Assessment of animal poisonings in Germany and severity scoring schemes: Needs for a One Health approach

Inaugural-Dissertation

to obtain the academic degree
Doctor medicinae veterinariae
(Dr. med. vet.)

submitted by
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Hannover 2017
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Day of the oral examination: 05 May 2017
Two publications form the basis of this dissertation:

**Systematic account of animal poisonings in Germany, 2012-2015**
Veterinary Record: 24 February 2017
DOI: 10.1136/vr.103973

**Comparison of the Poisoning Severity Score and National Poison Data System schemes for the severity assessment of animal poisonings: issues of a pilot study**
McFarland, S. E., Bronstein, A. C., Banerji, S., LeBlond, J., Mischke, R. H., Begemann, K., Desel, H., Greiner, M.
Clinical Toxicology: 28 March 2017
DOI: 10.1080/15563650.2017.1304554
Partial results of this dissertation were presented by the author at the following scientific events:


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1 Introduction

Currently there is a lack of comprehensive information as well as surveillance initiatives regarding the occurrence of animal poisonings in Germany and the European Union (EU). Additionally, animal poisonings in Germany and the EU are not required to be reported; Germany and the EU lack a centralised veterinary poisonings database as well as centralised process for toxicology laboratories that analyse veterinary samples to report case findings. This scarcity of publicly available data on animal poisonings is a challenge for the veterinary profession in Germany, as there is no country-specific source from which wide-ranging and up-to-date clinical, epidemiological, and toxicological information can be used for case management and poisoning risk assessment.

The majority of information on animal poisonings worldwide comes from human and veterinary Poison Centres (PCs) and surveys of veterinary practices (Berny et al., 2010; Gwaltney-Brant, 2012). PCs in particular are a primary source of data on animal poisonings and therefore play an important role in identifying poisoning trends and risks (Gwaltney-Brant, 2012). In Germany, there are no veterinary-specific PCs; however, there are eight human PCs that advise and record data on animal poisonings inquiries in addition to their main focus of providing medical advice for poisonings in humans (Federal Institute of Risk Assessment, 2015).

Several recent publications within the last decade have provided a review on animal poisonings in Europe (Berny et al., 2010; Caloni et al., 2012a; Guitart et al., 2010); a number of publications from countries including Belgium, the Czech Republic, Italy, and Switzerland have provided country-specific overviews of the occurrence of animal poisonings (Caloni et al., 2012b; Modrá and Svobodá, 2009; Schediwy et al., 2015; Vandenbroucke et al., 2010). In Germany, there is a need for current information on animal poisonings as there are no publications within the past ten years that provide a comprehensive overview of the occurrence of poisonings in companion animals and/or livestock. Instead, available information includes isolated case reports, the yearly reports of the German PCs, and a recent survey of samples from suspected animal poisoning cases sent to a toxicology laboratory between 1998 to 2006 (Allkämper et al., 2015).

Based on published data from Europe and the United States (US), dogs followed by cats are the most commonly reported species involved in poisonings (Berny et al., 2010; Buttke et al., 2012; Caloni et al., 2012a; Gwaltney-Brant, 2012); poisonings in food-producing animals and other pets (e.g., small mammals, reptiles) are rarely reported (Berny et al., 2010; Caloni et al., 2012a; Guitart et al., 2010; Gwaltney-Brant, 2012). The majority of reported animal poisonings are accidental, acute, involve oral exposure; and, for companion animals, occur in or around the home (Amorena, 2004; Gwaltney-Brant, 2012). The most frequently reported causative agents vary according to species and publication. However, medicinal products [both human (HMPs) and veterinary (VMPs)], pesticides, and plants have been consistently implicated as top causes of poisonings (Berny et al., 2010; Buttke et al., 2012; Caloni et al., 2012a; Guitart et al., 2010; Gwaltney-Brant, 2012).

* For this dissertation, the term poisoning refers to both toxic exposures and poisonings.
In addition to the fragmented information on animal poisonings in Germany and Europe, the use of diverse and non-standardised methods for the documentation and assessment of poisonings poses challenges for collating information from multiple sources, preparing summary statistics, and for the interpretation of data. For example, differences in the categorisation of causative agents, documentation and reporting of exposure patterns (e.g., route and length of exposure, reason for exposure, likelihood of exposure), and assessment of poisoning severity make comparison of reported data within and between countries difficult. Therefore, the use of harmonised and standardised methods for the documentation and assessment of animal poisonings would facilitate the evaluation of poisoning data.

Regarding the evaluation of poisonings, assessment of clinical severity is particularly important as it allows for identification of causative agents that can lead to severe clinical effects as well as cases that warrant follow-up for clinical, epidemiological, or research purposes (Casey et al., 1998). Assessment of poisoning severity also facilitates identification of poisoning risks in both animals and humans. To date, there are no publicly available schemes designed and evaluated specifically for the severity assessment of animal poisonings. For poisonings in humans, two well-established schemes for grading poisoning severity include the Poisoning Severity Score (PSS) (Persson et al., 1998) which is used in a number of countries worldwide, and the National Poison Data System (NPDS) medical outcome classification scheme, which is used by the American Association of Poison Control Centers (AAPCC) in the US (Mowry et al., 2015). Both schemes have been used for the assessment of animal poisonings in Germany and the US, respectively (McFarland et al., 2017; Mowry et al., 2015). However, they have not been evaluated or adapted for assessment of poisoning severity in animals; therefore, the application of these schemes to animal poisonings warrants study and could help inform their use as well as highlight future needs and considerations for the development of severity assessment schemes designed specifically for animals.

With increased emphasis in both the human and veterinary fields on a One Health approach to address animal and human health issues (Centers for Disease Control, 2016), the use of standardised methods for the documentation and assessment of both animal and human poisonings could also assist the detection of trends and signals when combining information across data sources. In recent decades, the concept of One Health has been gaining ground in the scientific community and has been promoted by a number of prominent organisations. One Health involves an integrative approach among multiple disciplines on a local, national as well as global level to achieve optimal health of animals, people, and the environment (American Veterinary Medical Association, 2017; Centers for Disease Control, 2016). Historically, the One Health concept worldwide and in Germany has focussed on infectious diseases; in particular the prevention, prediction, and control of zoonotic diseases (Buttke, 2011; Wendt et al., 2015). However poisonings in animals are also relevant to human health and it is increasingly being recognised that a One Health approach in the area of toxicology is needed and has the potential to improve early recognition of cases and outbreaks, understanding of risk factors, as well as prevention of poisonings in animals and humans (Buttke, 2011).

The topic of animals as sentinels for health risks in both animal and humans has a long history. For toxicological hazards in particular, there are numerous examples in which the occurrence of poisoning in animals acted to identify and/or prevent poisonings in humans.
These include the use of canaries in coal mines in the early 20th century to enable mine workers to predict exposure to toxic gases, programs in which animal deaths around water sources have been used for early detection of harmful cyanobacterial blooms, and the diagnosis of lead poisoning in companion animals leading to discovery of elevated lead levels in children in the same household (Buttke, 2011; Dowsett and Shannon, 1994; Hilborn and Beasley, 2015; Reif, 2011; Schmidt, 2009). There are also several well-known events in which the occurrence of poisoning in animals was retrospectively recognised as preceding the occurrence of poisoning in humans. These include an outbreak of methylmercury poisoning in Minamata Bay, Japan in the 1950s that was preceded by the occurrence of signs in cats and the great London fog of 1952 which resulted in thousands of human deaths and was preceded by a cluster of sudden death in cattle at a stock show (Buttke, 2011; Rabinowitz et al., 2010). A more recent event is the 2007 melamine pet food recall in the US that occurred as a result of the death of pets that consumed feed contaminated with melamine. This event preceded a scandal in 2008 in China which involved fatalities as well as acute health effects in thousands of infants exposed to melamine-contaminated milk and infant feed formula (Gossner et al., 2009; Rumbeiha, 2012; World Health Organisation, 2008).

Differences in susceptibility, exposure routes, latency periods, life spans, as well as the diversity of species places animals as potentially sensitive indicators of toxicological hazards (Buttke, 2011). In addition, some animal species show similar clinical responses to humans for specific poisonings (e.g., acetaminophen poisoning, pesticide poisoning) and therefore can also illustrate the clinical course of poisonings as well as inform diagnostic and treatment approaches (Buttke, 2011; Reif, 2011; Rumbeiha, 2012). Companion animals (e.g., cats and dogs) in particular have been cited as ideal sentinel species as they share a similar environment to humans and are therefore likely exposed to similar contaminants at similar concentrations (Reif, 2011; Schmidt, 2009). Other animal species such as livestock have also been indicated as potential sentinels for exposure to environmental toxins, contaminated animal products, contaminants in the food/feed chain, and, in some cases, common sources of food and water (Buttke, 2011). Intoxications of food-producing animals; for example, due to contaminated animal feed, may lead to carry-over of hazardous substances into animal-based food commodities (Buttke, 2011). This specific aspect of food safety is however beyond the scope of this project.

Despite there being numerous examples of animals as sentinels for poisoning risks in humans, there is a general lack of integration of animal and human health data worldwide and in Germany (Gossner et al., 2009; Rabinowitz et al., 2005; Rabinowitz et al., 2010; Scotch et al., 2009; Wendt et al., 2015). There is also limited use of animal data to quantitatively predict human health risks as well as an absence of clear, detailed guidelines for the use and integration of animal and human poisoning data for the purposes of informing public health measures (Rabinowitz et al. 2005, Scotch et al. 2009, Rabinowitz et al. 2010).
Due to the fragmented and sparse information on animal poisonings in Germany as well as the absence of publically available, standardised methods for the assessment of animal poisonings, the two main objectives of this joint project between the Federal Institute of Risk Assessment (BfR), Berlin, Germany and the University of Veterinary Medicine (TiHo), Hannover, Germany were as follows:

1) To systematically collect, assess, and analyse information from multiple data sources on the occurrence of animal poisonings (excluding wildlife) in Germany and compare findings to results from other European countries

2) To evaluate and compare two schemes for the severity assessment of animal poisonings

The two objectives are addressed in two publications, which are a part of this thesis (Sections 2.1, 2.2). In addition, the results from these two objectives were used to support an assessment of the applicability of the One Health concept to toxicology, with a particular emphasis on the use of animals as sentinels for poisonings.

For the first objective, the following approach was followed to investigate the occurrence of animal poisonings. Data was collected and analysed on exposure calls to five German PCs, poisoning cases presenting to the TiHo Small Animal and Equine Clinics, cases involving off-label use of VMPs reported to the Federal Office of Consumer Protection and Food Safety (BVL), and submissions for toxicological analysis to the Institute of Pharmacology, Toxicology, and Pharmacy, Faculty of Veterinary Medicine, Ludwig-Maximilians-University, Munich (IPTP, LMU). In addition, an announcement was made in three German veterinary journals introducing the project and asking for veterinarians to voluntarily report poisoning cases to the BfR (McFarland et al., 2015a, b, c). An evaluation of the data and data sources was also carried out in order to assess strengths, weaknesses, and biases associated with available information and to help determine where efforts could be focussed to optimise approaches for the collection and use of information on animal poisonings.

For the second objective, agreement between raters using the Poisoning Severity Score (PSS) and National Poison Data System (NPDS) medical outcome scheme for severity assessment of canine exposures reported to the Rocky Mountain Poison and Drug Centre in Denver, Colorado, US was assessed. Agreement between both schemes for the grading of exposure severity was also investigated. Issues regarding use of the schemes for severity assessment of animal poisonings were identified and the most commonly reported clinical effects were described.

Lastly, to explore the topics of One Health and animal sentinels in relation to poisonings, a survey of the literature was carried out first with worldwide coverage, and then with a focus on Germany. Findings from the literature survey along with the data on animal poisonings collected for the the project were evaluated in order to provide an overview of the One Health and sentinel concept in relation to toxicology. Needs for the use of One Health approaches and animals as sentinels of poisoning risks in humans were also identified.
2 Publications

2.1 Publication 1. Systematic account of animal poisonings in Germany, 2012-2015
Veterinary Record: 2017 Feb 24 [Epub]
DOI: 10.1136/vr.103973

Abstract
A systematic retrospective study on animal poisonings in Germany (wildlife excluded) between January 2012 and December 2015 was conducted. Data was collected on animal exposure calls to German Poisons Centres (PCs), poisoning cases presenting to the University of Veterinary Medicine, Hannover (TiHo) Small Animal and Equine Clinics, cases involving off-label use of veterinary medicinal products (VMPs) reported to the Federal Office of Consumer Protection and Food Safety (BVL), and toxicological submissions to the Institute of Pharmacology, Toxicology, and Pharmacy, Faculty of Veterinary Medicine, Ludwig-Maximilians-University, Munich (IPTP, LMU). Descriptive statistics were used to characterise animal type, exposure reason, type and substance, year/month of exposure, case severity, and outcome. An evaluation of the data and data sources was also carried out. Variation in poisoning patterns was seen. However, dogs and cats were the most frequently reported species and medicinal products, pesticides, and plants were consistently implicated as top causes of poisoning. Advantages and disadvantages were associated with each data source; bias was found to be an important consideration when evaluating poisoning data. This study provided useful information on animal poisonings in Germany and highlights the need for standardised approaches for the collection, evaluation, and integration of poisoning data from multiple sources.
2.2 Publication 2. Comparison of the Poisoning Severity Score and National Poison Data System schemes for the severity assessment of animal poisonings: issues of a pilot study

McFarland, S. E., Bronstein, A. C., Banerji, S., LeBlond, J., Mischke, R. H., Begemann, K., Desel, H., Greiner, M.
Clinical Toxicology: 2017 Mar 28 [Published online]
DOI: 10.1080/15563650.2017.1304554

Abstract

Context
To date, there are no publicly available schemes designed and evaluated specifically for severity assessment of animal poisonings. This poses challenges for the evaluation and comparison of animal poisoning exposure data.

Objective
Our objective for this pilot study was to evaluate agreement between raters using the Poisoning Severity Score (PSS) and National Poison Data System (NPDS) medical outcome scheme for severity assessment of canine exposures reported to a multistate poison center (PC) and to identify issues regarding their use for severity assessment of animal poisonings. Agreement between both schemes was also assessed.

Methods
The first 196 canine exposures reported to a multistate PC between January 1 to August 31, 2016 were selected and initial inquiry data from exposures was scored by four independent raters. Interrater agreement and agreement between the severity systems was calculated using weighted kappa (K) (Light’s kappa). Reported clinical effects were also described.

Results
Interrater agreement for both the PSS (K 0.31; 95% CI 0.19, 0.43) and NPDS schemes (K 0.34; 95% CI 0.22, 0.44) was low. Agreement between the schemes was slight (K 0.05; 95% CI -0.08, 0.16) for pooled results from all four raters. For the PSS, 71.7% (n=281) of ratings were minor, 23.0% (n=90) moderate, and 5.4% (n=21) severe. For the NPDS, 69.6% (n=273) of ratings were minor, 27.0% (n=106) moderate, and 3.3% (n=13) severe. The top three reported clinical effects included vomiting (n=86, 29.9%) drowsiness/lethargy (n=38, 13.2%), and diarrhea (n=24, 8.3%).

Discussion and Conclusions
This study shows considerable variability between raters using either the PSS or NPDS schemes for canine exposures severity assessment. The subjective nature of the schemes, the influence of intra- and interrater variation, and predominance of minor cases on the study findings should be taken into account when interpreting this data. Further evaluation of these schemes is warranted and could help inform their future use for animal poisoning severity assessment.
3 Discussion

The following discussion is divided into three main sections that mirror the three main focal points of the doctoral project. Section 3.1 provides an account and brief discussion of the main results of the literature review on animal poisonings in Germany and Europe as well as the data collected on animal poisonings as part of the project. The methods for the literature review for Germany and Europe are provided in the Appendix. Section 3.2 covers the documentation and assessment of poisonings in animals. Aspects regarding the severity assessment of poisonings are discussed along with the project study carried out to compare and assess two schemes for the severity assessment of poisonings in animals. The third section (3.3) examines the topics of One Health and animal sentinels in relation to toxicology and provides an overview of the needs for a One Health approach to poisonings.

3.1 Poisonings in Germany: an overview

3.1.1 Literature review: Germany and Europe

Germany

Eight publications on animal poisonings in Germany were identified that met the selection criteria (Appendix, Table 1). Three of the eight provided information on animal poisonings within the past ten years (Allkämper et al., 2015; Brauer et al., 2011; Zimmermann et al., 2010). Of these three publications, two were narrow in scope and focused only on poisonings in dogs that were associated with seizures (Brauer et al., 2011; Zimmermann et al., 2010). The third publication (Allkämper et al., 2015) reported information on samples from animals (companion animals, livestock) submitted to a veterinary laboratory from 1998 to 2006 as well as results from a survey of the literature on animal poisonings (including publications in the German language) from 1998 to 2013.

Pesticides; in particular, insecticides and molluscicides, were implicated as the top cause of poisoning in dogs presenting to veterinary practices with seizures (Brauer et al., 2011; Zimmermann et al., 2010). The study by Brauer et al., 2011 also indicated that poisonings were a top cause of reactive seizures in canine cases reviewed; therefore, it is important to consider a toxic aetiology for dogs presenting to veterinary practices with seizures or seizure disorders. Results from the literature survey carried out by Allkämper et al., 2015 indicated that the following causative agents played an important role in poisonings: pesticides and medicinal products (both HMPs and VMPs) in dogs; permethrin, pesticides, plants, and household chemicals in cats; plants in horses; substances in feed in livestock (Allkämper et al., 2015). The majority of studies reviewed for the study were case reports/series; therefore, care should be taken when generalising these results as case reports are subject to reporting and selection bias (Nissen and Wynn, 2014). Additionally, as the laboratory surveyed in the same study by Allkämper et al., 2015 tested for a restricted number of substances (e.g., acetylcholinesterase inhibitors and coumarin derivatives), assessment and generalisation of results is limited.
Europe
For Europe, there was more available data for assessment in comparison to Germany. Below are comments on the species affected, the causative agents, and exposure patterns reported in reviewed publications.

Species
Twenty-three publications were identified from the literature review (Appendix, Table 2). Information on poisonings in cats and dogs was included in the majority of publications (91.3%; n=21); dogs, followed by cats, were the most commonly reported species involved in poisonings. Data on livestock was reported in 70% (n=16) of the publications, data on horses in 60.1% of publications (n=14), and data on exotics in 34.5% of publications (n=8); however, only two publications had a main focus on livestock (Guitart et al., 2010; Wang et al., 2007) and none on horses and exotics. Cattle were the most commonly reported livestock species with the exception of a recent publication on pesticide poisoning in Italy (Caloni et al., 2016); cases involving small ruminants (goats, sheep), pigs, poultry, and exotics (e.g., pet birds, small mammals, zoo animals) were rarely reported (Caloni et al., 2012a; Caloni et al., 2012b, 2016; Curti et al., 2009; Schediwy et al., 2015; Vandenbroucke et al., 2010).

A number of reasons could influence the substantial number of cases reported in cats and dogs in comparison to other species. When considering companion animals (including horses), it is logical that cats and dogs are the top reported species involved in poisonings as they are the most numerous companion animal species kept in Germany as well as the EU (European Pet Food Industry, 2015; Statista, 2017). In both Germany and the EU, although cats outnumber dogs considerably (European Pet Food Industry, 2015; Statista, 2017), a substantially higher percentage of reported poisonings involve dogs (Berny et al., 2010; Caloni et al., 2012a; Caloni et al., 2012b). One major reason proposed for this discrepancy is the inquisitive nature of dogs and their tendency to investigate with their mouths in comparison to cats (Gwaltney-Brant, 2012). However, it should also be considered that the number of cat cases may be underrepresented due to the disparity with regard to veterinary medical care for cats in comparison to dogs. Data from the American Veterinary Medical Association (AVMA) indicate that in 2011, 44.9% of cat owners did not take their cat to a vet in the last year compared to 18.7% of dog owners (American Veterinary Medical Association, 2013). Additionally, a study carried out by Bayer HealthCare in association with the American Association of Feline Practitioners found that 52% of cats in the US had not been taken to a veterinarian for an exam within the last year of when they were interviewed (BayerDVM, 2013). Reasons given for this low percentage included reported perceptions by owners that cats were self-sufficient and independent in comparison to dogs as well as the stress involved for owners and cats with respect to transporting cats to veterinary facilities. It was also stated that cat owners, in comparison to dog owners, might not be as educated on cat care, and therefore disease and poisoning risks as the majority of cats (59%) were acquired without intent (e.g., the adoption of lost and/or abandoned cats) and a substantial number of cats (69%) were obtained at no to low cost (BayerDVM, 2013). Furthermore, it is possible that owners may be more likely to notice contact their dog has with poisonous agents in comparison to free-ranging cats, which tend to roam without owner supervision.
With regard to the apparently small number of reported poisonings in livestock in comparison to the large number of livestock in Germany and EU (Eurostat, 2017), several factors should be taken into account. Firstly, the low number of reported incidents in livestock may not reflect the number of animals affected as livestock are generally kept in groups and therefore individual poisonings incidents are likely to involve multiple animals (Guitart et al., 2010). Secondly, for both financial as well as social reasons (e.g., livestock are generally not considered pets), it is possible that livestock owners and farmers are less likely to use PCs and veterinary services and that veterinarians will not submit samples to a laboratory for analysis unless a case is severe and could have major economic as well as potential public health consequences (Guitart et al., 2010; Thrusfield, 2013). This is further supported by the general pattern that more cattle cases are reported than sheep or goats, which are of lower economic value (Guitart et al., 2010; Thrusfield, 2013). Lastly, it is also possible that the low number of reported poisonings in livestock is due to the fact that many livestock (including poultry) are intensively managed (e.g., kept solely indoors), which protects them from exposure to many toxic agents other than those introduced in feed (Guitart et al., 2010).

Causative agents
Pesticides were consistently named as a top cause of poisoning in cats and dogs and frequently cited as a cause of poisoning in livestock (Berny et al., 2010; Caloni et al., 2012a; Caloni et al., 2016; Guitart et al., 2010). The main pesticides implicated varied among publications as well as species. However, pyrethroid- or pyrethrin-containing insecticides were consistently reported as a significant cause of acute poisoning in cats; rodenticides, in particular anticoagulant rodenticides, were consistently cited as a significant cause of acute poisoning in dogs (Amorena, 2004; Caloni et al., 2012a; Caloni et al., 2012b; Ferrantelli et al., 2012; Guitart et al., 2010; Keck et al., 2004; Modrá and Svobodá, 2009; Perez-Lopez, 2004; Schediwy et al., 2015).

HMPs and VMPs were also cited as a top cause of poisonings in cats and dogs (Allkämper et al., 2015; Berny et al., 2010; Caloni et al., 2014; Cortinovis et al., 2015a; Curti et al., 2009; Guiliano, 2004; Schediwy et al., 2015). Livestock poisonings as a result of HMPs and VMPs were rarely reported (Caloni et al., 2014; Guitart et al., 2010). The most commonly reported HMPs included nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and central nervous system drugs (e.g., antidepressants, sedatives); the most commonly reported VMPs included parasiticides (e.g., avermectins, permethrin/pyrethroids). For cases involving cats, misuse of veterinary ectoparasiticide products (e.g., spot-on preparations, in particular with permethrin) was responsible for the majority of reported cases (Modrá and Svobodá, 2009; Schediwy et al., 2015). Although a variety of parasiticides were cited in cases involving dogs, avermectin poisoning was frequently cited (Allkämper et al., 2015; Caloni et al., 2012a; Caloni et al., 2014; Modrá and Svobodá, 2009; Schediwy et al., 2015).
Plants were the top reported cause of poisoning in horses and named as a major cause of poisoning in cattle and small ruminants (e.g., goats, sheep) (Berny et al., 2010; Caloni et al., 2012a; Guitart et al., 2010; Modrá and Svobodá, 2009; Schediwy et al., 2015). Black locust (Robinia pseudoacacia), oleander (Nerium oleander), sycamore (Acer pseudoplatanus), tansy ragwort (Senecio jacobaea), and yew (Taxus baccata) were frequently reported for horse poisonings (Berny et al., 2010; Caloni et al., 2013; Curti et al., 2009; Modrá and Svobodá, 2009; Schediwy et al., 2015; Vandenbroucke et al., 2010). For cattle, bracken fern (Pteridium aquilinum), oak (Quercus sp.), ragwort (Senecio sp.) and yew (Taxus baccata) were commonly reported; for sheep, oak and rhododendron (Rhododendron sp.) were commonly reported (Curti et al., 2009; Guitart et al., 2010; Schediwy et al., 2015; Vandenbroucke et al., 2010). A variety of plants were implicated for goats including cherry laurel (Prunus laurocerasus) and rhododendron (Cortinovis and Caloni, 2015; Curti et al., 2009; Schediwy et al., 2015). Plant poisoning was also commonly reported in cats and dogs. A variety of plants were implicated including ficus (Ficus benjamina), hydrangea (Hydrangea sp.), lilies (Lilium sp.) (especially in cats), oleander, poinsettia (Euphorbia pulcherrima) rhododendron, ricinus (Ricinus communis) (dogs), and sago palm (Cycas revoluta) (Berny et al., 2010; Caloni et al., 2013; Curti et al., 2009; Schediwy et al., 2015; Vandenbroucke et al., 2010). Plant poisoning was also commonly reported in cats and dogs. A variety of plants were implicated including ficus (Ficus benjamina), hydrangea (Hydrangea sp.), lilies (Lilium sp.) (especially in cats), oleander, poinsettia (Euphorbia pulcherrima) rhododendron, ricinus (Ricinus communis) (dogs), and sago palm (Cycas revoluta) (Berny et al., 2010; Caloni et al., 2013; Curti et al., 2009; Schediwy et al., 2015; Vandenbroucke et al., 2010).

Other commonly reported causative agents included food/feed, heavy metals, household products, cannabis and nicotine, and bites/envenomations from insects or animals. (Curti et al., 2009; Schediwy et al., 2015; Vainionpää et al., 2012). Food was not cited as a top cause of poisoning in cats and dogs in the reviewed publications; however, it should be noted that certain food items (e.g., chocolate, grapes, onions) were reported as being among the top common causes of poisoning by the Veterinary Poisons Information Service (VPIS) PC in the United Kingdom (UK) (Veterinary Poisons Information Service, 2017) and the PC of the American Society for Protection of Cruelty to Animals (ASPCA) (American Society for Prevention of Cruelty to Animals, 2017). Incidents involving feed were more commonly reported in livestock and included improper usage of drugs and/or nutritional additives in feed as well as feed contaminated with industrial by-products and chemicals or pesticides (Caloni et al., 2012a; Guitart et al., 2010; Modrá and Svobodá, 2009; Vandenbroucke et al., 2010). For household products (e.g., cleaning and maintenance products), the majority of incidents involved cats and dogs (Caloni et al., 2012b; Curti et al., 2009; Guiliano, 2004; Keck et al., 2004; Schediwy et al., 2015; Vandenbroucke et al., 2010); for heavy metals (copper, lead) and industrial chemicals [e.g., dioxin, polychlorinated biphenyls (PCBs)], the majority of incidents involved livestock (Caloni et al., 2012b; Guitart et al., 2010; Modrá and Svobodá, 2009; Sharpe and Livesey, 2005; Vandenbroucke et al., 2010).

Poisoning patterns
The majority of reported poisonings from the publications reviewed were accidental, acute, involved oral exposure, and occurred in and around the home (Amorena, 2004; Berny et al., 2010; Caloni et al., 2012a; Guitart et al., 2010; Vandenbroucke et al., 2010). Only two publications included information regarding seasonal variations in poisonings (Amorena, 2004; Sharpe and Livesey, 2005). One reported a higher frequency of samples testing positive for pesticide poisoning from March to June as well as in September (Amorena, 2004). The second described a possible seasonal association for copper poisoning in sheep and ionophore toxicity in turkeys, with peaks occurring in March, August and November for sheep cases, and in November for turkey cases (Sharpe and Livesey, 2005).
3.1.2 An overview of data collected on poisonings in Germany

Findings from data collected on animal poisonings for this project were similar to publications reviewed from other European countries as well as the US (Berny et al., 2010; Buttke et al., 2012; Caloni et al., 2012a; Gwaltney-Brant, 2012; Vandenbroucke et al., 2010). Dogs and cats, followed by horses, were the most commonly reported species; poisonings in livestock and exotics were rarely reported. Medicinal products (HMPs and VMPs), pesticides, and plants were the top causes of poisonings; canine spot-on preparations containing permethrin in cats, anticoagulant rodenticides in dogs, and sycamore (Acer sp.) in horses were consistently implicated in severe cases. Permethrin in cats, anticoagulants in dogs, and sycamore in horses, were also cited as important causes of poisonings in a recent publication from Germany on animal poisonings (Allkämper et al., 2015).

The majority of reported poisonings were acute, accidental, and involved oral intake. Although there was a wide range of ages of animals involved in poisonings, the median age ranged from 1.5 to 3 years for all species and from 1.5 to 2.8 years for cats and dogs. This indicates, as other publications have, that there may be an increased risk of toxic exposures in younger animals; particularly younger cats and dogs (Berny et al., 2010; Buttke et al., 2012; Gwaltney-Brant, 2012). Seasonal patterns were seen with chocolate around Valentine’s Day and the Easter and winter holidays, insecticides and herbicides in the spring months, rodenticides in the fall months, and cyanobacteria and mushrooms in the late summer and fall months. The occurrence of seasonal patterns for chocolate and rodenticide poisoning has also been reported in other publications (Gwaltney-Brant, 2012). More details of the project findings are reported in Publication 1.

3.1.3 Data sources, collection, and reporting

Data sources, collection methods, and reporting practices influence the information available for assessment of poisonings. Therefore, when interpreting reported poisoning data, it is essential to consider the advantages, disadvantages, as well as inherent biases associated with available information. This includes assessment of the data sources, data quality, as well as data collection, documentation, assessment, and reporting practices.

Data sources

Data for this project was collected from multiple sources including PCs, two veterinary practices, a federal institute that is responsible for oversight of reported adverse events involving VMPs (BVL), and a toxicology laboratory. In addition, an announcement was published in several veterinary journals requesting for veterinarians to voluntarily report poisoning cases to the BfR (McFarland et al., 2015a, b, c). The reporting form is included in the Appendix.

The laboratory and PCs that were accessed for this project specifically collect data on animal poisonings for the purpose of regular assessment (e.g., yearly reports). Within Germany, there is no veterinary reference laboratory that exclusively tests samples from suspected animal poisoning cases as well as no harmonised protocol among different laboratories for the documentation and reporting of poisoning data. Laboratories also have different testing
protocols, equipment, as well as diagnostic capabilities, which can limit the number of agents able to be tested for as well as comparison of results between laboratories.

Although several German PCs use the same documentation system and method for recording information on animal inquiries, there is currently no standard method or computer system used by all PCs for the documentation of animal inquiries. In addition, the primary focus of the PCs in Germany is to provide advice for medical treatment of human toxic exposures. No financial support is provided for the documentation and advising of animal poisoning cases; as a result, the German PCs have limited time and resources to invest in the recording, assessment, and quality control of animal exposure inquiries.

As the purpose of the BVL is to handle reports of all adverse events involving VMPs, there was no specific protocol in place to document poisonings involving VMPs that met the definitions established by the project (e.g., off-label use of VMPs, excluding reported cases due to veterinary treatment). The same applies to the veterinary practices, as their primary purpose is to advise owners and treat animals presenting for examination; not to separately document poisonings.

Voluntary reports as a result of the announcement of the project in several German veterinary journals resulted in reporting of four incidents (total of seven poisoning cases). This is clearly a gross underestimation of the true occurrence of animal poisonings. Additional efforts including sending of announcements to veterinary practices, networking with stakeholders, and follow-up announcements in veterinary journals over many years would be required to possibly increase the number of voluntarily reported cases. Although reports of disease can be a valuable source of information, there is a general under-reporting of notifiable diseases in both the animal and human health sectors. Therefore, efforts to continue voluntary reporting or implement mandatory reporting would still likely result in an underestimation of the true incidence of animal poisonings (Maudlin et al., 2009). In light of this, the use of data based on mandatory reporting alone would not be sufficient; collection of data from other sources (e.g., laboratories, PCs, veterinary practices) would be still needed to enable a more comprehensive assessment of the occurrence of poisonings.

Of the data sources for this project, the PCs provided the most information in terms of numbers of exposures. They also are a major source of information on animal poisonings from other countries (Berny et al., 2010; Buttke et al., 2012; Caloni et al., 2012b; Schediwy et al., 2015; Vandenbroucke et al., 2010). Cases from the veterinary practices and reports of adverse events involving veterinary medicines, although less in number, provided valuable clinical information and allowed for thorough assessment of clinical effects, case severity, as well as outcomes. Laboratory results allowed for insight into confirmed poisoning cases and were particularly useful for the assessment of pesticide poisonings. However, sources of bias should be considered when interpreting as well as making conclusions regarding reported data as certain species, causative agents, and types of cases (e.g., severe cases) may be over or underrepresented. Publication 1 provides a discussion of as the advantages, disadvantages, and primary sources of bias for the different data sources for poisonings.
Data collection and reporting

Poisoning data can be collected prospectively or retrospectively. Prospective methods allow for standardisation of data collection and recording methods; therefore, data tends to be more complete and accurate. They can however be time consuming, expensive, and lead to bias when those involved in a study are aware that they are being observed or that the information they are collecting is being used for research purposes. Retrospective methods are generally cheaper and less time-consuming to carry out; however, data may be incomplete as well as in a non-standardised format due to inconsistent or varying recording methods (Nagurney et al., 2005). Additionally, the data abstraction process can lead to reduction of data reliability or reproducibility. If data are collected over a short time period either prospectively or retrospectively, bias may also occur due to the inability to capture seasonal differences or variations over time (Nagurney et al., 2005). For this project, data was retrospectively collected; therefore, disadvantages associated with retrospective collection of data should be taken into account when interpreting findings.

As each data source had different information available as well as reporting practices, data collected for this project was converted into a standardised format to enable analysis. The conversion of data from multiple data sources into a standardised format suitable for analysis can be both complex and time-consuming. Additionally, the collection of data that has been recorded for another purpose (e.g., data from veterinary practices) is challenging; solutions are required to make the best use of such secondary data for surveillance purposes (Wendt et al., 2015).

Currently, there are no reporting guidelines for descriptive studies on poisonings. As many studies reporting data on poisonings are descriptive (Berny et al., 2010; Buttke, 2011; Caloni et al., 2012a; Gwaltney-Brant, 2012), this is also a critical point to consider as the variation in published data on poisonings makes interpretation and comparison of results difficult. The use of standardised reporting guidelines would enhance the consistency, quality, and transparency of available information. It would also enable better appraisal and interpretation of data as well as methods used to document and assess poisonings (Thabane and Akhtar-Danesh, 2008).

Many publications reviewed for this project did not include information on methods used for the documentation and assessment of cases, which limits the reliability findings. Additionally, for the standardisation of collected data, it was necessary to classify collected information into categories (e.g., type of toxic agent). This allowed for a consistent summary of information across data sources. Although errors in these post hoc classifications cannot be completely excluded, it is assumed that these errors were rare.
3.2 Documentation and assessment of animal poisonings

There are numerous schemes for the documentation of adverse events involving poisonings in animals and humans (e.g., involving pesticides, HMPs, VMPs) (Environmental Protection Agency, 2016; World Health Organisation, 2017a, b). However, there are currently no publically available, standardised guidelines and/or schemes specifically designed for the documentation and assessment of poisonings in animals. This contrasts with poisonings in humans, for which the World Health Organisation (WHO) (World Health Organisation, 2017c) and European Union (EU) (European Council Resolution 90/C 329/03) both have general documentation guidelines.

Several factors unique to poisonings are necessary to consider and require standardised definitions to enable a systematic approach for documentation and assessment of reported cases:
- Route of exposure (e.g., oral, dermal, inhalational)
- Dose of exposure
- Duration of exposure (e.g., acute, subacute, chronic)
- Location of exposure
- Causative agent(s) involved
- Likelihood that an exposure occurred
- Likelihood that clinical effects (e.g., signs/symptoms) are related to the substances involved in the exposure
- Severity of exposure

Information on the route, dose, duration, and location of exposure enables assessment of exposure patterns in relation to particular causative agents. Assessment of the likelihood that an exposure occurred as well as the likelihood that clinical effects are related to the reported causative agent(s) enables assessment of the strength of the evidence that an exposure and outcome are related. Regarding the documentation of causative agents, there are numerous schemes for the classification of substances involved in poisonings. Some include all possible causative agents [e.g., Toxicological Category System (TDI-CSA, TKS)] (Klinitox, 2017) whereas others cover certain classes of agents such as biocides (BPR, Regulation (EU) 528/2012), cleaning and detergent agents (Regulation (EC) 1272/2008), and HMPs and VMPs (World Health Organisation, 2017a, b).

PCs and government health institutions that routinely record information on poisonings most likely document the factors discussed above. However, other institutions such as laboratories and veterinary practices, which are also valuable sources of data on poisonings, may not routinely record such data or have information in an easily obtainable format to enable timely analysis. Therefore, in addition to the use of standardised definitions and protocols for the documentation and assessment of poisonings, a key consideration for data harmonisation efforts includes how to best integrate data from disparate sources that have different reporting practices, purposes, structures, as well as information systems for the recording of data.
3.2.1 Documentation and assessment of animal poisonings in Germany

Major sources of information on poisonings in Germany are the BfR and eight PCs. Since 1990, when compulsory reporting of poisoning cases in humans was enacted within the framework of the German Chemicals Act (Chemikaliengesetz - Chem G), the BfR has been in charge of oversight of human poisoning incidents in Germany. Responsibilities of the BfR include recording and assessment of reported poisonings as well as management of a product database, from which toxicological information regarding the composition of individual commercial products can be obtained. Data on reported cases as well as product formulations is used for poisoning risk assessments and also shared with the eight PCs in Germany to assist their management of poisoning cases.

Both the BfR and PCs have their own methods and standardised definitions for the documentation and assessment of poisonings in humans. Although their primary focus is on human poisonings, both also document information on reported animal poisonings. However, as documentation methods were designed for human poisonings, there is a lack of standardised methods for recording of information specific to animals (e.g., animal type, species, breed). Additionally, the case severity assessment scheme used by the BfR and several of the PCs (the PSS) was not developed for the assessment of poisonings in animals.

3.2.2 Severity assessment of animal poisonings

Severity scoring schemes can be used for multiple purposes including assessment of a patient’s current status, guiding case management and therapy, assistance with prediction of outcomes (e.g., morbidity, mortality), identification of cases that warrant follow-up, and hazard and risk assessment (Casey et al., 1998; Hayes et al., 2010). A differentiated reporting of poisonings using severity scores (e.g., minor, moderate, severe) is also more informative than just reporting poisonings without any indication of severity. In veterinary medicine, although the use of clinical severity scoring schemes is increasing, they are much less widely adopted than in the field of human medicine (Hayes et al., 2010).

There are several challenges with regard to the creation of standardised schemes for the severity assessment of poisonings in animals. These include the following:

- The wide variety of animal species and breeds
- The large number of causative agents
- The range of clinical effects that can occur

Different animal species can have anatomical and/or physiological differences that preclude the use of a common scale or common parameters for severity assessment. For example, a heart rate of 200 beats per minute would be interpreted as within the normal range for a cat but as tachycardia for a dog (Smith et al., 2008). Additionally, for some species, there are breed specific characteristics that need to be kept in mind when assessing severity. Small breed dogs for example generally have higher resting heart rates than large dogs and greyhounds have on average higher red blood cell counts than other breeds; therefore, a higher normal range for parameters such as packed cell volume (PCV) and haemoglobin (Smith et al., 2008; Zaldívar-López et al., 2011).
Discussion

There are numerous causative agents that can be involved in isolation or combination in poisonings. Some such as anticoagulant rodenticides result in a restricted set of clinical effects and laboratory findings whereas others such as the plants (e.g., autumn crocus - *Colchicum autumnale*) can result in a wide spectrum of clinical effects and test findings (Means, 2001; Pet Poison Helpline, 2017). Therefore, a scheme that is suitable for all causative agents must be broad enough in scope to encompass a variety of clinical effects and findings. This hinders the use of a completely objective scale for all causative agents, as there are a number of clinical effects (e.g., neurological effects such as ataxia, tremor) for which there are no completely objective measures that can be used to assess severity. Additionally, the use of a completely objective scale would restrict severity assessment to cases that have detailed clinical data (e.g., vital signs, laboratory results) and substantially limit the number of cases that could be assessed. For the severity assessment of specific poisonous agents (e.g., anticoagulant rodenticide poisonings) or for specific clinical research purposes, the development of an objective scale may however be possible because more precise definitions of severity levels is feasible for a restricted, more specific set of clinical effects and laboratory findings.

*Comparison of two severity assessment schemes for poisonings in animals*

For human poisonings, several studies have compared the PSS with other schemes for specific poisonings (e.g., pesticide poisonings) (Akdur et al., 2010; Davies et al., 2008; Sam et al., 2009). However, only two studies (one published in Polish, one in conference proceedings) were found that evaluated the application of the PSS for the general severity assessment of poisonings (Achour et al., 2010; Pach et al., 1999) and no studies that specifically evaluated the NPDS medical outcome scheme. Further to this, there is no publically available information regarding the reliability of schemes used by veterinary-specific PCs for poisoning severity assessment.

A key finding of the project study evaluating and comparing the PSS and NPDS medical outcome schemes for the severity assessment of canine poisonings was that substantial variability between raters using either scheme to assess poisoning severity was found (see Appendix for an example of the schemes). When ratings between the schemes were compared, agreement ranged from poor to low-moderate depending on the groupings of raters compared. The finding of limited agreement between raters and the schemes is likely due to the lack of precise definitions for many clinical effects provided in both schemes, which results in subjective scoring of severity from raters. Subjective scoring schemes are generally less reliable than objective schemes and can show considerable variability in both intra- and interrater scores (Ridley, 1998). A number of other factors can also influence case ratings including case details and clinical information provided, rater experience, previous or recent case exposure, training, as well as language if the scoring system being used is not in the native language of the rater (Hayes et al., 2010).
As variability in scoring may occur due to lack of precise definitions for clinical effects provided in subjective scoring schemes such as the PSS and NPDS medical outcome scheme, identification of commonly reported clinical effects for which scoring may be particularly variable is important as it could allow for determination of clinical effects for which more detailed definitions may be needed to increase the accuracy of ratings. For example, a commonly reported clinical effect in animal poisonings is vomiting (Caloni et al., 2014; Caloni et al., 2012b; Campbell, 1998; Cortinovis et al., 2015b). However, determination of what constitutes minor, moderate, and severe vomiting is largely subjective. Therefore, establishment of definitions for each severity category (e.g., minor vomiting involves one to three episodes within 24 hours) may assist with decreasing variability of scoring for vomiting. Additionally, definition of species-specific reference ranges for physical findings (e.g., heart rate) and criteria for interpretation of laboratory and diagnostic tests should also be considered as it could also decrease variability of case severity ratings.

3.3 Toxicology and One Health: an overview

Key benefits of a One Health approach to poisonings in both the human and veterinary sectors are similar to those for infectious diseases. They include improved prediction, control and prevention of disease as well as understanding of risk factors and possible outcomes (Buttke, 2011; Wendt et al., 2015). For poisonings, the following areas have been identified as important for the identification of common health hazards in animals and humans: common environments shared between animals and humans, common food and water sources, and consumption of contaminated animal products (Buttke, 2011; National Research Council, 1997; Reif, 2011). Additionally, as medicinal products (both HMPs and VMPs) are consistently named as a top cause of poisoning, particularly in companion animals, knowledge-sharing between the human and veterinary sectors regarding poisonings due to medicines has the potential to benefit both animal and human health (Caloni et al., 2014; Cortinovis et al., 2015b; Fitzgerald et al., 2006; Schmidt, 2009).

Common environments

Animals and humans often share a common environment and therefore have the potential to be exposed to the same toxic agents. The pattern of sharing varies and is influenced by cultural practices and attitudes towards animals, geographical location (e.g., rural vs. urban), as well occupation. There are numerous examples of companion animals and livestock serving as indicators of exposure to environmental hazards such as air pollution, algal blooms, heavy metals (e.g., lead), industrial chemicals (e.g., brominated flame retardants (BFRs), PCBs), and pesticides (Buttke, 2011; Dye et al., 2007; Reif, 2011; Schmidt, 2009). Further to this, as companion animals often very closely share environments with humans, they have the potential to additionally act as indicators for exposure to substances in indoor environments (e.g., BFRs in house dust, lead in paint) as well as indicators for risks posed by household products (e.g., cleaning agents, laundry detergents) (Dye et al., 2007; Hungerford et al., 1995; Schmidt, 2009).
Common food and water sources
Shared food and water sources can also be a common route of exposure to toxic agents for animals and humans. The 2007 melamine pet feed adulteration scandal that occurred in the US is one of the most well-known examples of a feed-related event that served as a warning of possible risks in the human food chain (Gossner et al., 2009). During the outbreak, renal failure and death occurred in thousands of pet cats and dogs that consumed pet feed with melamine-contaminated wheat gluten and rice protein concentrate imported from China. Numerous brands of pet foods were recalled and it was also brought to light that chickens and pigs intended for human consumption had also been exposed to feed adulterated with melamine (Food and Drug Administration, 2016). One year later, in 2008, another outbreak associated with melamine occurred in infants in China that were fed formula contaminated with melamine (World Health Organisation, 2008). The occurrence of this outbreak, just one year after the melamine-associated outbreak in animals, highlighted that feed contamination incidents in animals can potentially act as early indicators for risks in human food and that joint, multi-sectoral investigation of such events could act to safeguard both animal and human health.

Further examples of contamination of food sources common to animals and humans include the presence of aflatoxin or pyrrolizidine alkaloids (PAs) in feed/food. Aflatoxin is a widespread safety hazard in grains including maize, which is widely cultivated throughout the world. As chickens are often fed maize that is intended for human consumption and are also very susceptible to aflatoxicosis, the occurrence of signs in chickens characteristic of aflatoxicosis can act as an indicator for human exposure if a common food source is being consumed (Buttke, 2011). This was the case for an outbreak of jaundice in Kenya in 2004, for which deaths in animals fed maize that was also consumed by humans helped guide investigators to identify aflatoxicosis as the primary differential diagnosis (Centers for Disease Control, 2004). Another example of the occurrence of similar signs and symptoms in animals and humans leading to implication of a common food source includes outbreaks in Afghanistan and Ethiopia associated with consumption of vegetation containing PAs (Buttke, 2011; Molyneux et al., 2011). Although occurrence of illness in humans due to exposure to PAs has previously been associated with developing countries, recent detection of PAs in food, herbal teas, and honey in developed countries including Germany has brought it to attention as a public health issue and illustrates the continued need for collaboration and information exchange between different health and regulatory sectors (Federal Institute of Risk Assessment, 2017; Molyneux et al., 2011).

Contaminated animal products
A major focus of One Health has been on food safety; particularly illness in humans due to the consumption of contaminated animal products (Buttke, 2011; Wendt et al., 2015). Food animals are exposed to numerous agents that can accumulate in their bodies and therefore be subsequently ingested by humans. Over the past decades, a number of large-scale events involving exposure of humans to contaminated animal products (e.g. meat and milk) have occurred. These include exposure of humans to chicken meat and eggs containing dioxin in Belgium and Germany in 1999 and 2011 respectively, the discovery (in the 1970s) that dairy cattle from thousands of farms in the US had consumed feed contaminated with polychlorinated biphenyls (PBBs), and the occurrence of an outbreak of liver disease in Ethiopia in 2007 that has been linked to possible consumption of milk and organs from
animals that showed signs indicative of PA intoxication (Bernard et al., 2002; Kupferschmidt, 2011; Stewart and Steenkamp, 2001). The occurrence of all of these events highlights that the contamination of animal products is a global issue that can have large-scale consequences and therefore merits a cohesive, One Health approach for the recognition, prevention and control of food/feed associated outbreaks.

3.3.1 One Health and sentinel surveillance

In order to cover the topic of One Health in relation to toxicology, two important concepts need to be addressed: 1) surveillance of poisonings; 2) the use of animal sentinels for surveillance of poisonings. Although the majority of One Health as well as veterinary surveillance efforts have been focussed on infectious diseases, many of the concepts, definitions, and approaches for surveillance of infectious diseases can be applied to surveillance of poisonings. The World Health Organisation defines surveillance as “the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice” (World Health Organisation, 2017d). Aims of surveillance include identification of the absence, presence, and/or changes in disease in animal and/or human populations. When using sentinels for surveillance, efforts are focussed on the identification of diseases in specific subpopulations (e.g., cats, dogs, livestock) in order to enhance detection of health-related events in a specific population(s). Sentinel surveillance can offer a more targeted, cost-effective method for disease detection and is currently an underused approach for surveillance and risk assessment (Halliday et al., 2007; Rabinowitz et al., 2005).

In the veterinary and clinical scientific literature, the term sentinel is widely used and is frequently defined based on the context in which it is described (Halliday et al., 2007). However, a generally applicable definition of an animal sentinel is an individual animal or population of animals that can serve as an indicator for exposure to substances and/or diseases. For poisonings, sentinels can be used for a number of purposes including the following:
- Detection of the presence of toxic substances
- To determine changes in the prevalence/incidence of poisonings
- Early detection of poisonings, including outbreaks
- To assess the geographic distribution of poisonings
- Determination of risk factors for poisonings
- Assessment of possible outcomes from poisonings
(Buttke, 2011; Halliday et al., 2007; National Research Council, 1997; Rabinowitz et al., 2005; Schmidt, 2009)

General features of an animal sentinel include the following: 1) that the animal is susceptible to the exposure of interest; 2) exposure results in a measurable response (e.g., clinical and/or diagnostic); 3) there is a spatiotemporal relationship between the sentinel and target population (Halliday et al., 2007; Rabinowitz et al., 2005; Schmidt, 2009). Further to serving an indicator function, animal sentinels can be classified according to multiple criteria including the following: 1) what they are being monitored for (e.g., exposure, effect, or both); 2) the type of animals being monitored; 3) if they are intentional or incidental sentinels. Intentional sentinel animals are deliberately placed in an environment (e.g., experimental
animals) or observed in their natural environment whereas incidental sentinels are not purposely placed or observed for a sentinel function (Halliday et al., 2007; Schmidt, 2009). A classic example of an intentional sentinel for toxic exposures is the use of canaries in coal mines in the early twentieth century to enable detection of exposure to toxic gases. An example of an incidental sentinel is diagnosis of lead poisoning in dogs leading to discovery of lead toxicity in children living in the same household (Dowsett and Shannon, 1994).

As illustrated with the classic example of the use of canaries in coal mines, many animal species are more sensitive than humans to certain toxicants and therefore can serve as early, sensitive indicators of disease. Many species also have a shorter lifespan and therefore shorter latency period for the development of certain conditions as a result of exposure to toxins. Select examples of this include the association between exposure to asbestos and the development of mesothelioma in dogs, the potential role of pesticides in the development of bladder cancer in dogs, and investigations into possible associations between hyperthyroidism in cats and exposure to BFRs (Dye et al., 2007; Glickman et al., 2004; Reif, 2011). Furthermore, depending on the situation, animals may offer the advantage of being free from a number of concurrent exposures such as alcohol consumption, cigarette smoking, diet, and occupation that act as confounders in human studies (Reif, 2011; Schmidt, 2009).

### 3.3.2 Implementation of One Health approaches and sentinel surveillance

There are a number of barriers to implementation of both One Health and animal sentinel surveillance approaches for poisonings worldwide as well as in Germany. These include a lack of standardised and harmonised procedures for the documentation and assessment of poisonings in animals, segregation between professionals (e.g., human, veterinary, toxicology), separation of data sources, and gaps in knowledge and guidelines regarding linking animal and human health data (Rabinowitz et al., 2010; Scotch et al., 2009). Another challenge for the surveillance of poisonings is that toxicological confirmation of poisoning cases is rarely carried out and can be cost prohibitive (Russo et al., 2013). Additionally, assessment of the likelihood that an exposure occurred as well as the probability that an exposure resulted in reported clinical effects also needs to be considered for the surveillance of toxic exposures, particularly from data sources (e.g., veterinary practices) that do not routinely record information that allows these factors to be easily determined (Rabinowitz et al., 2005).

Standardised and harmonised procedures for the assessment and documentation of animal poisonings are a cornerstone for surveillance initiatives as well as integration of data between different sources. While many individual data sources (e.g., government health institutions, laboratories, PCs, veterinary practices) may have their own methods for documentation and assessment of poisonings, a major challenge remains with regard to how to integrate disparate data from multiple sources. A recent feasibility study evaluating the use of disparate data for One Health surveillance of zoonoses in Germany found that missing data, missing pathogen information, and a lack of timely reporting posed major obstacles to data integration (Wendt et al., 2016). Additionally, as data can be documented in different formats (e.g., paper, electronic, different computer systems/databases) and has often been recorded or collected for a different purpose (e.g., recording of case notes at veterinary practices), another challenge is
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how to best use secondary data for surveillance (Rabinowitz et al., 2010; Scotch et al., 2009; Wendt et al., 2016).

Within Germany as well as worldwide, surveillance for animals and humans is typically performed separately; contact between human and veterinary agencies is often limited (Wendt et al., 2016). Studies on animal sentinels and sentinel surveillance may also not be routinely read by health professionals and researchers as they are published in a wide variety of journals that may not be frequently accessed (Rabinowitz et al., 2005). As a result of these factors, data exchange and sharing between animal and human health professionals and organisations is limited. Although there is awareness of the benefits of increased collaboration, segregation of the professions as well as data remains a substantial barrier for One Health surveillance approaches (Rabinowitz et al., 2010; Wendt et al., 2016; Wendt et al., 2015). In the publication by Rabinowitz et al., 2010, it is discussed that there is a tendency among health professionals to view animals in terms of the risk they pose to human health rather than to consider that animals and humans share risks and that linkage of data between both disciplines can benefit both animal and human health. This point illustrates the need for an increased understanding among all health sectors of the mutual benefits of One Health and sentinel surveillance approaches for addressing health problems in animals as well as humans.

Another barrier for One Health and sentinel surveillance approaches is the gap in knowledge and understanding of how to link animal and human data (Rabinowitz et al., 2005; Rabinowitz et al., 2010; Scotch et al., 2009). Clear linkages to human health are frequently absent from studies on animal sentinels. In particular, there is limited use of data on animals to quantitatively predict risks in humans as well as limited understanding on how to extrapolate data from animals to humans. Furthermore, there are no clear guidelines or protocols for integrating animal and human health data as well as how to use sentinel data for public health decision making (Scotch et al., 2009). This is an essential point as the use of One Health and sentinel surveillance approaches are only good if there are protocols in place for the timely use of sentinel information for the prevention and/or mitigation of poisoning risks (Halliday et al., 2007; Wendt et al., 2015).

3.3.3 One Health in Germany

The lack of well-established surveillance initiatives for poisonings in animals is a major obstacle for the establishment of One Health approaches in Germany. In contrast to human poisonings, there is no requirement for the reporting of animal poisonings in Germany. This further limits data available for integration and comparison with human data. Additionally, the lack of standardised and harmonised methods for the assessment and documentation of poisonings impedes collection and integration of data from multiple sources for surveillance purposes. Findings from the project highlight this issue as considerable time was required to standardise and harmonise collected data to enable analysis. Based on this, data on animal poisonings in Germany is currently not suitable for One Health and/or sentinel surveillance as it is not readily available in a standardised, accessible form for timely evaluation and use. However, there is future potential for implementation of One Health and sentinel surveillance approaches due to efforts by the BfR and Society for Clinical Toxicology (GfKT) to develop a national monitoring system for human poisonings in Germany (Desel, 2014). Establishment
of a national monitoring system for poisonings in humans could pave the way for monitoring initiatives for animal poisonings as well as the integration of animal and human data.

From the literature survey on the use of animal as sentinels in Germany, numerous publications were identified that investigated or referred to the use of animals, particularly wildlife, as sentinels for infectious diseases (Achazi et al., 2011; Imhoff et al., 2015; Ziegler et al., 2010). However, only two publications were found that examined the potential use of animals as sentinels for toxic exposures. Both focussed on wildlife (one on roe deer, one on grey seals) as indicators for exposure to environmental pollutants (Kierdorf and Kierdorf, 2001; Lehnert et al., 2014). This finding indicates that initiatives involving animal sentinel surveillance for toxic exposures are currently not widespread in Germany, especially for companion animal and livestock species. Nevertheless, as stated before, efforts to develop a national monitoring system for poisonings may provide future opportunities for the establishment and use of sentinel surveillance for poisonings in Germany.

3.3.4 Needs for a One Health approach to animal poisonings

Key issues for moving forward with One Health and sentinel surveillance approaches include improving interdisciplinary collaborations, increasing understanding of how to link animal and human data to predict risks and outcomes in both populations, and creation of practical and sustainable options for the linkage and use of surveillance data for poisonings. To facilitate data exchange and integration for One Health efforts in the area of toxicology, the following are necessary to consider:

- The use of standardised methods for the documentation and assessment of poisonings
- Establishment of transparent and sustainable data exchange initiatives within and between the animal and human health sectors
- Establishment of protocols for the incorporation and linkage of animal and human data
- Creation of practical solutions for the technical linkage of data from multiple sources
- The use of precise questions and well-defined goals for surveillance and research efforts
- The development of more economical testing methods for toxic exposures
- Collaboration with government health institutions, laboratories, PCs, and veterinary practices for the surveillance of animal poisonings
4 Conclusion

This project provided a first systematic account of animal poisonings in Germany from multiple data sources and allows for comparison of findings to other European countries. It also provided a first formal assessment of two schemes, the PSS and NPDS medical outcome scheme, for the severity assessment of poisonings in animals. In addition, results from the project as well as a survey of the literature were used to assess the application of the One Health concept to toxicology, with an emphasis on the use of animals as sentinels for poisonings in humans.

Results from the data collected on poisonings were largely similar to reports from other European countries. However, variation in the most commonly reported species, causative agents, and patterns of case severity was seen for the different data sources. Therefore, when evaluating animal poisoning data, it is essential to consider the strengths, weaknesses, and biases associated with reported data. Additionally, due to a lack of standardised protocols and definitions for the documentation, assessment, and reporting of poisoning cases, care should be taken when comparing results to other countries.

Considerable variability between raters using either the PSS or the NPDS scheme for the severity assessment of canine poisonings was found and many factors were identified that could influence the variability of poisoning severity assessment. The results indicate that the PSS and NPDS schemes, which were originally developed for the assessment of poisonings in humans, may be applicable for use in animals. However, further efforts are needed to improve the consistency of ratings. Furthermore, the subjective nature of both schemes and the absence of a gold standard scheme by which to compare ratings pose a challenge with regard to their evaluation for the severity assessment of animal exposures.

Through this project, a number of barriers to the implementation of One Health and sentinel surveillance methods in Germany were identified. It was also concluded that data on animal poisonings in Germany is currently not suitable for One Health and/or sentinel surveillance and can only be used on a haphazard basis to inform human health as it is not readily available in a standardised, accessible form for timely evaluation and use. To realise the potential of One Health and animal sentinel surveillance strategies, the following key needs were identified: harmonised and standardised documentation methods, improved interdisciplinary collaborations and communication between different health sectors, practical and sustainable options for sharing data, and guidelines regarding the use of animal health data to inform human health interventions.

This project has highlighted the need for monitoring initiatives as well as standardised and harmonised methods for the documentation and assessment of poisonings in Germany. Implementation of approaches to systematically collect, document, assess, and integrate poisoning data has the potential to provide a more consistent and comprehensive overview of poisonings. In addition, the adaption of standardised and harmonised methods would facilitate comparison of data as well as enable the availability of larger datasets for assessment of poisoning trends and risks.
5 Summary

Sarah McFarland (2017)
Assessment of animal poisonings in Germany and severity scoring schemes:
Needs for a One Health approach

Introduction: Currently there is a lack of comprehensive information regarding the occurrence of poisonings in animals in Germany as well as no publically available, standardised protocol for the assessment of clinical severity. The latter is necessary for harmonised reporting of poisonings as cases can cover a range of clinical severities from mild to fatal. There is also a need for the exploration and development of One Health and sentinel surveillance approaches in the area of toxicology. The two main objectives of this project were therefore to systematically collect, assess, and analyse information on the occurrence of animal poisonings (excluding wildlife) in Germany and to evaluate and compare two schemes for the severity assessment of animal poisonings. A further aim was to assess the application of the One Health concept to toxicology, with a particular emphasis on the use of animals as sentinels for toxic exposures and poisonings in humans.

Methods: A review of the literature was carried out for Germany and Europe to identify publications on the occurrence of animal poisonings as well as data sources for the reporting of poisonings. Data on animal exposure calls to German Poisons Centres (PCs), poisoning cases presenting to the University of Veterinary Medicine, Hannover (TiHo) Small Animal and Equine Clinics, cases involving off-label use of veterinary medicinal products (VMPs) reported to the Federal Office of Consumer Protection and Food Safety (BVL), and toxicological submissions to the Institute of Pharmacology, Toxicology, and Pharmacy, Faculty of Veterinary Medicine, Ludwig-Maximilians-University, Munich (IPTP, LMU) were retrospectively collected and analysed with descriptive statistics. The data from these sources was not publicly available and was accessed as part of the project as well as converted into a standardised format to enable analysis.

Agreement between raters using the Poisoning Severity Score (PSS) and the National Poison Data System (NPDS) medical outcome scheme for severity assessment of canine exposures reported to a multistate PC in the US was assessed using Light’s kappa (K). Agreement between the schemes was also evaluated and issues regarding use of the schemes for the severity assessment of animal poisonings were determined. A survey of the literature and assessment of data collected for the project was also carried out to identify points to consider for the use of One Health and sentinel surveillance approaches in the area of toxicology.

Results and discussion: Although a variation in poisoning patterns was seen, findings from data collected for this project were similar to reports from other European countries and the United States (US). Dogs and cats, followed by horses were the most commonly reported species; medicinal products (both human and veterinary), pesticides, and plants were consistently reported as top causes of poisonings. The majority of poisonings were acute, accidental, and involved oral intake; for severe cases, canine spot-on preparations containing permethrin in cats, anticoagulant rodenticides in dogs, and sycamore (Acer sp.) in horses played an important role. Appraisal of the literature resulted in the identification of four distinct data sources for animal poisonings: PCs, veterinary practices, laboratories, and
government public health institutions. Advantages and disadvantages were associated with each data source; bias was found to be an important consideration when evaluating poisoning data.

Considerable variability between raters using either the PSS or the NPDS schemes for severity assessment of canine poisonings was found (PSS: $\kappa$ 0.31; 95% CI 0.19, 0.43; NPDS: $\kappa$ 0.34; 95% CI 0.22, 0.44). When the schemes were compared, agreement ranged from poor to low-moderate, depending on the sets of raters evaluated ($\kappa$ -0.40; 95% CI -0.50, -0.30; $\kappa$ 0.05; 95% CI -0.08, 0.16; $\kappa$ 0.42; 95% CI 0.21, 0.60). Many factors were identified that could influence poisoning severity assessment including whether a scheme is objective or subjective, case details and clinical information available, as well as rater experience and background.

A number of barriers to the implementation of One Health and animal sentinel surveillance approaches for poisonings in animals in Germany were identified. These include a lack of standardised documentation and assessment protocols, a lack of well-established surveillance initiatives, segregation between health professionals, separation of data sources, and gaps in knowledge and guidelines regarding linking animal and human health data. Key issues for moving forward include the use of harmonised and standardised documentation and assessment methods, improved interdisciplinary collaborations, and creation of practical and sustainable options for data exchange within and between the animal and human health sectors. Additionally, in the absence of a systematic system for the collection and reporting of poisonings, the identification of exposure scenarios or poisoning risks in animals that can be used to inform human health may only be able to be utilised on a haphazard basis.

**Conclusion:** This project provided a systematic account of the occurrence of animal poisonings in Germany and allowed for comparison of results to other European countries. It also indicated that the PSS and NPDS medical outcome schemes may be applicable for the assessment of poisoning severity in animals and that further efforts are required to improve the consistency of ratings. The need for standardised approaches for the collection, assessment, and integration of poisoning data as well as One Health and sentinel surveillance approaches in the area of toxicology in Germany was identified and could contribute to the prediction, prevention and control of poisonings in animals and humans.
6 Zusammenfassung

Sarah McFarland (2017)
Bewertungen von Tiervergiftungen in Deutschland und deren Schweregrad:
Anforderungen für einen One-Health-Ansatz


Methoden: Eine Analyse des aktuellen Forschungsstandes für Deutschland und Europa wurde durchgeführt, mit dem Ziel, Veröffentlichungen zum Vorkommen von Vergiftungen bei Tieren sowie Datenquellen für die Berichterstattung über Vergiftungen zu identifizieren. Rückblickend gesammelt und mit Hilfe von deskriptiven Statistiken analysiert wurden Daten zu Anrufen bezüglich Expositionen bei Tieren an deutsche Giftinformationszentren; Vergiftungsfälle der Kliniken für Kleintiere bzw. Pferde der Tierärztlichen Hochschule Hannover (TiHo); Fälle von Off-Label-Use von Tierarzneimitteln, die dem Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) gemeldet wurden, sowie Proben, die dem Institut für Pharmakologie, Toxikologie und Pharmazie der Ludwig-Maximilians-Universität in München (IPTP, LMU) zur toxikologischen Analyse eingesandt wurden. Die Daten aus diesen Quellen waren nicht öffentlich zugänglich und mussten im Rahmen des Projektes gesammelt und strukturiert werden, um eine Analyse zu ermöglichen.


Ergebnisse und Diskussion: Obwohl Unterschiede im Vergiftungsmuster zu erkennen waren, decken sich die Forschungsergebnisse dieses, auf deutschen Daten beruhenden

Bei Bewertern, die entweder die PSS- oder die NPDS-Schemen anwendeten, wurde eine erhebliche Variabilität festgestellt (PSS: K 0.31; 95% CI 0.19, 0.43; NPDS: K 0.34; 95% CI 0.22, 0.44). Ein Vergleich der Schemata ergab, dass der Grad der Übereinstimmung zwischen gering bis niedrig-moderat und abhängig von den beurteilten Bewertern war (K -0.40; 95% CI -0.50, -0.30; K 0.05; 95% CI -0.08, 0.16; K 0.42; 95% CI 0.21, 0.60). Es wurden viele Faktoren identifiziert, die auf die Beurteilung der Schwere der Vergiftung Einfluss haben könnten, einschließlich der Objektivität bzw. Subjektivität eines Schemas, Falleinzelheiten und verfügbare klinische Information sowie die Erfahrung der Bewerter und deren Hintergrund.


References


Caloni, F., Cortinovis, C., Rivolta, M., Davanzo, F., 2012b. Animal poisoning in Italy: 10 years of epidemiological data from the Poison Control Centre of Milan. The Veterinary Record 170, 415.


References


Pach, J., Persson, H., Sancewicz-Pach, K., Groszek, B., 1999. Comparison between the poisoning severity score and specific grading scales used at the Department of Clinical Toxicology in Krakow. Przeglad lekarski 56, 401-408.


Appendix

Literature review: Europe and Germany

Inclusion criteria:
- Studies in English and/or German from 1994 to 2016 for Germany and from 2004 to 2016 for Europe
- Studies providing information on the occurrence of poisoning in companion animals (including horses) and/or livestock (pigs, poultry, ruminants) over a time frame greater than one year
- Studies focussing on one or more major substance category (e.g., medicinal products, pesticides, plants)

Exclusion criteria:
- Studies focussing only on bacterial toxins (e.g., clostridial toxins, *Escherichia coli*) and/or fungal toxins (e.g., aflatoxin)
- Case reports and/or series
- Experimental studies
- Studies focussing only on the treatment of poisoning cases
- Studies providing only background information, clinical information, and/or case management advice regarding poisonings
- Studies focussing only on intentional poisonings
Table 1. Publications from literature review of animal poisonings in Germany, 1994 to 2016

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Time frame</th>
<th>Study type</th>
<th>Data source(s)</th>
<th>Species</th>
<th>Causative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allkämper et al., 2015</td>
<td>Germany</td>
<td>1998 – 2006</td>
<td>R, Rev</td>
<td>La, Lit</td>
<td>C, D, E, L</td>
<td>Pe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1998 – 2015*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brauer et al., 2011</td>
<td>Hannover</td>
<td>2004 – 2008</td>
<td>R</td>
<td>V</td>
<td>D</td>
<td>M</td>
</tr>
<tr>
<td>Meiser H., 2005</td>
<td>Munich</td>
<td>1996 – 2003</td>
<td>NAD</td>
<td>La</td>
<td>C, D, E, L, W</td>
<td>A</td>
</tr>
<tr>
<td>Schrader et al., 2001</td>
<td>Northeast</td>
<td>NAD</td>
<td>NAD</td>
<td>V</td>
<td>L (r)</td>
<td>Pl</td>
</tr>
<tr>
<td>Thiemann &amp; Kowalewski,</td>
<td>Cottbus</td>
<td>1987 – 1992</td>
<td>NAD</td>
<td>G</td>
<td>C, D, E, L, W</td>
<td>M</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Völker &amp; Scherkl, 2001</td>
<td>Northeast</td>
<td>NAD</td>
<td>NAD</td>
<td>V</td>
<td>L (p)</td>
<td>M</td>
</tr>
<tr>
<td>Völker et al., 2002</td>
<td>Northeast</td>
<td>NAD</td>
<td>NAD</td>
<td>V</td>
<td>L (r)</td>
<td>M</td>
</tr>
<tr>
<td>Zimmerman et al., 2010</td>
<td>Munich</td>
<td>2002 – 2009</td>
<td>R</td>
<td>V</td>
<td>D</td>
<td>M^</td>
</tr>
</tbody>
</table>

*1998 – 2006, time frame for data collection; 1998 to 2015 time frame for literature review; ^Causative agents for seizure disorders
NAD = not able to be determined
Study type: P = Prospective, R = retrospective, Rev = review
Data source(s): G = government health institution, La = laboratory, Lit = literature, PC = Poison Centres, V = veterinary practices
Species: C = cats, D = dogs, E = exotics, H = horses, L = livestock, W = wildlife, p = pig, r = ruminant
Exotics include ferrets, small mammals (e.g., rabbits, rodents) amphibians/reptiles, pet birds, zoo animals; Livestock includes cattle, goats, sheep, pigs, poultry
- Causative agents: A = anticoagulants, M = multiple, Pe = Pesticides, Pl = plants
Table 2. Publications from literature review of animal poisonings in Europe, 2004 to 2016

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Time frame</th>
<th>Study type</th>
<th>Data source(s)</th>
<th>Species</th>
<th>Causative agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allkämper et al., 2015</td>
<td>EU, Other</td>
<td>1998 – 2015</td>
<td>R, Rev</td>
<td>La, PC, V</td>
<td>C, D, E, H, L, W</td>
<td>M</td>
</tr>
<tr>
<td>Amorena et al., 2004</td>
<td>IT</td>
<td>1999 – 2003</td>
<td>P, R</td>
<td>La, PC, V</td>
<td>C, D, E, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Berny et al., 2010</td>
<td>EU</td>
<td>NAD</td>
<td>R</td>
<td>La, PC, V</td>
<td>C, D, H</td>
<td>M</td>
</tr>
<tr>
<td>Caloni et al., 2012a</td>
<td>EU</td>
<td>NAD</td>
<td>Rev</td>
<td>Lit</td>
<td>C, D, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Caloni et al., 2012b</td>
<td>IT</td>
<td>2000 – 2010</td>
<td>P</td>
<td>PC</td>
<td>C, D, E, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Caloni et al., 2013</td>
<td>IT</td>
<td>2000 – 2011</td>
<td>R</td>
<td>PC</td>
<td>C, D, E, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Caloni et al., 2014</td>
<td>IT</td>
<td>2006 – 2012</td>
<td>R</td>
<td>PC</td>
<td>C, D</td>
<td>Me (h,v)</td>
</tr>
<tr>
<td>Caloni et al., 2015</td>
<td>IT</td>
<td>2011 – 2013</td>
<td>P (c)</td>
<td>PC</td>
<td>C, D</td>
<td>M</td>
</tr>
<tr>
<td>Caloni et al., 2016</td>
<td>IT</td>
<td>2011 – 2013</td>
<td>R</td>
<td>PC</td>
<td>C, D, H, L</td>
<td>Pe</td>
</tr>
<tr>
<td>Cortonovis &amp; Caloni, 2013</td>
<td>EU</td>
<td>NAD</td>
<td>Rev</td>
<td>PC</td>
<td>C, D, H, L</td>
<td>Pl</td>
</tr>
<tr>
<td>Cortonovis et al., 2015</td>
<td>EU, Other</td>
<td>NAD</td>
<td>Rev</td>
<td>Lit</td>
<td>C, D</td>
<td>Me (h)</td>
</tr>
<tr>
<td>Curti et al., 2009</td>
<td>CH</td>
<td>1997 – 2006</td>
<td>R</td>
<td>PC</td>
<td>C, D, E, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Ferrantelli et al., 2012</td>
<td>IT</td>
<td>2010 – 2011</td>
<td>P (c)</td>
<td>La</td>
<td>D</td>
<td>Pe</td>
</tr>
<tr>
<td>Gutart et al., 2010</td>
<td>EU</td>
<td>NAD</td>
<td>Rev</td>
<td>Lit</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>Modrá &amp; Svobodá, 2009</td>
<td>CZ</td>
<td>NAD</td>
<td>NAD</td>
<td>NAD</td>
<td>C, D, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Perez-Lopez et al., 2004</td>
<td>ES</td>
<td>2001 – 2002</td>
<td>NAD</td>
<td>La, PC</td>
<td>C, D, L</td>
<td>M</td>
</tr>
<tr>
<td>Schediwy et al., 2015</td>
<td>CH</td>
<td>2003 – 2012</td>
<td>Re</td>
<td>PC</td>
<td>C, D, E, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Vandenbroucke et al., 2010</td>
<td>BE</td>
<td>1997 – 2009</td>
<td>NA</td>
<td>La, PC</td>
<td>C, D, H, L</td>
<td>M</td>
</tr>
<tr>
<td>Vainionpää et al., 2012</td>
<td>FI</td>
<td>2009 – 2010</td>
<td>Re (c)</td>
<td>V</td>
<td>C, D, E</td>
<td>M</td>
</tr>
<tr>
<td>Wang et al., 2007</td>
<td>AT</td>
<td>1999 – 2004</td>
<td>Re</td>
<td>La</td>
<td>C, D, E, H, L</td>
<td>Pe</td>
</tr>
</tbody>
</table>

Note: Refer to Table 1 for abbreviation descriptions
Country: Other = outside of the EU; Study type: (c) = conference proceedings; Causative agents: h = human; v = veterinary
## Mitteilung bei Tiervergiftungen

*Zusendung von Mitteilungen bis zum 31.12.2016*

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**Bundesinstitut für Risikobewertung**  
Vergiftungs- und Produktdokumentation  
Postfach 12 69 42  
10609 Berlin

Tel. 030 18142 3924  Fax 030 18412 3929  projekt.tiervergiftung@bfr.bund.de  www.bfr.bund.de

---

1. ☐ Vergiftung  ☐ Verdachtsfall

2. Datum und Uhrzeit des Ereignisses__________ der Arztvorstellung___________  
   [TT/MM/JJJJ] [HH:MM]

3. Informationen von einem Giftinformationszentrum wurden eingeholt  ☐ Ja  ☐ Nein  
   Name des Zentrums ______________________

4. Angaben zum Tier  
   Tierart ___________  Geschlecht _______  Geb.__________________________  
   Rasse___________  Gewicht _______  Patientin-Nr. (o.ä.)___________________

5. verursachende Noxe (bei Produkten möglichst Handelsname und Firma angeben)
   ___________________________________________________________________

   Aufge nommene Menge/Dosis __________________________

---

6. Exposition  
   Ort:__________________________________________  PLZ __________
   
   im Wohnbereich des Besitzers:  ☐ Innen  ☐ Außen  
   im öffentlichen Bereich:  ☐ Innenraum (z.B. Büro, Markt)  ☐ Im Freien (z.B. Park, Wald)  
   Nutztiere und Pferde:  ☐ Innen (Stall)  ☐ Außen
   ☐ Unbekannt  ☐ sonstiges ____________________

   Eintrittspforte:  ☐ Oral  ☐ Haut  ☐ inhalativ  ☐ Auge  ☐ sonstiges ____________

7. Symptome, Verlauf – stichwortartig (ggf. Epikrise beilegen)
   ___________________________________________________________________

---

8. Diagnostik (z.B. Labor-Nachweis, ggf. bitte beilegen)  ☐ Ja  ☐ Nein

---

9. zusätzliche Informationen
   ___________________________________________________________________

---

Hinweis: Bitte keine personenbezogenen Daten vom Tierbesitzer übermitteln. Alle Angaben werden vertraulich behandelt.
Appendix: Poisoning Severity Score (PSS)

Poisoning Severity Score (adapted for dogs) (Persson et al., 1998)
- Changes are indicated in bold italics.

<table>
<thead>
<tr>
<th>Organ</th>
<th>None</th>
<th>Minor</th>
<th>Moderate</th>
<th>Severe</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4a, b*</td>
</tr>
<tr>
<td>No symptoms or signs</td>
<td>- Mild, transient, and spontaneously resolving signs or symptoms</td>
<td>- Pronounced or prolonged signs or symptoms</td>
<td>- Severe or life-threatening signs or symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI-tract</td>
<td></td>
<td>- Vomiting, diarrhoea, pain</td>
<td>- Pronounced or prolonged vomiting, diarrhoea, pain, ileus</td>
<td>- Massive hemorrhage, perforation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Irritation, 1st degree burns, minimal ulcerations in the mouth</td>
<td>- 1st degree burns of critical localization or 2nd and 3rd degree burns in restricted areas</td>
<td>- More widespread 2nd and 3rd degree burns</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Endoscopy: erythema, oedema</td>
<td>- Dysphagia</td>
<td>- Severe dysphagia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Endoscopy: ulcerative transmucosal Lesions</td>
<td>- Endoscopy: ulcerative transmural lesions, circumferential lesions, perforation</td>
<td></td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td>- Irritation, coughing, breathlessness, mild dyspnoea, mild bronchospasm</td>
<td>- Prolonged coughing, bronchospasm, dyspnoea, stridor, hypoxemia requiring extra oxygen</td>
<td>- Manifest respiratory insufficiency (due to e.g. severe bronchospasm, airway obstruction, glottal oedema, pulmonary oedema, ARDS, pneumonitis, pneumonia, pneumothorax)</td>
<td>- Chest X-ray: abnormal with severe symptoms</td>
</tr>
</tbody>
</table>
## Appendix: Poisoning Severity Score (PSS)

<table>
<thead>
<tr>
<th>Nervous system</th>
<th>- Drowsiness, vertigo, tinnitus, ataxia</th>
<th>- Unconscious with appropriate response to pain</th>
<th>- Deep coma with inappropriate response to pain or unresponsive to pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Restlessness</td>
<td>- Brief apnoea, bradypnoea</td>
<td>- Respiratory depression with insufficiency</td>
</tr>
<tr>
<td></td>
<td>- Mild extrapyramidal symptoms</td>
<td>- Confusion, agitation, hallucinations, delirium</td>
<td>- Extreme agitation</td>
</tr>
<tr>
<td></td>
<td>- Mild cholinergic/anticholinergic</td>
<td>- Infrequent, generalised or local seizures</td>
<td>- Frequent, generalized seizures, status epilepticus, opisthotonus</td>
</tr>
<tr>
<td></td>
<td>symptoms</td>
<td>- Pronounced extrapyramidal symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Paraesthesia</td>
<td>- Pronounced cholinergic/anticholinergic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Mild visual or auditory disturbances</td>
<td>- Localized paralysis not affecting vital</td>
<td>- Generalized paralysis or paralysis affecting vital functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>functions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Visual and auditory disturbances</td>
<td>- Blindness, deafness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardio-vascular system</th>
<th>- Sinus bradycardia <em>(HR&lt;50-60 bpm)</em></th>
<th>- Sinus tachycardia <em>(HR&gt;180 bpm)</em></th>
<th>- Sinus bradycardia <em>(HR&lt;50-60 bpm)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Isolated extrasystoles</td>
<td>- Frequent extrasystoles, atrial</td>
<td>- Sinus tachycardia <em>(HR&gt;180 bpm)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fibrillation, AV-block I-II,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>prolonged QRS and QTc-time,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>repolarization abnormalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Mild and transient hypo/hypertension</td>
<td>- Myocardial ischemia</td>
<td>- Life-threatening ventricular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- More pronounced hypo/hypertension</td>
<td>dysrhythmias, AV block III, asystole</td>
</tr>
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</tr>
</tbody>
</table>
## Appendix: Poisoning Severity Score (PSS)

<table>
<thead>
<tr>
<th>Metabolic balance</th>
<th>- Mild acid base disturbances</th>
<th>- More pronounced acid-base disturbances</th>
<th>- Severe acid-base disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Mild electrolyte and fluid disturbances</td>
<td>- More pronounced electrolyte and fluid disturbances</td>
<td>- Severe electrolyte and fluid disturbances</td>
</tr>
<tr>
<td></td>
<td>- Mild hypoglycaemia</td>
<td>- More pronounced hypoglycaemia</td>
<td>- Severe hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>- Hyperthermia of short duration</td>
<td>- Hyperthermia of longer duration</td>
<td>- Dangerous hypo- or hyperthermia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver</th>
<th>- Minimal rise in serum enzymes ALT, AST ULN-5x ULN</th>
<th>- ALT, AST &gt;5xULN but no diagnostic biochemical (e.g. ammonia, clotting factors) or clinical evidence of liver dysfunction</th>
<th>- ALT, AST &gt;5xULN or biochemical (e.g. ammonia, clotting factors) or clinical evidence of liver failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Creatinine ULN-180 µmol/L, ULN-2.0 mg/dl</td>
<td>- Creatinine 181-439 µmol/L, 2.1-5.0 mg/dl</td>
<td>- Creatinine Dog - &gt;440 µmol/L, &gt;5.0 mg/dl</td>
</tr>
<tr>
<td></td>
<td>- Minimal proteinuria/haematuria</td>
<td>- Massive proteinuria/haematuria</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kidney</th>
<th>- Mild haemolysis</th>
<th>- Haemolysis</th>
<th>- Coagulation disturbances with bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Mild methemoglobinaemia</td>
<td>- More pronounced methemoglobinemia</td>
<td>- Severe methemoglobinaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anaemia, leukopaenia, thrombocytopaenia</td>
<td>- Severe anaemia, leukopaenia, thrombocytopaenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood</th>
<th>- Mild pain, tenderness</th>
<th>- Pain, rigidity, cramping and fasciculation</th>
<th>- Intense pain, extreme rigidity, extensive cramping and fasciculation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Mild CPK increase</td>
<td>- Rhabdomyolysis, moderate CPK increase</td>
<td>- Rhabdomyolysis with complications, severe CPK increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Compartment syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscular system</th>
<th>- Mild pain, tenderness</th>
<th>- Pain, rigidity, cramping and fasciculation</th>
<th>- Intense pain, extreme rigidity, extensive cramping and fasciculation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Mild CPK increase</td>
<td>- Rhabdomyolysis, moderate CPK increase</td>
<td>- Rhabdomyolysis with complications, severe CPK increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Compartment syndrome</td>
</tr>
</tbody>
</table>
### Appendix: Poisoning Severity Score (PSS)

<table>
<thead>
<tr>
<th>Local effects on skin</th>
<th>Local effects on eye</th>
<th>Local effects from bites and stings</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Irritation, 1st degree burns (reddening) or 2nd degree burns in &lt;10% of body surface area</td>
<td>- Intense irritation, corneal abrasion</td>
<td>- Local swelling, itching</td>
</tr>
<tr>
<td></td>
<td>- 2nd degree burns on 10-30% of body surface or 3rd degree burns on &lt;2% of body surface area</td>
<td>- Local swelling, itching, local necrosis</td>
</tr>
<tr>
<td></td>
<td>- 2nd degree burns on &gt;30% of body surface or 3rd degree burns on &gt;2% of body surface area</td>
<td>- Swelling involving the whole extremity, more extensive necrosis</td>
</tr>
<tr>
<td></td>
<td>- 2nd degree burns on &gt;30% of body surface or 3rd degree burns on &gt;2% of body surface area</td>
<td>- Swelling involving the whole extremity and significant parts of adjacent area, more extensive necrosis</td>
</tr>
<tr>
<td></td>
<td>- Intense irritation, corneal abrasion</td>
<td>- Critical localization of swelling threatening the airways</td>
</tr>
<tr>
<td></td>
<td>- Minor (punctate) corneal ulcers</td>
<td>- Severe pain</td>
</tr>
<tr>
<td></td>
<td>- Corneal ulcers (other than punctate), perforation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Permanent damage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ULN=upper limit of the normal range; 4a = death; 4b = euthanasia</td>
</tr>
</tbody>
</table>
**NPDS medical outcome scheme** (Mowry et al., 2015, p.1125)

*Minor effect:* The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes (e.g., self-limited gastrointestinal symptoms, drowsiness, skin irritation, first-degree dermal burn, sinus tachycardia, without hypotension, and transient cough).

*Moderate effect:* The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement (e.g., corneal abrasion, acid-base disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment).

*Major effect:* The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, oesophageal stricture, and disseminated intravascular coagulation).
Acknowledgements

I would first like to sincerely thank Prof. Dr. Matthias Greiner for his help, support, and input.

Many thanks to Kathrin Begemann, Dr. Herbert Desel, and colleagues from the Poisoning and Product Documentation group at the BfR for their support and the nice working atmosphere.

Thanks to Prof. Dr. Reinhard Mischke for his continued support throughout the project and helpful suggestions.

Thanks to the other numerous people that contributed to and supported this project including Prof. Dr. Herman Ammer, Dr. Alvin Bronstein, Shireen Banerji (PharmD), Charlotte Hopster-Iversen (PhD), Dr. Xenia von Krueger, Jane LeBlond, Prof. Dr. Heidrun Potschka, Dr. Andreas Stürer.

Thanks also to the German Poison Centres that contributed data to this project.

Thanks to Deborah Cohen for her help with the summary in German.

Lastly, thanks to Matthew for the moral support.