also been previously sedated.

These cases illustrate the need to have an alternative means of euthanasia available, in case the first attempt is not successful. In horses, euthanasia complications are not only distressing for the owner but also pose a risk of injury to all persons present.

Other medicines that did not perform as expected were an NSAID administered to a horse when it developed abdominal pain shortly post vaccination, an ectoparasiticide cream and an injectable anaesthetic. In the latter example, several horses developed limb rigidity and remained standing during anaesthesia.

Off-label use of authorised veterinary medicines

Table 7 summarises the clinical signs observed in 21 cases following ‘off-label’ use of authorised veterinary medicines in horses and donkeys.

Therapeutic group	Type of unauthorised use	Number of cases(species)	Clinical signs observed
Vaccine	Wrong species	1 (donkey)	Injection site swelling
	Treatment program not respected	1 (horse)	Injection site abscess, swelling, lethargy
Internal parasites	Wrong species	1 (donkey)	Abdominal pain, muscle tremor
Pain killer	Administration route	1 (horse)	Sedation, seizures, euthanasia
Dopamine agonist	Treatment program not respected	4 (horse)	Anorexia, depression, seizures
	Contraindication	1 (horse)	Perinatal death
Euthanasia	Wrong product	1 (horse)	Sedation
Internal & external parasites	Wrong species	1 (horse)	Skin sores, inappetence
	Wrong species & concurrent use with another product	1 (horse)	Neurological signs
	Overdose	1 (horse)	Neurological signs
	Contraindication	1 (horse)	Abortion
Antimicrobial	Wrong species	2 (horse)	Oral oedema, intestinal torsion, euthanasia
Immunosuppressant	Wrong species	1 (horse)	Corneal ulcer
Immunomodulator	Wrong indication	1 (horse)	Oral haemorrhage, epistaxis, euthanasia
NSAID	Administration route	1 (horse)	Injection site swelling, abscess
Hormone	Administration route/site	1 (horse)	Implant site pain, swelling, lesion
Multivitamin	Administration route	1 (horse)	Death

Table 7. Therapeutic groups and clinical signs associated with AEs following off-label use of authorised veterinary medicines in horses and donkeys

Imported medicines

We received three reports of adverse reactions following the use of authorised products imported from elsewhere in Europe. In one case, a horse developed a golfball-sized nodule within 10 minutes of an allergen-specific immuno-therapy injection. The nodule had almost resolved after 2 days, but more severe pruritus developed.

In the second case, a 5-months pregnant broodmare developed intermittent epilepsy and ataxia two weeks post-vaccination with an inactivated equine rhinopneumonitis virus vaccine. The foal was delivered uneventfully, and it is thought the product was not connected with the signs observed. The mare continued to suffer intermittent seizures.

In the final case, a horse exhibited excessive sedation, recumbency, hyperthermia and hyperhidrosis after the use of an acepromazine product.

Authorised human medicines (including extemporaneous 'vet specials')

We received two reports describing the use of products authorised for human use. Both cases involved diazepam, which was used in conjunction with sedatives and anaesthetics. The first case, already described above in relation to SLEE after

concurrent use of an authorised product, involved multiple horses exhibiting unusual limb rigidity and standing up during anaesthesia. The second described ataxia, pacing, painful urination and excessive sweating following initial recovery from anaesthesia for castration. Improvement was gradual over the next 3 days.

Veterinary non-medicinal products

We received one report following intra-tendon administration of equine stem cells. Four days later the site of application was inflamed and infection was suspected.

In another report, a horse developed swellings which progressed to sores and infection at the sites of application of an oily non-medicinal product. The product, of unknown composition, claimed to ‘help itchy legs’.

Rabbits

We received a total of 148 reports involving pet rabbits during 2014. Sixty-seven of the reports described adverse reactions observed after use of products according to the instructions. Fifty-nine reports described instances of SLEE after correct use of a product. Twelve reports resulted from off-label use of authorised medicines. Finally, 10 reports were received involving the use of exempt veterinary medicines.

Adverse reactions following authorised use

In 64 of 67 reports, clinical signs were observed after the administration of a combination vaccine against myxomatosis and rabbit haemorrhagic disease (RHD). Many of the reported cases resulted in death, either sudden or unexpected, or by euthanasia. Often no PME was carried out. Other signs observed were head-tilt, periorbital oedema, skin lesions and lumps, anorexia and weight loss. Signs of myxomatosis were seen, but these developed before immunity could have been expected, indicating exposure to the disease before or shortly after vaccination.

In the remaining 3 reports, the vaccine was administered in conjunction with an ectoparasiticide (2) or an ectoparasiticide was administered in conjunction with an antimicrobial.

Lack of expected efficacy following authorised use

In all 59 cases, SLEE was reported after authorised use of a vaccine against myxomatosis and RHD. Fifty of these cases related to myxomatosis, eight to RHD and one to both diseases.

Off-label use of authorised veterinary medicines

Table 8 summarises the clinical signs associated with 12 cases of off-label use.

Therapeutic group	Type of unauthorised use	Number of cases	Clinical signs observed
Sedative reversal	Wrong species	2	SLEE, death
NSAID	Wrong species	3	SLEE, anorexia, limpness, convulsion, death(2)
Vaccine	Wrong species	1	Malaise, death
	Treatment program not respected	1	Found dead
Ectoparasiticide	Wrong species	1	Convulsion, anorexia, constipation, death
	Underdose	1	Head tilt, somnolence, nystagmus, hypothermia, death
Antimicrobial	Wrong species	2	Diarrhoea, death (2)

Table 8. Therapeutic groups and clinical signs associated with AEs following off-label use of authorised veterinary medicines in rabbits

The vast majority of reports were classified as off-label use due to the product not being authorised for use in rabbits, which is not surprising given the relatively small number of authorised products for this species. However, two rabbits were vaccinated in error using a dog vaccine against *Leptospira spp.* One of the rabbits was found dead 3 days later; no PME was performed.

Exempt veterinary medicines

We received 10 reports relating to six different exempt veterinary medicines. These

products each contained one of the following active ingredients: fenbendazole, ivermectin, permethrin.

Table 9 summarises the clinical signs associated with these cases.

Ingredient	Number of cases	Clinical signs observed
Permethrin	7	Dyspnoea, death(2), pruritus, irritation, skin scaling, skin reddening (3), trembling (2), scratching, hyperactivity (2), alopecia (2), inflammation (2), pruritus, anorexia (2), lethargy, intestinal stasis, vocalisation, circulatory shock
Ivermectin	1	Anorexia, lethargy, ileus
Fenbendazole	2	Head tilt, dyspnoea, nasal discharge, sneezing, anorexia(2), lethargy (2), diarrhoea, electrolyte disorder, renal insufficiency, death

Table 9. Ingredients and clinical signs associated with AEs following the use of exempt veterinary medicines in rabbits

Other 'pet' animals

During 2014, 29 reports were received involving other species, which are considered to be pets. Most are small and furry in nature, but caged birds are also included in this group. Exotic species are also included in this group, if they are kept in domestic circumstances i.e. not agricultural or zoological. For 2014 these were an African pygmy hedgehog, a micro pig and a Vietnamese pot-bellied pig.

Adverse reactions following authorised use

Four reports of adverse reactions following the correct use of authorised medicines were received.

A 3-week-old 'micro' pig was treated for mites with an injectable ivermectin product. It developed neurological signs and died 5 days later.

An 8-week-old Vietnamese pot-bellied pig was vaccinated against Erysipelas and parvovirus. The pig vomited, became tachypnoeic, depressed and was shaking within 20 minutes, but recovered the same day without treatment.

Two ferret owners reported the deaths of their animals after the administration of proligestone. In one case, the ferret died suddenly 2 weeks post-administration. In the other, two ferrets developed lethargy, had blood in faeces and were not eating and drinking. One died within a week of the administration of a second dose. In neither case were further diagnostic investigations undertaken or a PME performed.

Off-label use of authorised veterinary medicines

We received 13 reports of unauthorised use of authorised veterinary medicines. For most cases the reason for off-label use was use in an unauthorised species. Table 10 summarises the cases reported.

Therapeutic group	Type of unauthorised use	Number of cases(species)	Clinical signs observed
Hormone suppressant	Use in females	1 (ferret)	Death
NSAIDs	Wrong species	1 (parrotlet)	Emesis, diarrhoea, ataxia, death
	Wrong species	1 (Syrian hamster)	Death
Antimicrobial and hormone stimulant	Wrong species	1 (parrot)	Dyspnoea, death
Vaccine	Wrong species	1 (ferret)	Lethargy, diarrhoea, erythema, ocular discharge
Vaccine	Wrong species	1 (ferret)	Lethargy, pyrexia, pale mucous membranes, renal insufficiency
Antimicrobial	Wrong species	1 (ferret)	Pruritus, self-trauma
	Wrong species	1 (guinea pig)	Depression, inappetence, death
	Wrong species	1 (Syrian hamster)	Death
Anaesthetic	Wrong species	1 (rat)	Disorientation, dyspnoea, death
	Wrong species	1 (chinchilla)	Death
Antimicrobial and ectoparasiticide	Wrong species	1 (African pygmy hedgehog)	Death

Table 10. Therapeutic groups and clinical signs associated with AEs following off-label use of authorised veterinary medicines in various exotic species

Exempt veterinary medicines

We received 12 reports of adverse reactions following the use of exempt veterinary medicines. One report involved a ferret, six reports involved guinea pigs, one report each for a rat, a hamster and a degu; the remaining two reports involved small cage birds.

Table 11 summarises the clinical signs associated with these cases.

Ingredient	Number of cases(species)	Clinical signs observed
Ivermectin	1 (ferret)	Convulsions, dilated pupils, low temperature, hypersensitivity to external stimuli, death
	2 (caged birds)	Skin burn, death (2)
	4 (guinea pigs)	Death (3), hypersensitivity reaction, pruritus, distress, lethargy, anorexia
Permethrin	2 (guinea pigs)	Hyperactivity, distress
	1 (rat)	Convulsion, twitching
	1 (hamster)	Death
(S)-methoprene	1 (degu)	Convulsion, death

Table 11. Ingredients and clinical signs associated with AEs following the use of exempt veterinary medicines in various exotic species

Food animals

A grand total of 874 reports were received that described adverse events occurring in production animals. Table 12 shows the number of reports received for each species group, broken down by the type of use.

Species	Total number	Authorised use	Other use	Imported products	Clinical trials
Cattle	399	362	36	1	1
Sheep	379	251	71	-	57
Pig	35	22	12	-	1
Poultry	21	19	2	-	-
Fish	25	5	3	13	4
Others	13	1	12	-	-
	872	660	136	14	63

Table 12. Numbers of AE reports in production animals, by species and type of product use

Using figures obtained from Defra's Farming Statistics[22], Livestock Populations at 1 December 2014, United Kingdom, for cattle the number of adverse event reports received represents a rate of one report per 24,250 animals. For sheep, they represent a rate of one report per 60,250 animals, and for pigs they represent a rate of one report per 128,600 animals.

[22] Farming statistics – livestock populations at 1 December 2014 – UK, www.gov.uk/government/statistics/farming-statistics-livestock-populations-at-1-december-2014-uk

Cattle

We received a total of 399 AE reports associated with cattle. Figure 19 shows the proportion of different types of adverse event reported that resulted from authorised and unauthorised use of veterinary medicines.

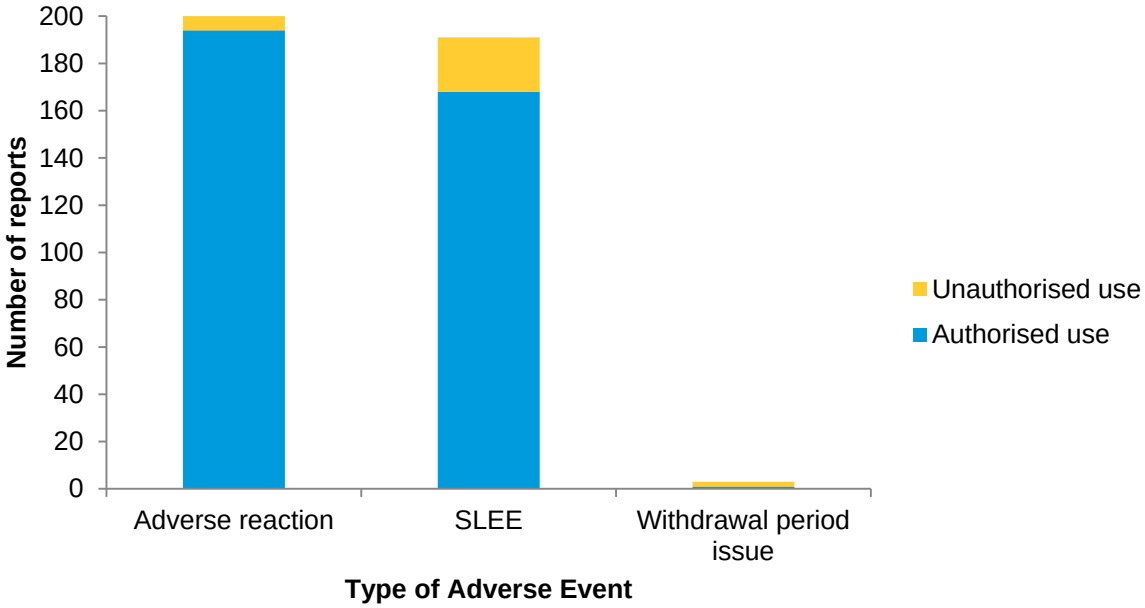


Figure 19. Type of AE report received following authorised and unauthorised use in cattle

A further two reports related to the use of an unauthorised product bought at a local market in Wales, and a final report of a product authorised south of the Irish border, but used in Northern Ireland. There was one report arising from a clinical trial.

Adverse reactions following authorised use

We received a total of 200 reports describing adverse events, excluding SLEE, that occurred after authorised use of one or more authorised veterinary medicines. A total of 279 products were involved in these cases. Over 65% of the products mentioned were vaccines.

Figure 20 shows the specific therapeutic groups included in these reports.

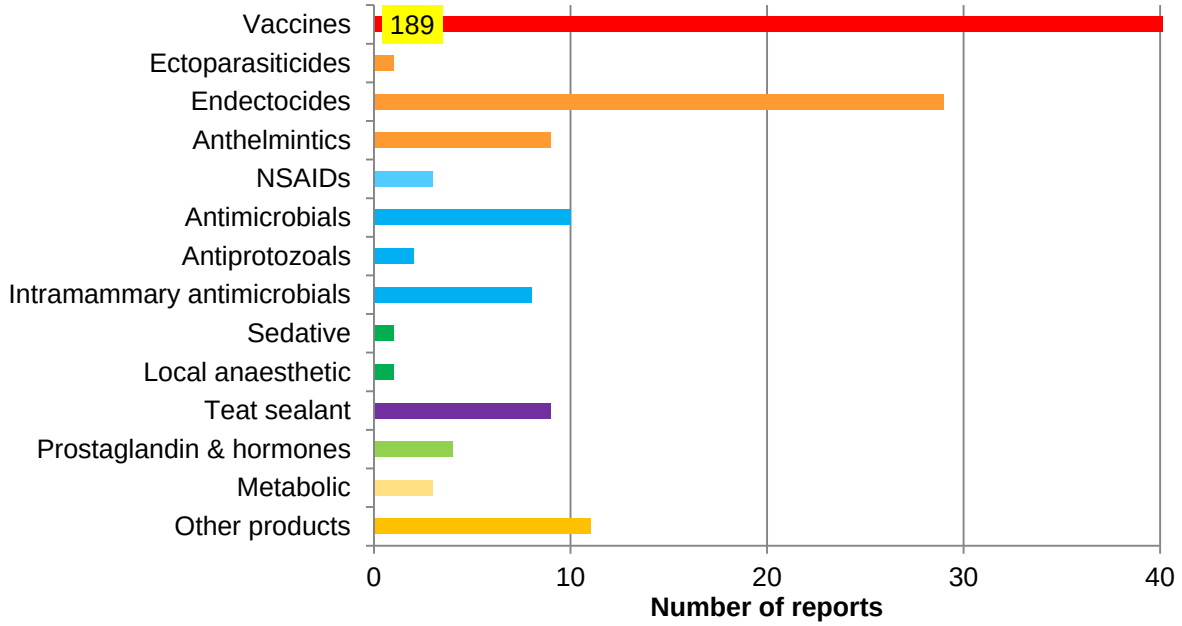


Figure 20. Therapeutic groups associated with SARs following authorised use of veterinary medicines in cattle

Vaccines

The number of cases linked to the use of the vaccine Pregsure BVD has continued to fall, with 93 reports in 2014. Figure 21 shows the number of reports we have received each year since 2006, and the dramatic increase from 2009 onwards, when the link to bovine neonatal pancytopenia was recognised, and the subsequent decline. The product was removed from the market in 2011.

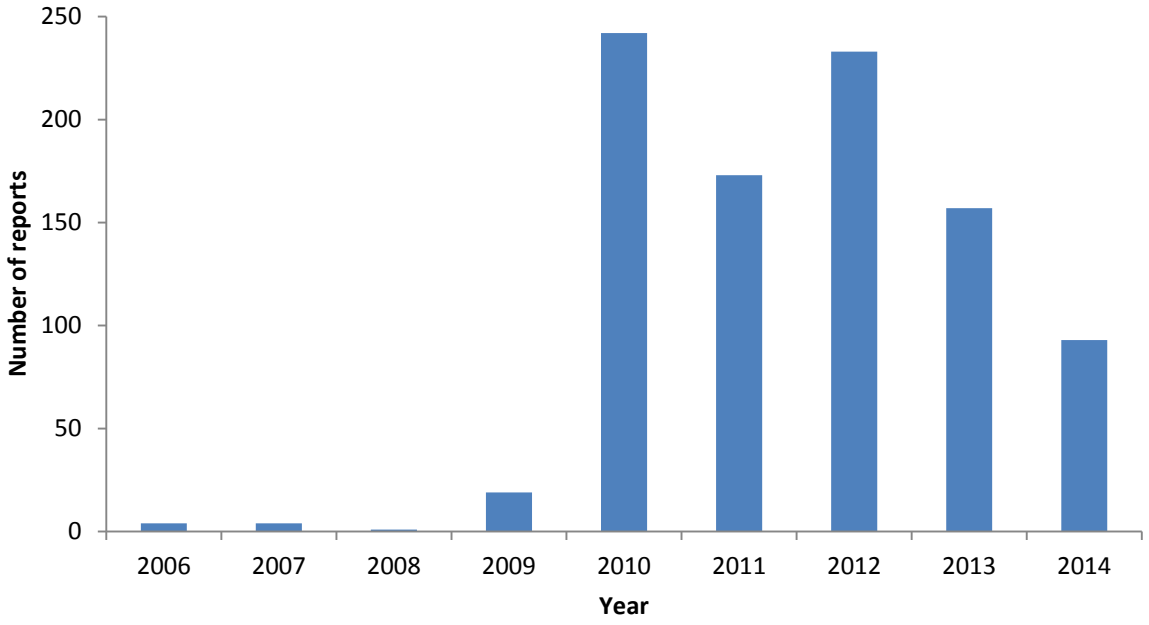


Figure 21. Number of Pregsure BVD AE reports received per year since product authorisation in 2005

Other vaccines accounted for another 34% of the products mentioned in reports. The majority of these were other Bovine Viral Diarrhoea vaccines. The remaining vaccines were for protection against respiratory diseases, mainly Infectious Bovine

Rhinotracheitis. Clinical signs most commonly observed (after haemorrhage linked to Pregsure BVD use was removed) were death, hyperthermia, pneumonia and lethargy.

Endectocides

The use of endectocides most commonly resulted in death, ataxia or blindness. The product involved in approximately one third of cases showing these signs is an endectocide/flukicide combination pour-on, containing closantel and ivermectin, which has recently been under close scrutiny within Europe due to a significant number of serious cases in France. A comprehensive review[23] of all the available information concluded that the benefits of the product outweighed the risks but that particular care should be taken if treating animals in poor condition. Other products associated with these signs were injections of moxidectin and doramectin.

Anthelmintics

Use of anthelmintics, including products that also protect against liver fluke, most commonly resulted in death, cough, photosensitivity and eye redness.

Other veterinary medicines

For NSAIDs, antimicrobials (including those for intramammary use), antiprotozoals, neurological agents, teat seals, reproductive hormone products and medicines for the treatment of metabolic disorders, the number of reports was too few to observe any patterns of clinical signs.

However, one report related to the detection of antimicrobial residues in milk, 10 weeks post administration of a dry cow treatment. Investigations revealed that the residue levels detected were too high to have been due to the suspect product, and were more likely to have been due to milk from another cow that was undergoing antimicrobial treatment at the time of milking.

Other products included in reports were an autogenous vaccine, a sodium hydroxide compound for removing horn buds from young calves, an immunomodulator and 11 other unidentified products.

Lack of expected efficacy following authorised use

We received a total of 168 reports of SLEE following authorised use of between one and three veterinary medicines at the same time. Only 16% of these cases related solely to pharmaceutical (non-vaccine) products. The most commonly reported pharmaceutical products associated with lack of efficacy were anthelmintic flukicides, followed by products for the treatment of protozoal infections and intramammary antimicrobials.

Figure 22 shows the therapeutic groups reported in SLEE reports.

[23] Committee for Medicinal Products for Veterinary Use (CVMP) Meeting of 6-8 October 2015. Community referrals and related procedures. Closamectin Pour-On Solution and associated names, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002412.jsp&mid=WC0b01ac058004d5c1

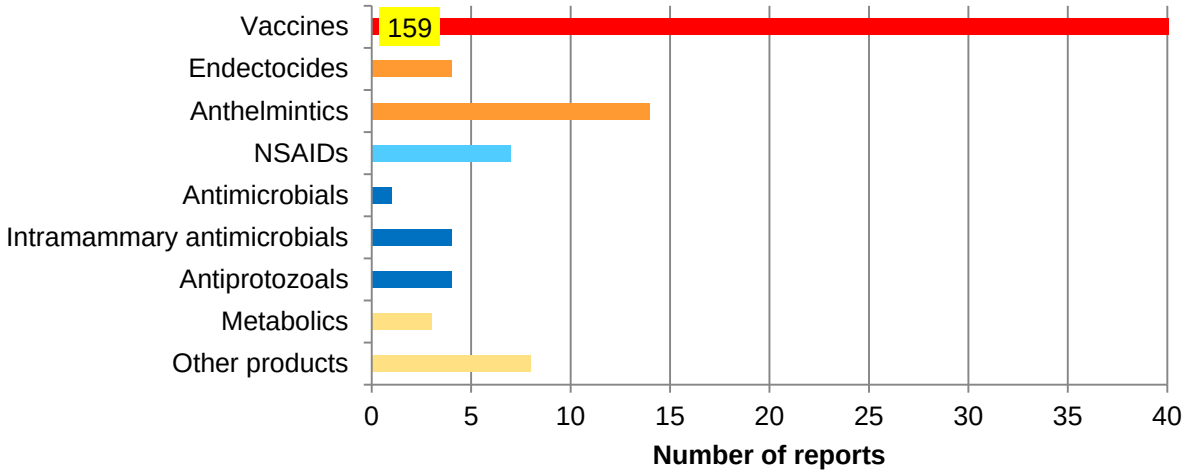


Figure 22. Therapeutic groups associated with SLEE after authorised use of veterinary medicines in cattle

For all vaccines, after SLEE, the most commonly reported clinical signs were death, pneumonia, abnormal test result, abortion, respiratory tract disorder, hyperthermia, rhinitis, diarrhoea, dyspnoea and other immune system disorders.

For pharmaceutical products, the number of reports was too few to determine a pattern of other clinical signs.

Off-label use of authorised veterinary medicines

We received a total of 36 reports that described events resulting from off-label use of authorised veterinary medicines.

Almost all of the 21 reports of SLEE after off-label use of one or more products occurred when the treatment program of a product was not followed as recommended. Most involved vaccines. Table 13 summarises these cases.

Therapeutic group	Type of unauthorised use	Number of cases	Clinical signs observed
Vaccines	Treatment program not respected	17	Death, abnormal test result, abortion, persistent infection, melaena, scour, dyspnoea, appetite loss, pneumonia, tracheitis,
Endectocide	Treatment program not respected	1	Death
Flukicide	Treatment program not respected	1	Diarrhoea, milk drop, weight loss
Antiprotozoal	Expiry date exceeded	1	Haemolytic anaemia
Mineral	Treatment program not respected	1	Death

Table 13. Clinical signs observed with SLEE, following off-label use of authorised veterinary medicines in cattle

Two reports of off-label use were received that led to the detection of product residues. In one case, antimicrobial residues were found in milk over 4 days after product withdrawal. Investigations revealed that a cow had been treated with another antimicrobial product up until the day before treatment was started with the second product which affected the elimination phase of the active substance. The milk finally

passed residue testing on the 7th day.

In the second case, phenylbutazone residues were found in a cow carcass, an unknown time after the product was administered to horses on the same farm. It is not known how the product came to be in the carcass.

This case highlights the need to ensure that products containing phenylbutazone are not used in food-producing animals, and are not accessible so that they might be accidentally ingested by an animal intended to enter the food chain.

More than half of the remaining 11 reports resulting from off-label use involved antimicrobial products. Other products included products for the treatment of internal and/or external parasites and local anaesthetics. Many cases involved dosage errors, but other problems were concurrent use with other products, unauthorised species and incorrect route of administration.

Do not either mix different drenches before administration or administer them at the same time. This avoids ingredients interacting and becoming ineffective, and helps ensure the appropriate dose of each drench is administered. Follow the instructions carefully. Incorrect dosing of wormers can lead to the build-up of resistance.

Imported medicines

One report involved a product that was bought by a farmer in Ireland and used in Northern Ireland. Information regarding this case was limited, but there were indications that the clinical signs observed following dosing, were possibly due to closantel toxicity.

Veterinary non-medicinal products

Two reports were received from Wales that involved the use of the same product. In the first case, a dairy cow developed acute respiratory signs and died shortly after drenching. Aspiration pneumonia was confirmed at PME. In the second case, the product was mixed with a second product, also not authorised, and an authorised fluke drench in the same drench gun. Two out of three cows treated developed acute respiratory signs and died within minutes of administration. PME revealed interstitial emphysema.

These cases illustrate the dangers of using products obtained from unauthorised sources. These products may have no medicinal value and will not have been officially assessed for their quality, safety or efficacy. Also, if buying medicines online we recommend that you look for a website that we have approved through the Accredited Internet Retailer Scheme.

Reports from studies

There was one report from a clinical trial authorised through an ATC.

Sheep

We received 379 AE reports associated with sheep during 2014. In total, 251 of these related to authorised use, of which 63 described adverse reactions and 188 described SLEE. Off-label use accounted for 70 of the remaining 128 reports, with the final 57 reports originating from clinical trials.

Adverse reactions following authorised use

We received 63 reports of adverse reactions following use of products according to the instructions. The largest group of reports resulted from the use of vaccines; mainly those used for combined immunisation against clostridial, Mannheimia and pneumonic pasteurellosis infections, but also another used to help prevent footrot.

Figure 23 shows the therapeutic groups involved in these reports.

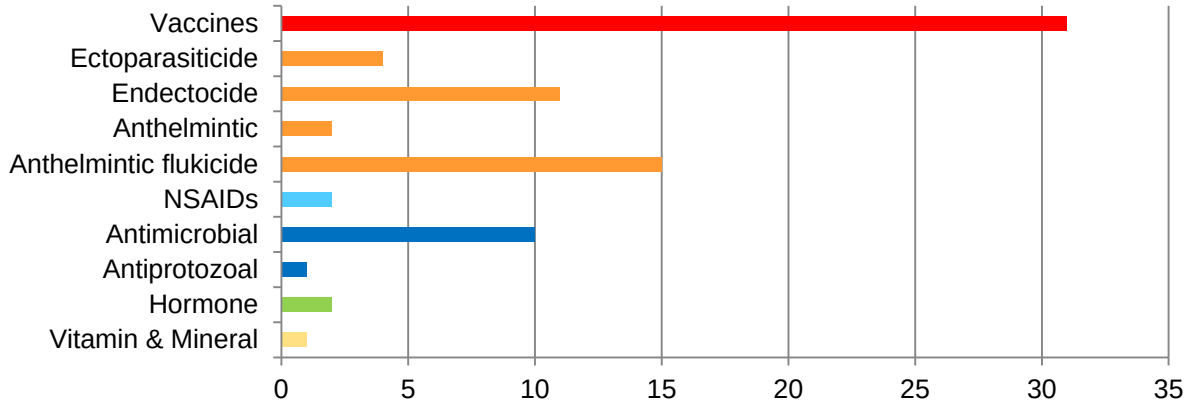


Figure 23. Therapeutic groups associated with SARs following authorised use of veterinary medicines in sheep

Vaccines

Death was the most commonly reported clinical sign following the use of vaccines, mainly those used for combined immunisation against clostridial, Mannheimia and pneumonic pasteurellosis infections, but also another used to help prevent footrot. The next most common signs were lethargy, abnormal test result, abortion, recumbency and ataxia.

Endectocides

Death occurred in nine cases associated with endectocide use. Also reported were stomach disorder, recumbency, eye disorder, blindness and convulsion.

Anthelmintic flukicides

Death was also reported on nine occasions after use of combined anthelmintic and flukicide products. Other signs reported were lethargy, allergic oedema, recumbency, diarrhoea and blindness.

Antimicrobials

Clinical signs associated with antimicrobial use were death, injection site haemorrhage, loss of consciousness, recumbency, pulmonary oedema, ataxia and dyspnoea.

Lack of expected efficacy following authorised use

We received 188 reports of SLEE following the use of products according to the instructions. The largest group of reports (62) resulted from the use of vaccines used

for combined immunisation against various clostridial diseases, Mannheimia and pneumonic pasteurellosis (C + M + P) infections. Figure 24 shows the number of reports associated with SLEE linked with vaccines intended to protect against different diseases.

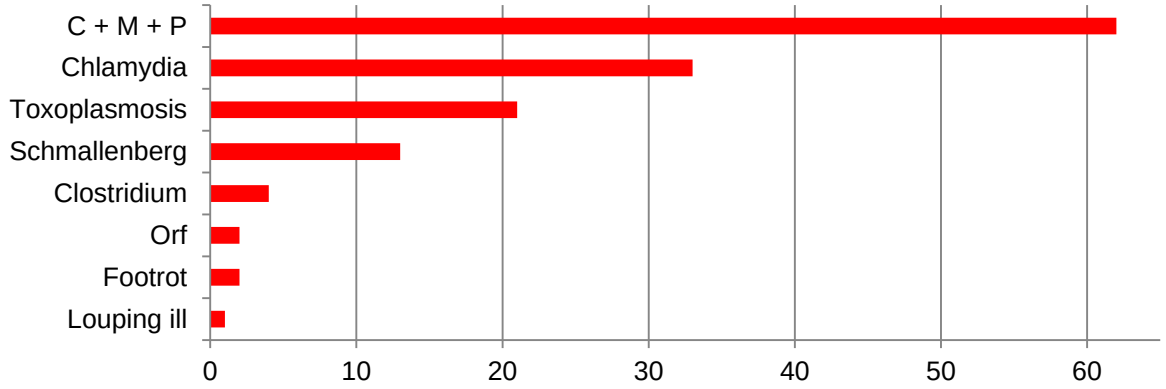


Figure 24. Vaccine types associated with SLEE following authorised use of veterinary medicines in sheep

Of the 62 SLEEs to C + M + P vaccines, target organisms were recovered in 23 of the cases. The majority of these were respiratory pathogens; clostridial organisms were only isolated in seven cases.

Ectoparasiticide pour-on products were the next most commonly reported group of products, followed by combination anthelmintic flukicides, anthelmintics, endectocides and anti-protozoals.

Off-label use of authorised veterinary medicines

We received 68 reports of off-label use of authorised veterinary medicines. Of these, 44 resulted in a lack of efficacy, as detailed in Table 14.

Therapeutic group	Type of unauthorised use	Number of cases	Clinical signs observed
Ectoparasiticide	Treatment program not respected	24	Death (23), loss of condition (1)
	Overdose	6	Death (5), localised hair loss (1)
	Underdose	5	Death (5)
	Under/overdose	1	Death
	Wrong equipment	1	Dermatosis, death
	Inadequate training	1	Death
Vaccine	Treatment program not respected	3	Birth defect (1), stillbirth (1), death (3)
Mineral	Maladministration	1	Death, oesophageal injury
Endectocide	Overdose	1	No other signs
Combination anthelmintic flukicide	Overdose	1	Death

Table 14. Clinical signs observed with SLEE following off-label use of authorised veterinary medicines in sheep

The vast majority of off-label SLEEs were associated with parasite treatments, often due to dosing equipment issues. In one case both under- and overdose were likely to

have occurred, as the dosing gun was not calibrated, and the sheep varied in size. In another, the wrong dosing gun was used, possibly leading to incorrect dosing.

Dosing guns are usually product-specific, as the viscosity of products can vary, so one product's gun may not work correctly for another. In yet another case, the product warnings and contraindications were ignored; the lambs treated were not clean prior to product use, the person applying the product had not been trained in the correct use of the product, the weights of the lambs were estimated and the gun used was not calibrated.

These cases emphasise the need for correctly calibrated dosing equipment and the need for adequate training of persons administering these products.

The 24 cases of SARs associated with unauthorised are summarised in Table 15.

Therapeutic group	Type of unauthorised use	Number of cases	Clinical signs observed
Vaccine	Treatment program not respected	4	Abortion, anorexia, lethargy, death (3), moribund, injection site lesion
	Wrong route/site	2	Stiffness, injection site abscess, death(2)
	Out-of-date product	1	Blindness (concurrent endectocide)
	Wrong species	1	Abortion, off-colour, lethargy
Antimicrobial (intramammary)	Wrong species	1	Drop in milk production, death of lambs
Antimicrobial	Wrong species	2	Dyspnoea, neurological signs, ataxia, convulsion, death (2)
	Treatment program not respected	1	Death
	Wrong indication	1	Dyspnoea, collapse, recumbency, death
Endectocide	Wrong route (intramuscular)	2	Injection site pain, ataxia, abortion, death (2), still birth, recumbency
	Wrong route (intravascular)	1	Hypersalivation, collapse, seizure, death
	Overdose, animal too young	1	Hypersalivation, collapse, death
	Close temporal use of a vaccine	2	Anaphylactic-type reaction, malaise, death (2)
Anthelmintic/flukicide	Wrong species	1	Lethargy, pneumonia, death
	Overdose	4	Blindness (2), neurological signs (2), death (4), circling, muscle tremor, convulsion, shaking
	Underdose	1	Ataxia, recumbency, death

Table 15**. Clinical signs observed in SARs following off-label use of authorised veterinary medicines in sheep**

Reports from studies

There were 57 reports from clinical trials authorised through ATCs.

Pigs

We received 35 reports of adverse events that occurred in commercial pig herds during 2014. In total, 23 of these related to authorised use, of which 10 described adverse reactions and 13 described SLEE. Off-label use accounted for a further 11 reports, with the one remaining report arising from a clinical trial.

Adverse reactions following authorised use

Nine of the 10 reports described events following the use of vaccines; the other followed the use of an iron deficiency treatment. Table 16 summarises the details of the cases related to vaccine use. Some cases involved more than one vaccine.

Vaccine type(s)	Number of cases	Clinical signs observed
Porcine circovirus (PCV)	3	Lethargy, collapse, impaired consciousness, muscle tremor, emesis, vocalisation, death
PCV Mycoplasma	1	Anorexia, ataxia, recumbency, death
Mycoplasma	1	Hyperthermia, convulsion
Erysipelas Erysipelas + porcine parvovirus	2	Anaphylaxis, convulsion, eye redness, anorexia, lethargy, hypothermia, hyperthermia, cyanosis, lameness, joint pain, loss of consciousness
Erysipelas + porcine parvovirus	1	Lethargy, ataxia, recumbency
Mycoplasma + Haemophilus parasuis	1	Death

Table 16. Summary of SARs following use of authorised medicines in pigs

Clinical signs observed after treatment for iron deficiency were collapse and death.

Lack of expected efficacy following authorised use

Thirteen cases of lack of efficacy were reported, eight of which involved vaccines.

Table 17 summarises the details of all 13 cases.

Therapeutic group Vaccine type (s)	Number of cases	Other clinical signs observed
Vaccine PCV Mycoplasma	1	Death
PCV	2	Oedema, lymphadenitis, abnormal test result, respiratory tract disorder, digestive tract disorder, death
Actinobacillus	2	Death (2), respiratory tract disorder
E coli Clostridium	1	Diarrhoea, death
Erysipelas + porcine parvovirus	1	Foetal mummification, abortion, abnormal test result
Porcine respiratory and reproductive syndrome (PRRS)	1	Return to oestrus, abnormal test result
Injectable anaesthetic (ketamine)	2	Hyperthermia, convulsion, sedation
Antimicrobial (tiamulin)	1	Death
Mineral (iron)	2	None

Table 17. Summary of SLEEs after authorised use in pigs

Off-label use of authorised veterinary medicines

There were 11 reported instances of off-label use, 6 of which resulted in SLEE.

Table 18 summarises the details of all cases that were associated with the use of pharmaceutical products.

Therapeutic group	Type of unauthorised use	Number of cases	Clinical signs observed
Anthelmintic	Underdose	1	Paralysis, thrombosis, septicaemia, coagulation abnormality, death
Sedative	Overdose	1	Pericardial haemorrhage, hypoxia, pulmonary congestion, abnormal test result
Antimicrobial	Underdose	1	SLEE, death

Table 18. Summary of SLEE cases after 'off-label' use associated with pharmaceutical products in pigs

Table 19 summarises the details of the cases associated with vaccine use.

Therapeutic group Vaccine type(s)	Type of unauthorised use	Number of cases	Clinical signs observed
Vaccine PCV	Treatment program not respected	2	Death (2)
PCV Mycoplasma	Concurrent use Frequency too high	1	Lethargy, ataxia, recumbency, impaired consciousness, death
PCV Mycoplasma	Concurrent use Dose	2	SLEE (2), lethargy (2), death (2)
PCV Mycoplasma PRRS	Concurrent use, dose Concurrent use, dose	1	Lethargy, malaise, pale mucous membrane, anorexia, SLEE, lymphadenopathy, death
Haemophilus parasuis	Treatment program not respected	1	SLEE, death
PRRS	Unknown	1	SLEE, hyperthermia, abortion

Table 19. Summary of vaccine SLEE cases after 'off-label' use of vaccines in pigs

Reports from studies

One report was received from a clinical trial authorised through an ATC.

Poultry and other avian species used in food production

Twenty-one reports involving avian species used in food production were received during 2014. Of these, 16 related to chickens, two to partridges, two to pheasants and one to geese. Three of 19 cases that occurred after correct use of products, resulted in adverse reactions, whilst the remaining 16 resulted in SLEE. There were two reports of off-label use.

Adverse reactions following authorised use

The two cases of adverse events in chickens followed the use of a vaccine against avian reovirus and a *Mycoplasma gallisepticum* vaccine.

In another case, a flock of geese developed injection site swellings and ulceration 6 months after vaccination with an autogenous vaccine.

Lack of expected efficacy following authorised use

Lack of efficacy following authorised use occurred in chickens in 10 cases relating to live parasitic vaccines, one relating to an antimicrobial product, one to a *Mycoplasma gallisepticum* vaccine and one to an avian reovirus vaccine.

In partridges, one case of lack of efficacy followed use of an anti-coccidial. Two others followed use of an anti-coccidial and an anthelmintic in pheasants.

Off-label use of authorised veterinary medicines

One report of off-label use involved an anti-coccidial, authorised for use in chickens, being used to treat red-legged partridges. This resulted in a lack of efficacy and death. In the other report, an antibiotic for use in drinking water was provided at too low a concentration resulting again in a lack of efficacy and death of chickens.

Fish

We received 25 reports of adverse events in food producing fish species during 2014. Of these, 23 related to Atlantic salmon and the remaining two to trout.

Adverse reactions following authorised use

Three reports were received following authorised use of a furunculosis vaccine. Each case resulted in internal melanisation, and in one case, internal adhesions.

Lack of expected efficacy following authorised use

Three reports were received describing a lack of expected efficacy following authorised use of vaccines for protection against furunculosis, pancreas disease and enteric redmouth disease. One report followed the treatment of Rainbow trout, and the others Atlantic salmon.

Off-label use of authorised veterinary medicines

Two of three cases that were received resulted in a greater than expected incidence of parietal melanisation and/or adhesions after vaccination. These were probably due to poor injection technique. The third case also involved vaccination, but the problem was not due to the vaccine itself, but to the length of anaesthesia prior to vaccination.

Imported medicines

13 reports resulted from the use of products, all vaccines, imported under SICs. 11 of these related to combined vaccines for furunculosis, infectious pancreatic necrosis virus, *moritella* (winter ulcers) and vibriosis (F + IPNV + M + V) in Atlantic salmon and two to a combined vaccine for furunculosis and vibriosis (F + V) in trout.

Table 20 summarises the details of these cases, including products concurrently.

Vaccine type ***[+ concurrent product(s)]***	**Species treated**	**Number of cases**	**Clinical signs observed**
F + IPNV + M + V	Atlantic salmon	6	SLEE (1 A + 3 IPNV), malaise, internal adhesions, melanisation, increased mortality, death (6)
[+ antimycotic]	Atlantic salmon	2	Anorexia(2), pale mucous membrane, hepatopathy (2), renal disorder, cardiac disorder (2), respiratory disorder(2), death (2)
[+ antimycotic, SPDV vaccine]	Atlantic salmon	2	Anorexia (2), hepatopathy, renal disorder, cardiac disorder, respiratory disorder, death(2)
[+ antimycotic, ectoparasiticide, SPDV vaccine]	Atlantic salmon	1	Internal adhesions, melanisation, anorexia, cardiac disorder, increased mortality, death
F + V	Trout	1	Injection site granuloma, moribund, bloated, death
[+ antimycotic]	Trout	1	Internal adhesions, melanisation, granuloma, inflammation, death

Table 20**. Summary of cases after use of imported vaccines in fish**
(SPDV – salmon pancreas disease virus)

Reports from studies

Four reports were received from clinical trials authorised through ATCs. All involved Atlantic salmon.

Other animals

The remaining species involved in 13 adverse event reports may or may not be bred for food production. Honey bees appear in three reports, goats, usually kept for milk, appear in four reports, whilst llamas (one report) and alpacas (five reports) are reared for their fleeces.

Llamas

An emaciated llama, with an existing worm burden, was treated with a fluke and worm drench, followed by a spot-on insecticide. It was found dead within a couple of days of treatment with evidence of scouring.

Alpacas

Nine of a group of 21 alpacas developed anaphylactic-type reactions after testing for bovine TB. All recovered.

Injection site abscesses were noted in four of 50 animals, 6 weeks after treatment with an imported vitamin and mineral supplement.

A group of alpacas was treated, on seven occasions between September 2011 and March 2014, with a triclabendazole oral solution to control liver fluke. Two alpacas died an unknown time after the last administration, and PME revealed chronic liver disease. The attending vet suspected that the dose was too low and too infrequent for successful control.

An alpaca was treated for mites with a fipronil spray, and a macrolide antibiotic for an unknown reason. The animal became lethargic and off-colour within 8 hours. The outcome is unknown.

A 10-day-old animal was anaesthetised for a leg fracture repair. Respiratory arrest occurred after the inadvertent migration of an intrathecal morphine administration. However, the animal recovered with appropriate symptomatic support.

Goats

Dams vaccinated against Schmallenberg virus (SBV) gave birth to kids with blindness, convulsions and brain damage. This vaccine is not licensed for use in goats, so efficacy cannot be claimed. Nevertheless, SBV was not detected in any of the samples taken from the affected kids.

Six goats died an unknown time after *Clostridium* vaccination. The vaccine is not licensed for use in goats, and no PME or other investigations were carried out to determine the involvement of any disease.

In two cases, herds of goats vaccinated against toxoplasmosis aborted, and had high toxoplasmosis titre blood tests. Investigations were inconclusive; the vaccine is not licensed for use in goats and may have exceeded its shelf-life at the time of use.

Bees

All three cases involved treatment of Varroa mite with a formic acid beehive strip.

In two cases, the instructions were not followed correctly; in one case the hive openings were restricted during treatment, in the other, the paper wrap was removed from the strips. In the first case, queens were lost from four hives. In the second, uncapped brood was destroyed, and many bees had deformed wings.

In the final case, two complete hives were lost within days of treatment, but Varroa infestation was high prior to treatment, and the colonies may have been too weak to recover.

Exotic animals

We received 36 reports of adverse events involving wildlife, laboratory and other exotic species, including aquarium fish and pigeons or doves, during 2014.

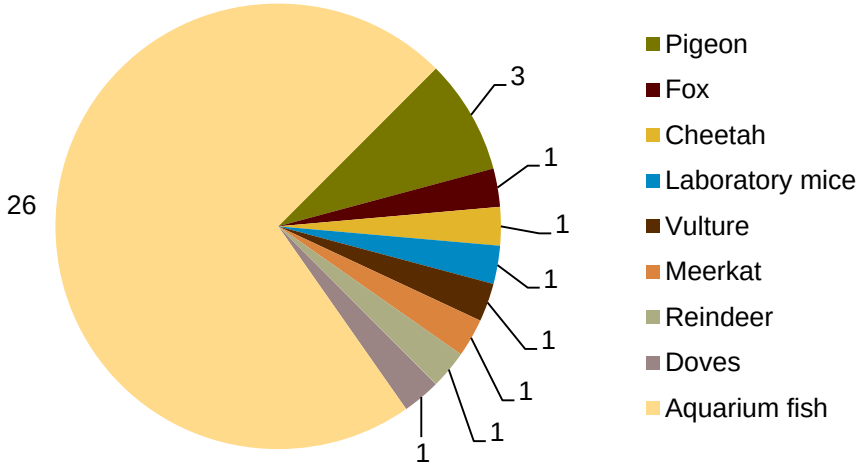


Figure 25. Number of reports involving wildlife and exotic species

Only three of the reports received involved the authorised use of veterinary medicines. 27 reports involved exempt veterinary medicines, and six involved the 'off-label' use of authorised veterinary medicines.

Adverse reactions following authorised use

We received three separate reports of adverse reactions in pigeons following vaccination against paramyxovirus.

One of a group of pigeons suffered an episode of ataxia and disorientation shortly after vaccination.

Twenty-two of 62 pigeons died within 4 days of vaccination. PME revealed pneumonia and blood poisoning due to *E.coli*.

A pigeon owner killed 14 of 37 birds 2 weeks post-vaccination, when the birds developed diarrhoea, anorexia and excessive drinking, and did not improve. The cause of the signs was not investigated.

Off-label use of authorised veterinary medicines

A pregnant fox was treated with meloxicam both by injection and oral routes for a broken foot. Meloxicam is contraindicated in other species during pregnancy. Two weeks later, the fox produced two dead and two live cubs. Seven weeks later, both cubs were unwell and one cub was euthanased due to jaundice and anaemia. The remaining cub is now doing well.

A cheetah was treated with oral meloxicam, tramadol, amoxicillin/clavulanic acid and clindamycin, prior to surgery under general anaesthesia for a leg fracture repair. Initial recovery was good, but then the animal went off its food and began panting. This culminated in emesis and death. PME revealed pulmonary oedema.

Enrofloxacin was administered to over 700 transgenic laboratory mice, together with some of their litters of 5-6 pups, for an opportunist *Proteus* infection. Two days later two litters were found dead. There was evidence of polydipsia and polyuria.

An unknown species of vulture developed diarrhoea, possibly due to the sloughing of gut lining, after being given two daily doses of fenbendazole.

A meerkat was treated with oral fenbendazole and was found dead the following day. No PME was performed.

A reindeer was vaccinated against clostridium. Ten months later the stag died and PME revealed a clostridial infection.

Exempt veterinary medicines

Thirteen of 30 doves died suddenly over a 3-day period, starting 24 hours after administration of a wormer in their drinking water. The role of the product in the event was not determined.

Twenty-six reports involving aquarium fish were received. Active ingredients included formaldehyde, methylene blue, copper and flubendazole. In most cases, the involvement of the products could not be determined, but in three cases there was evidence of underdosing, overdosing and the use of expired product.

Overview of Human Adverse Event Reports

During 2014, 126 reports of reactions occurring in humans were received, following the use of products associated with the care of animals. Three of those reports were not linked to the treatment of animals; one case involved self-treatment with a veterinary medicine, the other two involved household pesticides.

Reports linked to the treatment of animals

Veterinary professionals

Vets and vet nurses accounted for 30 of the human incidents; 23 of these were needlestick injuries and occurred whilst administering vaccines and other injectable products to dogs (13), cats (4), rabbits (2), other unidentified companion animals (2), a group of cattle and a group of sheep. In none of these incidents were any lasting effects reported. Most symptoms were due to physical trauma and resolved within a week or less.

Another four cases involved splashes into the eye of a sedative reversal agent, a vaccine, a flea spot-on and a euthanasia agent. These cases resulted in symptoms that persisted for no longer than 24 hours, and resolved without medical treatment.

One of the remaining three cases involved the inhalation of vapour or aerosol of an ectoparasiticide cutaneous wash. The patient had worn protective gloves and apron whilst bathing several dogs a day, but experienced lethargy afterwards. The reporter of this case mentioned other vet nurses who had experienced similar symptoms, and also that the room used for bathing the dogs was poorly ventilated.

People administering veterinary medicines must be fully aware of the user safety information provided in the product literature, and take every precaution to minimise any risks to themselves and any bystanders.

The final two cases were linked and resulted from exposure whilst using inhaled anaesthetics.

In the first case, three members of staff at a single vet practice had miscarriages at under-ten-weeks' gestation throughout a 12-month period. The staff members reported having smelt the product involved, but upon investigation no equipment leaks were detected. The two vets involved were exposed for up to 3 hours during a day, but not on a daily basis. The exposure of the vet nurse was considerably less.

The second case described the premature birth, at 32-weeks' gestation, experienced by a vet covering at the same practice for only 2 days per week during the same time period. The MAH of the product involved in these cases has contacted the practice to emphasise the warnings in relation to pregnancy, and to provide advice on the use of active scavenger systems that were not in use at the time of these incidents.

Particular care should be taken during pregnancy; inhalation anaesthetics appear to pose the most serious risk, but the risks can be minimised by taking appropriate measures. You should also be aware of the risks posed by infectious agents (eg live vaccines)

Farm workers and others working with food-producing animals

Farm workers and other food production workers accounted for 34 of the human cases reported.

14 reports described the after-effects of coming into contact with liquid products; ectoparasiticide pour-ons (13) and a vaccine (1). In the vaccine case, a farm worker felt unwell after spilling the vaccine on his hands and possibly transferring it to his face. The pour-on cases resulted from spillages or equipment leaks (7), contact with recently treated animals (1), inhalation of aerosols or vapour (2) and unknown exposure (3). Some of these reports indicated that the use of personal protective equipment was not always according to the recommendations in the product leaflet. Also, it was often not clear whether the dosing equipment used was correct for the product being applied.

It should be noted that dosing equipment for one brand of product cannot be relied upon to be compatible with another brand of product.

Protective clothing should be worn and if you spill or splash any veterinary medicine onto your skin or into your eyes, it is essential you take appropriate action immediately.

Symptoms experienced after exposure to pour-on products were either systemic, for example, flu-like symptoms or generally feeling unwell, or more specifically related to the type of exposure e.g. rashes, itching, localised pain, migraine or headache. Most symptoms resolved within a few days.

20 cases involved accidental self-injection ('needlestick') of vaccines (17) or antibiotics (3). Two of the antibiotic cases resulted in minor symptoms that did not require medical treatment; the third required a course of antibiotics to treat the infection introduced by a dirty needle.

Four of the vaccine cases involved products with a mineral oil adjuvant that carry a particularly high risk of causing serious physical damage. In one case, involving a fish vaccine, the vaccinator was unable to work for 7 days due to the surgical incisions incurred in an index finger when the wound was excised and flushed to remove residues of the vaccine.

In another case, a farm worker was admitted to hospital for 9 days, whilst she received treatment, including three operations. She had punctured a finger tendon sheath whilst vaccinating sheep. 10 weeks later she was still undergoing physiotherapy, but the prognosis was good.

In a third case, a farmer stabbed the base of his thumb whilst vaccinating sheep against footrot, and reported that no product was injected. However, he visited his local A & E that evening and was prescribed antibiotics. Two days later he was unable to move his thumb due to swelling. It was not possible to gain any further information, so the final outcome is unknown.

The final mineral oil adjuvanted vaccine case involved the injection of an unknown quantity of the vaccine near a farm worker's wrist. She attended hospital, where the wound was opened and flushed. 12 days later she was reported to have fully recovered.

You must take particular care when using vaccines with a mineral oil adjuvant. It is very important to seek immediate medical attention if you injure yourself with the needle whilst using one of these products. Make sure you take the product information leaflet with you, so that you receive the correct medical attention.

The remaining 13 cases, involving non-oil-adjuvanted vaccines, mostly resulted in

either no or minor treatment. In only one case was in-patient treatment required; a farmer thought he had possibly injected 0.5 ml of a vaccine for the control of clostridial diseases and pasteurellosis. He remained in hospital for four days; a thumb tendon sheath was excised and flushed, and he experienced low blood pressure.

The Health and Safety Executive (HSE) provides comprehensive information and advice on the means to minimise risks whilst working in an agricultural environment. There is specific information[24] in relation to the hazards posed whilst using veterinary medicines, including a leaflet[25] you can print off and keep.

Pet owners, their friends and relatives

Pet owners and their close associates reported the widest range of exposure routes. There were a total of 59 reports received. The number and type of exposure are listed in Table 20.

Product Type	Exposure Type	Number of reports
Spot-on	Contact with treated animal	15
	Skin splash	13
	Ocular	4
	Ingestion	1
Tablet/capsule	Handling	3
	Ingestion	3
	Unknown	1
Injectable solutions	Injection	5
	Ocular	1
	Skin splash	1
Oral solution	Unknown	1
Shampoo	Aerosol	1
Spray	Unknown	2
Collar	Vapour	3
Nasally administered vaccine	Dog sneeze	1
Gel	Skin contact	1
Ear drops	Topical	2
Unauthorised feed additive	Dust	1

Table 21. Number of reports by product and exposure type

The majority of human reactions to spot-on products resulted in minor short-lasting symptoms that required little or no treatment to resolve. In one case, however, an owner suffered from pruritus for one month following the use of a spot-on. Three reports described more major reactions resulting in chest tightness or asthmatic episodes. It is not clear from any of the reports whether these attacks were actually triggered by exposure to veterinary products. In 2015 we published an article[26]

[24] Veterinary medicines – Using veterinary medicines, including sheep dips, http://www.hse.gov.uk/agriculture/topics/veterinary-medicines.htm
[25] Veterinary medicines: Safe use by farmers and other animal handlers, http://www.hse.gov.uk/pubns/as31.htm
[26] Focus on: human adverse events to companion animal spot-ons and sprays, *Veterinary Record* 2015;176:1 14-15

highlighting the need to follow user warnings for these products.

Two reports of single tablets being accidentally ingested by adults were received. Little or no reaction occurred. In another report, a baby picked up and mouthed a worming tablet that had been regurgitated by a dog together with the cheese that had been intended to disguise it. Fortunately the child found it unpleasant and drooled it out again.

One report was associated with the handling of capsules for the treatment of Cushing's disease. It involved a male dog owner who for a period of weeks was discovered to have been opening the capsules in order to give them to his dog. This was only revealed when the man became unwell, and it was determined that his testosterone levels were near zero.

By their nature, the reactions associated with injectable solutions, including vaccines, could not normally have been self-inflicted by pet owners. There was, however, one report where a dog owner pricked her thumb whilst administering insulin. Apart from haemorrhage, there were no other symptoms. All other needle stick injuries, eye and skin splashes involving animal owners were inflicted by veterinarians, fortunately without serious consequences.

No other human reactions from recent exposure were serious, though there have been a number of reports of exposure to products up to 30 years ago, and the recent development of serious medical conditions. Whilst these cases cannot be dismissed, it would be very difficult to draw any conclusions regarding product involvement, as the aetiology of the conditions that have now developed are generally poorly understood, and evidence of product involvement is often solely anecdotal.

Other reports, not linked to the treatment of animals

Two reports arose from the use of household pesticide (flea and bed bug) sprays. As these occurred in a non-workplace setting, these reports should be referred to the appropriate local authority (trading standards[27]) or the product manufacturer, as we have no legal jurisdiction over these types of products.

One report was received that arose from the deliberate application of an antimicrobial spray intended for production animal use to a woman's foot wound. The woman developed blood clots; it is not clear whether the signs observed were directly connected to the use of the product.

[27] Reporting incidents of exposure http://www.hse.gov.uk/biocides/reporting.htm

Overview of Environmental Reports

During 2014, 25 environmental reports were received. Only one of these incidents actually occurred in 2014, the others had occurred in earlier years, one as early as 1984.

The case reported as having occurred in 2014 involved a dead red kite that was found beside a minor road without any apparent injuries, but in poor physical condition. Anti-coagulant rodenticide residues were detected, as was diazinon. It is not clear whether the bird was exposed to the diazinon during legitimate veterinary use, following incorrect disposal of product or deliberate malicious use.

Five of the historical reports did not in fact involve an unintended species being exposed to a suspected veterinary product in the environment. In these cases, the animals were deliberately treated with veterinary or other products and developed adverse reactions and should have been reported to us directly.

The first case occurred in 1985 when lambs were treated with a cypermethrin ectoparasiticide on a hot day. Ataxia, recumbency and death occurred, and cypermethrin was detected in body tissues.

In the second case (1993), three of 40,000 commercial birds were culled when they showed signs of organophosphate poisoning. Their housing had been treated for mites with a product containing pirimiphos-methyl. This was not a veterinary medicine.

The third case (2005) involved racing pigeons that were treated with a ‘veterinary medicine’ imported from the Irish Republic, thought to contain ivermectin. The product was subsequently found to contain 38.6% diazinon.

The fourth case (2009), involved a cat that was found dead. The owner had treated the cat with a non-medicinal household treatment product to control ants, cockroaches and fleas. Bendiocarb was detected in tissue from the cat.

In the fifth case (1999), fluvalinate was detected, but no other agricultural pesticides, in dead bees. Their hive had been treated with an authorised veterinary product.

Table 22 summarises the remaining 19 historical environmental reports received during 2014. Of the substances associated with these cases, only diazinon (also known as dimpylate) and fluvalinate are present in currently authorised veterinary medicines.

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

Substance	Number of reports	Species affected	Comments
Diazinon	1	Guinea fowl	Misuse – rodent control
	1	Duck	Incorrect disposal
	2	Red kite	Possible deliberate abuse
	1	Raven	Probable uptake from treated lamb carcasses
Diazinon + chlorfenvinphos[a]	1	Commercial chickens	Incorrect disposal
Diazinon + propetamphos[c]	1	Red kite	Possible deliberate abuse
Dichlorvos[d]	2	Seagulls	Deliberate abuse
	1	Commercial poultry	Deliberate abuse
Dioaxathion[e]	1	Dog	Access to sheep dip
Dioxathion + lindane[e]	1	Dog	Access to sheep dip
Fenthion[b]	1	Cat	Possible deliberate abuse
	1	Rook, jackdaw, starling, gull, blackbird	Possible deliberate abuse
Fenthion + alphachloralose[e]	1	Raven	Possible deliberate abuse
Phosmet[c]	1	Rook	Unknown source
Propetamphos[c]	1	Dog	Access to sheep dip
	1	Cattle	Incorrect disposal
	1	Red kite	Possible deliberate abuse

Table 22. Substances involved and species affected in historical environmental incident reports
Products marked were last present in a UK authorised veterinary medicine in [a] 1998, [b] 1999, [c] 2000, [d] 2001 or [e] have never been used in UK veterinary medicines.

Adverse events related to dispensing errors

In 2014, the VMD received 13 reports of adverse events associated with dispensing errors. Of these, seven affected cats, four involved dogs, one related to a horse and one to a rabbit. Of these reports, two involved accidental administration of hypertonic saline instead of Hartmann's solution, two involved administration of the incorrect vaccine to an unauthorised species, for two reports a higher strength of tablet was dispensed than was intended and a NSAID was dispensed in error instead of an antibiotic for one report. For the remaining six reports, the incorrect injectable products were administered via the incorrect route of administration for an unauthorised indication using the incorrect dose.

In 2015, we published an article reviewing all the cases involving dispensing errors[28] that we received over the 15-year period between 2000 and 2014.

[28] Adverse events relating to dispensing errors, *Veterinary Record* 2015, 177: 360-362

Conclusions

We received almost 6,000 adverse event reports during 2014. This is a large number of reports, and is increasing from one year to the next. However, when the number of reports is put into context with the number of doses of all medicines that may have been administered to animals throughout the year, the chance of an adverse event happening in any particular animal or person is very low.

Although death is commonly reported for some products, in many cases there are other factors more likely to be responsible, such as underlying disease or the age of the animals concerned.

We estimate that on average less than 1 AE is reported for every 2,000,000 animals treated. It is accepted that there is probably a degree of under-reporting of these events, particularly in relation to food producing animals, but even with a two- or four-fold increase in the number of reports, the overall incidence of events would still be very low.

Measures you can take to avoid adverse events

Vets and SQPs

- when administering veterinary medicines, make sure you observe all user safety warnings. This is especially the case if you or others are pregnant or immunocompromised
- ensure that you provide owners with full instructions and warnings about any medicines they take away with them, and that they understand what you have told them
- remember that the most comprehensive and up-to-date information on all veterinary medicines can be accessed via the Product Information Database[29].

All animal owners

- you should only buy medicines from reputable sources and, if buying online, we recommend that you look for a website that we have approved through the Accredited Internet Retailer Scheme[30].
- make sure you read, understand and follow the safety instructions given to you by veterinary professionals, and included with the medicines. They are there to keep you, your animals and anyone else who may come into contact with them, safe
- ensure you store medicines for your animal(s) separately from any medicines you may be taking yourself, and out of the sight and reach of children

Small animal (pet) owners and keepers

- do not change the way you give your pet its medicine (eg crushing tablets or opening up capsules) unless you have discussed the change with your vet as
    - the effectiveness of the medicine may be reduced
    - you put yourself at risk of harm from the medicine
- when treating your pets for fleas, unless the product claims to treat the

[29] Product Information Database, http://www.vmd.defra.gov.uk/ProductInformationDatabase
[30] Accredited Internet Retailer Scheme, https://www.gov.uk/government/publications/accredited-internet-retailer-scheme-airs

environment, you should also thoroughly vacuum the house and use a suitable household pesticide spray to treat the areas frequented by your pets

Farmers

- make sure you are using the correctly calibrated equipment (eg dosing or drenching guns) for the product you are administering.
- Do not mix drenches or injectable products unless your vet has specifically told you that you can

When adverse events occur

- Seek medical or veterinary attention as soon as possible, taking the package leaflet of any medicines involved with you. This is especially important if you have accidentally injected yourself with a mineral oil-based vaccine.
- Report adverse events associated with pesticides to the appropriate authority[31].
- Report all other adverse events (including SLEE) even if the product was used off-label, as soon as possible, either to the MAH or the VMD [32]. Remember, a separate form exists for microchips.
- As either a vet or animal owner, you should let the other party know that you have reported, to avoid a duplicate report being sent.
- Please provide as much information as possible to help us identify the correct product(s) involved. Providing full information about the animal(s) affected will help us to detect new, and monitor known, breed-related problems.
- If you are subsequently contacted by either the VMD or by an MAH, please respond to any request for further information, so that the final outcome can be determined. This is especially important for human and serious animal reports.

Note from Authors

We would like to thank everyone who reported adverse events during 2014. The information you have provided has continued to enlarge and enrich our knowledge about the safety and efficacy of veterinary medicines when used in the 'real world'.

This is the first year that we have produced our Annual Review in this format, in an attempt to make it more accessible, interesting and relevant to as wide a readership as possible. We would therefore welcome any feedback you may have.

If you have any questions or comments about this report, or have any suggestions for topics you would like us to cover in future Annual Reviews or our regular articles on specific issues, please email them to adverse.events@vmd.defra.gsi.gov.uk.

January 2016

[31] Reporting incidents of exposure http://www.hse.gov.uk/biocides/reporting.htm
[32] Report a problem with an animal medicine or microchip, https://www.gov.uk/report-veterinary-medicine-problem

Glossary of clinical terms used in adverse event reports

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

Clinical term	Meaning
Alopecia	Hair loss
Anaphylaxis	Severe allergic reaction
Anaemia	Low levels of red blood cells
Ataxia	Lack of muscle coordination
Cardiovascular	Relating to the heart and blood vessels
Cyanosis	Blue tinge to mucous membrane
Dyspnoea	Difficult or laboured breathing
Emesis	Vomiting
Epistaxis	Nosebleed
Erythema	Reddening of the skin
Euthanasia	Put to sleep (dead)
Haemorrhagic	Bloody
Hepatopathy	Liver disease or disorder
Hyperaesthesia	Exaggerated response to stimuli ('twitchy')
Hyperhidrosis	Excessive sweating
Hyperthermia	Fever, high temperature
Hypotension	Low blood pressure
Hypothermia	Low temperature
Ileus	Lack of intestinal motility
Jaundice	Yellowing of skin/eyes/gums
Lethargy	Lack of energy, inactivity
Leucopenia	Decrease in number of all types of white blood cells
Lymphadenopathy	Enlarged lymph nodes
Malaise	Discomfort, illness

Clinical term	Meaning
Melanisation	Excessive pigmentation due to tissue damage in fish
Melaena	Dark (digested) blood in faeces
Moribund	Lifeless (close to death)
Mydriasis	Dilated pupils
Neoplasm	Tumour
Neutropenia	Low levels of certain white blood cells (neutrophils)
Neutrophilia	High levels of certain white blood cells (neutrophils)
Nystagmus	Flickering of eyes from side to side
Oedema	Swelling
Paresis	Slight or partial paralysis
Periorbital	Around the eyes
PME	*Post mortem* examination
Polydipsia	Excessive drinking
Polyuria	Excessive urination
Pruritus	Severe itching
Pyrexia	High temperature
Rale	Abnormal rattling breathing sound
Rhinitis	Inflammation of nasal membranes
Somnolence	Sleepiness
Tachycardia	Fast heart rate
Tachypnoea	Breathing quickly
Thrombocytopenia	Low levels of platelets (needed for clotting)
Urticaria	Itchy raised rash ('hives')

Veterinary
Medicines
Directorate

Report a Suspected Adverse Event

Microchips

NEW From April 2014 the VMD is monitoring reports of adverse events following microchipping of companion animals. Details of the scheme can be found in this leaflet Microchip Adverse Event ReportingScheme

To report an adverse event following microchipping please click here

Veterinary Medicines

You can report a suspected adverse reaction or lack of efficacy to a veterinary medicine by clicking on the buttons below - this will take you to the online reporting site.

This scheme is run by the VMD's Pharmacovigilance Unit and is used to collect information from veterinary professionals and the general public on suspected adverse reactions and lack of efficacy to veterinary medicines. We collect reports on both licensed and unlicensed veterinary medicines, and human medicines used to treat animals under the cascade. The information that you provide can help to improve the safe and effective use of veterinary medicines.

When you fill in the report you will need to provide basic information about:

- The name of the product which you think caused the adverse reaction or lack of efficacy.
- The animal(s) or person(s) in which the adverse reaction or lack of efficacy occured.
- The signs observed of the adverse reaction or lack of efficacy that is suspected.
- Your contact details as the reporter of the adverse reaction or lack of efficacy.

You can record this information in the four sections of the reporting screen. It might be useful, although not essential, to have the product, its packaging or the package leaflet that came with it with you when you fill out this report. Your report can be submitted

without any additional information, but if you are able to provide further details, these can be added in the final section of the report.

To report an ANIMAL adverse reaction or lack of efficacy to a veterinary medicinal product or to a human product, click here

To report a HUMAN adverse reaction to a veterinary medicinal product, click here

If you would prefer to use a paper copy, download and print an Animal Form to report an adverse reaction in an animal to a veterinary medicine or to a human product. Post the form to the address at the top of the report.

Click here to download and print a Human Form to report an adverse reaction in a human to a veterinary medicinal product. Post the form to the address at the top of the report.

If you have any questions please call the pharmacovigilance team on 01932 338427.

Online form

Microchip Adverse Event Reporting Form

Chip Details

Chip Number:*

Chip Manufacturer:

Implantation Date:

Implantation Site:* Please select

Name of Implanter:

Postcode of Implanter: Lookup address

Implanter Occupation:* Please select

Animal Details:

Species:* Please select

Date Of Birth:

Sex: Please Select

Weight (kg):

Event Details

Event first detected:*

Event Type:* Please select

Reporter Details

Name: *

Postcode: Lookup address

Telephone Number:

Occupation: * Please select

E-mail: *

Reference:

Vet Details

If the Vet and Reporter are the same person please check this box:

Name:

Postcode: Lookup address

Telephone Number:

E-mail:

Submit Cancel

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Microchips and cancer: a review

The VETMED email list had a discussion of the potential link between implanted identification microchips and cancer. I did some research to see what has been published on this topic.

A lot of our assessments of risk are based not on evidence, but on general impressions, as in "Everybody says [something commonly held to be true]" or "I've never seen [some rare adverse effect]." But sometimes, what "everybody says" is wrong. I prefer to look for evidence from scholarly studies when figuring out the risks of a specific drug or device.

When you look at scholarly research, you may not find the large-scale studies that would give you an accurate, quantified assessment of risk. Some years back, one of my dogs had his broken hock rebuilt by an orthopedic surgeon. I wanted to know whether we should remove the implanted bone nails and plates after he recovered, because some implantable devices, such as hip replacements in human patients, are associated with an increased rate of cancer.

When I discussed this with his surgeon and with other vets, it turned out that none of them could give me any evidence-based statistics on the incidence of bone cancer or other malignant neoplasms at the site of bone fixation devices. So, being the curious type, I looked at some of the research on that. I never did find any firm numbers, but what I found was the following things were all associated with an increased risk of cancer: Breaking a bone, implanting metal into the body, and implanting many other types of material into the body. Basically, it seems like anything that encourages more bone to grow increases the bone cancer risk (Goldschmidt and Thrall, 1985). (This is probably one reason that early-age spaying and neutering of dogs is associated with a significant increase in bone cancer risk. (Cooley et al, 2002 and Ru et al, 1998) Early desexing is known to produce taller animals. In intact dogs, the sex hormones of puberty help trigger the closure of the growth plates of the bones. If you spay or neuter a young puppy, the bones grow for a longer period and more bone growth increases the risk of bone cancer.

So, there is some risk of cancer from bone fixation devices, and the risk they pose is higher than the risk of simply breaking a bone - but I never did find research that quantified that specific risk. And I'm certain that the benefit of having a sound leg to walk and run on far outweighs the small risk of cancer from implanting bone fixation devices.

Going back to the issue of microchips, I did find multiple studies and some case reports that indicate that implanting a microchip raises the risk of cancer in animals. Here are some relevant principles that we know from veterinary research on related risks:

- Malignant tumors in animals have been linked to implantation of foreign bodies (Brand, 1975b and Moizhess, 1989). Even foreign bodies consisting of relatively inert materials such as glass (McCarthy, 1996 and Brand, 1975a) have been found to cause malignant tumors in animals.

- Vaccinations and injections have been found to lead to sarcomas in cats (Kass, 2003), dogs (Vascellari, 2003), and ferrets (Munday, 2003). In the cat study by

Kass, the sarcomas are not linked to one brand or type of vaccine, as was previously thought. (In some older studies, specific brands of vaccines were thought to be implicated, but some researchers now feel that was simply a reflection of the popularity of those brands.)

- Inflammation, usually transient, occurs at the implantation sites of microchips (Mader, 2002, and Lambooij, 1995).

- Tissue inflammation has a role in the development of cancer (Cousins, 2002, and Balkwill, 2001).

- A fibrous capsule is formed around implanted microchips (Ball, et al, 1991, Gruys, 1993, Troyk, 1999) even in the absence of a gross inflammatory reaction (Jansen, 1999). This indicates that there is enough inflammation to cause fibrous tissue growth. Fibrosarcoma, which is the most common sarcoma associated with vaccinations in animals, is also rich in fibrous tissue.

So, if you're wondering how microchips could be harmful, the answer is that they can cause inflammation, fibrous tissue growth, and are implanted via injections, a method that is already known to increase the sarcoma risk. Then, add the fact that implanted foreign bodies are known to increase the risk of cancer. It follows that we have good reason to be cautious about microchip implantation.

When people want to dismiss out of hand the idea that there may be a cancer risk in implanting microchips, they should think about the many years that vaccines were given to cats before the issue of injection-site sarcomas was recognized and understood to be a risk.

I am not saying that the risk of implanting a microchip necessarily outweighs the benefit. I think each pet owner needs to decide that for themself. Vaccines are linked to sarcomas, but I vaccinate all my pets for rabies, because I believe the protection from a fatal disease is worth the small risk. The situation with microchips is different, as there are other identification methods available.

It would be unfortunate if the government mandated microchipping of pets and took this decision out of the hands of pet owners. There have been a few municipalities that have passed laws requiring this. I believe that the decision of whether to microchip an animal should be left to the pet owner, particularly since the owner is the one who will foot the bill for veterinary treatment in the case of any adverse effect.

Looking at the studies and case reports that link implanted microchips (also known as "passive transponders") to the development of tumors in various species of animal, it's interesting to note that most of the studies were not done specifically to find problems with microchips. Rather, the researchers implanted microchips in the animals they were using for some other study, and they noticed that their research subjects were developing tumors at the microchip implantation sites.

Some of these articles refer to specific lines of laboratory animals that may be more prone to cancer than the species as a whole. That's not a reason to dismiss the research. Just as some humans carry certain genes predisposing them to some form of cancer, a similar phenomenon is found in some dogs and cats. With implanted microchip devices becoming common as an identification method for pets, you have to assume that some of the dogs and cats that get them will have health issues, such

as a genetic susceptibility to cancer. When deciding if a device or drug is safe, you don't just look at the risk to healthy animals, you have to look at the risk to the most vulnerable animals. too.

If anyone wishes to repost or republish this, please email me and ask for permission. I usually say yes, but I like to be asked.

Contact the author.

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Articles Linking Microchips (Transponders) AND Tumors

[Where possible, I've quoted an excerpt from the abstracts or articles. Follow the links for the full abstracts or full-text.]

Vascellari M, Melchiotti E, Mutinelli F.

Fibrosarcoma with typical features of postinjection sarcoma at site of microchip implant in a dog: histologic and immunohistochemical study.
Veterinary Pathology. 2006 Jul; 43(4):545-8.
<http://www.vetpathology.org/cgi/content/abstract/43/4/545>

> *"A 9-year-old, male French Bulldog was examined for a subcutaneous mass located at the site of a microchip implant. [...] A diagnosis of fibrosarcoma morphologically similar to feline postinjection sarcomas was made. Fibrosarcomas at the site of injections have been reported in dogs and ferrets. Furthermore, neoplastic growth at the site of microchip implant in dog and laboratory rodents has been described."*

Le Calvez S, Perron-Lepage MF, Burnett R.
Subcutaneous microchip-associated tumours in B6C3F1 mice: a retrospective study to attempt to determine their histogenesis.
Experimental and Toxicologic Pathology. 2006 Mar; 57(4):255-65. Epub 2006 Jan 19.
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&list_uids=16427258>

> *" Fifty-two subcutaneous tumours associated with microchip were collected from three carcinogenicity B6C3F1 mice studies. Two of these 52 tumours were adenocarcinoma of the mammary gland located on the dorsal region forming around the chip. All the other 50 were mesenchymal in origin and were difficult to classify on morphological grounds with haematoxylin-eosin."*

Vascellari M, Mutinelli F, Cossettini R, Altinier E.
Liposarcoma at the site of an implanted microchip in a dog.
Veterinary Journal. 2004 Sep; 168(2):188-90.
Link to conference presentation on this subject by the authors:
<http://www.aipvet.it/APIVMeetings/2003_ATTI_APIV/vascellarireprint2003.PDF>

European Medicines Agency, CHMP Safety Working Party. CHMP SWP Conclusions and Recommendations on the Use of Genetically Modified Animals Models for Carcinogenicity Assessment. 2004 June 23.
Full text:
<http://www.emea.eu.int/pdfs/human/swp/259202en.pdf>

> *[From Section 3, "C57BL/6(N5) - TRP53 KNOCKOUT (page 2)]*
> *"3.2.1. Spontaneous Tumour Incidences*
>
> *The overall spontaneous tumour incidence in studies of 26 weeks duration was low, 2.8% in males (n=283) and 6% in females (n=284) in studies without transponders (microchip implants for identification), and 8% in males (n=150) and 11.3% in females (n=150) in studies with transponders. Lymphomas, subcutaneous sarcomas and osteosarcomas were the three most common tumours. Other tumours had a much lower incidence (0.0-0.2%_).*
>
> *Implantation of transponders results in particular in higher incidence of spontaneous sarcomas with up to 6.7% in female mice (as compared to 1.4% in females without biochips). The use of this method is therefore not recommended. It has also been suggested that displacement of the transponder can be induced by handling whihc may result in confounding tumours at a site distant from that of the implantation site. "*

Floyd E, Mann P, Long G, Ochoa R.
The Trp53 hemizygous mouse in pharmaceutical development: points to consider for

pathologists.
Toxicologic Pathology. 2002 Jan-Feb; 30(1):147-56.
Full text available:
<http://www.toxpath.org/stp_journal_archive/VOL%2030,%20NO%201,%20PART%20NA,%202002.PDF>

" Use of implanted electronic transponders can increase the incidence of sarcomas."

Elcock LE, Stuart BP, Wahle BS, Hoss HE, Crabb K, Millard DM, Mueller RE, Hastings TF, Lake SG.
Tumors in long-term rat studies associated with microchip animal identification devices.
Experimental and Toxicologic Pathology. 2001 Feb; 52(6):483-91.
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&list_uids=11256750>

" Tumors surrounding implanted microchip animal identification devices were noted in two separate chronic toxicity/oncogenicity studies using F344 rats. The tumors occurred at a low incidence rate (approximately 1 percent), but did result in the early sacrifice of most affected animals, due to tumor size and occasional metastases. No sex-related trends were noted. All tumors occurred during the second year of the studies, were located in the subcutaneous dorsal thoracic area (the site of microchip implantation) and contained embedded microchip devices. All were mesenchymal in origin and consisted of the following types, listed in order of frequency: malignant schwannoma, fibrosarcoma, anaplastic sarcoma, and histiocytic sarcoma. The following diagnostic techniques were employed: light microscopy, scanning electron microscopy, and immunohistochemistry. The mechanism of carcinogenicity appeared to be that of foreign-body induced tumorigenesis."

Cohen SM, Robinson D, MacDonald J.
Alternative Models for Carcinogenicity Testing
Toxicological Sciences. 2001; 64:14-19
Full text available:
<http://toxsci.oxfordjournals.org/cgi/content/full/64/1/14>

" With respect to the sarcomas, it is important to distinguish between those occurring at the site of transponder implantation (used for identification) versus those that arise at other sites. Those related to transponders may be more likely related to foreign body sarcomagenesis rather than being chemically related."

European Society of Toxicologic Pathology. (2000) "MICROCHIP-ASSOCIATED TUMOUR IN A C57/BL MOUSE"
GTP [Gesellschaft für Toxikologische Pathologie] Meeting 2000: Case No 15.
<http://212.227.190.64/eurotoxpath/meetings/index.php?id=2000/case15>

" In a long-term study using 2554 mice, the possible influence of parental radiation exposure on tumour development in the descendants was investigated." [...] "In single animals of this ongoing study, circumscribed subcutaneous nodules occurred at the site of implanted microchips. A firm, pale white nodule, up to 30 mm in diameter, completely embedding the microchip completely was found in a 39-weeks-old female C57BL mouse." [...] "Researchers/pathologists must be aware of foreign body tumorigenesis (microchip-induced neoplasms) possibly complicating the interpretation of data from carcinogenicity studies."

Blanchard KT, Barthel C, French JE, Holden HE, Moretz R, Pack FD, Tennant RW, Stoll RE. Transponder-induced sarcoma in the heterozygous p53+/- mouse. *Toxicologic Pathology.* 1999 Sep-Oct; 27(5):519-27.
Full text available:
<http://www.toxpath.org/stp_journal_archive/VOL%2027,%20NO%205,%20PART%20NA,%201999.PDF>

" Heterozygous p53+/- transgenic mice are being studied for utility as a short-term alternative model to the 2-yr rodent carcinogenicity bioassay. During a 26-wk study to assess the potential carcinogenicity of oxymetholone using p-cresidine as a positive control, glass/polypropylene microchips (radio transponder identification devices) were subcutaneously implanted into male and female p53+/- mice. During week 15, the first palpable mass was clinically observed at an implant site. This rapidly growing mass virtually quadrupled in size by week 25. Microscopic examination of all implant sites revealed that 18 of 177 animals had a subcutaneous histologically malignant sarcoma. The neoplasms were characterized as undifferentiated sarcomas unrelated to drug treatment, as indicated by the relatively even distribution among dose groups, including controls. An unusual preneoplastic mesenchymal change characterized by the term "mesenchymal dysplasia" was present in most groups and was considered to be a prodromal change to sarcoma development. The tumors were observed to arise from dysplastic mesenchymal tissue that developed within the tissue capsule surrounding the transponder. The preneoplastic changes, including mesenchymal dysplasia, appeared to arise at the transponder's plastic anchoring barb and then progressed as a neoplasm to eventually surround the entire microchip. Capsule membrane endothelialization, inflammation, mesenchymal basophilia and dysplasia, and sarcoma were considered unequivocal preneoplastic/neoplastic responses to the transponder and were not related to treatment with either oxymetholone or p-cresidine."

Tillmann T, Kamino K, Dasenbrock C, Ernst H, Kohler M, Morawietz G, Campo E, Cardesa A, Tomatis L, Mohr U.
Subcutaneous soft tissue tumours at the site of implanted microchips in mice. *Experimental and Toxicologic Pathology.* 1997 Aug; 49(3-4):197-200.
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&list_uids=9314053>

" An experiment using 4279 CBA/J mice of two generations was carried out to investigate the influence of parental preconceptual exposure to X-ray radiation or to chemical carcinogens. Microchips were implanted subcutaneously in the dorsolateral back for unique identification of each animal. The animals were kept for lifespan under standard laboratory conditions. In 36 mice a circumscribed neoplasm occurred in the area of the implanted microchip. Females were significantly more frequently affected than male mice. An influence of age or different treatment on the s.c. tumour incidence in two mice generations could not be observed. Macroscopically, firm, pale white nodules up to 25 mm in diameter with the microchip in its center were found. Microscopically, soft tissue tumours such as fibrosarcoma and malignant fibrous histiocytoma were detected."

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