Acetaminophen toxicosis in dogs and cats: reports at the Dutch Poisons Information Center (2010 – 2019)

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Abstract

Background. Pain management in dogs is an important and challenging task in veterinary medicine. Various types of analgesics are available to a veterinarian to fulfil this task, for example glucocorticosteroids, nonsteroidal anti-inflammatory drugs and opioids. However, these drugs are not applicable in every situation and every canine patient, among others, because of their side effects. In compromised patients, acetaminophen appears to be a solution to induce analgesia in some cases. Besides, acetaminophen is also used in addition to other analgesics. As a consequence, there are signs that acetaminophen has been used more often by veterinarians in recent years. However, the use of acetaminophen in animals is not without risks. The therapeutic window is not wide in dogs, and its use in cats is even contraindicated. In addition, acetaminophen, along with ibuprofen, has been at the top of the list of exposures to human medications in dogs and cats for years, according to data from the Dutch Poisons Information Center. When veterinarians are using acetaminophen in dogs more often, this may lead to an increase in self-medication with acetaminophen by pet owners, putting both dogs and cats at risk for toxicosis.

Aim. The aim of this study was to analyse the number of dogs and cats supposedly exposed to acetaminophen about which the Dutch Poisons Information Center was consulted and to evaluate the circumstances of those exposures, with special regard to whether the medication was stolen by the animal or administered by a person.

Method. A dataset concerning acetaminophen exposures of dogs and cats, provided by the Dutch Poisons Information Center, was analysed. A dataset with regard to ibuprofen exposures was also analysed, in order to make a comparison with another over-the-counter available analgesic. The cases studied were reports of veterinarians of supposed exposures by ingestion during the period 2010 – 2019. The analysis was based on worst case scenarios, as actual ingestion could not be proven in every case.

Results. This study demonstrates that the number of dogs suspectedly exposed to acetaminophen about which the Dutch Poisons Information Center was consulted, both absolute and relative, has increased over the years 2010-2019. The same findings were observed with dogs exposed to ibuprofen. Furthermore, the absolute number of cats exposed to acetaminophen has increased, but no trend could be demonstrated regarding the relative number of cats exposed to acetaminophen in the same period. The same applied to cats exposed to ibuprofen.

Conclusions. A likely reason for the increase in dogs about which the Dutch Poisons Information Center was consulted, could be an increased awareness of the Dutch Poisons Information Center and their services among veterinarians, as there was also an absolute and relative increase of consultations concerning ibuprofen. The increase concerning acetaminophen is less likely to be due to an increase in self-medication by pet owners.

Keywords

Acetaminophen, Paracetamol, Ibuprofen, Cats, Dogs, Intoxications, Self-medication.

Background of the study

Pain management in veterinary medicine, especially dogs

Pain management in animals is an important and challenging task in veterinary medicine. Various types of analgesics are available to a veterinarian to fulfil this task, for example glucocorticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids.

First, glucocorticosteroids officially are not considered analgesics, but they indirectly relieve pain because of their anti-inflammatory characteristics. They intervene early in the arachidonic acid cascade by inhibiting the activity of phospholipase A_2, which eventually inhibits the production of prostanoids. These prostanoids, including prostaglandins, play a role in inflammation, but also in homeostatic physiological processes. Disrupting these processes causes, for example, a risk of gastrointestinal disorders such as ulceration. Glucocorticosteroids also affect the immune system: they suppress the immune response, resulting in an increased susceptibility of infection. Furthermore, they slow down tissue healing.[1] In general, glucocorticosteroids have a widespread effect in the body, but they also have many side effects. The effects that are mentioned, are not desirable in dogs undergoing surgery, for example, or in patients with gastrointestinal disease. Because of the many side effects, veterinarians do not prefer the use of glucocorticosteroids for pain relief.

Besides, NSAIDs are widely used for the control of pain and inflammation in dogs and cats given their direct analgesic effects and anti-inflammatory effects.[2,3] As well as glucocorticosteroids, NSAIDs interfere with the arachidonic acid cascade, although more downstream than glucocorticosteroids. NSAIDs inhibit prostanoids synthesis by inhibiting cyclooxygenase (COX) enzymes.[1] Therefore, COX-inhibitors also disturb homeostatic physiological processes, as a result of which they are associated with adverse effects such as gastrointestinal (GI) ulceration, renal and hepatic failure.[4,5] For example, NSAIDs negatively affect the healing of gastrointestinal lesions. As a consequence, not using NSAIDS in patients with pre-existing gastrointestinal lesions or during surgical procedures should be considered. In addition, COX enzymes play an important role in maintaining renal perfusion in hypovolemic situations and in case of renal ischemia. Therefore, the use of NSAIDs in hypotensive or hypovolemic dogs increases the risk of renal failure, especially when anesthetics are used that also reduce the renal blood flow themselves.[3]

Opioids, such as morphine and buprenorphine, are also effective analgesics, acting by a mechanism different from disturbing the arachidonic acid cascade. Opioids affect nociception, by binding opioid receptors located in the central and peripheral nervous system, resulting in a reduction of pain. Due to the interference with the nervous system throughout the body, opioids can have wide-ranging side effects. A disadvantage of the use of opioids is, for example, that these drugs have a sedative effect, which is not desirable when only achieving analgesia is intended. Besides, opioids can pose a risk of respiratory depression and bradycardia, but also tolerance and addiction.[6–8]

Partly due to the adverse effects these types of analgesics can cause, these drugs cannot be used in every situation and every patient. Therefore, it is desirable to expand the arsenal of analgesics where possible.

Advantages of acetaminophen use in dogs over other analgesics

Because of all mentioned disadvantages, one keeps searching for alternatives which can be used as an analgesic and antipyretic in compromised dogs, such as hypovolemic or dehydrated patients, patients with gastrointestinal disorders or patients with renal dysfunction. Acetaminophen appears to be an alternative drug. In addition, acetaminophen is also used in addition to another analgesic, such as an NSAID. Despite years of research, the exact mechanism of action in mammals remains unknown. Acetaminophen appears to play a role in inhibiting COX enzymes, and also the endocannabinoid system and serotonergic pathways appear to be involved.[9] Nevertheless, acetaminophen is extensively used in human medicine for years and safety has also been tested in animals. Administration of a recommended dose of acetaminophen in dogs is not associated with gastrointestinal or renal side effects.[2,3] A dose of 10–15 mg/kg orally every eight hours is mentioned as safe for short-term administration.[10,11] In addition, acetaminophen appears to be effective in reducing post-operative pain in dogs, for example after ovariohysterectomy.[2] In the latter study, the analgesic effect was even comparable to that of meloxicam and carprofen, commonly used NSAIDs in dogs.

Acetaminophen is not registered for use in dogs in The Netherlands. Administration of acetaminophen to cats is contraindicated at any dosage, but in dogs there is a therapeutic window.[10,11] Therefore, there is a possibility to use acetaminophen safely in dogs, even though this window is narrow. Clinical signs of acetaminophen intoxication generally occur after an single dose of ≥ 200 mg/kg, see Table 1.[12]

Risks of acetaminophen use in dogs

Acetaminophen is available in several formulations in The Netherlands and multiple acetaminophen-containing drugs have been identified as over-the-counter medicines (OTC).[13,14] An example of those acetaminophen-containing drugs is an oral combination preparation of acetaminophen and coffeine.[14]

The use of acetaminophen in dogs has advantages and in recent literature several cases can be found in which acetaminophen is actually administered to dogs by veterinarians. Especially in recent years, veterinarians administered or prescribed acetaminophen to dogs (off-label use), for example as a perioperative analgesic.[15–20] This does not pose a risk of toxic effects to dogs, as long as a safe dose is administered for a short period. However, providing dog owners with acetaminophen to take home results in the greatest risk of acetaminophen overdose. For example, because they misinterpret the dosage once they get home. Further, people consciously

administer human medication to their pet. Since acetaminophen is commonly used by humans and considered to be safe and effective in this species, concerned but uninformed pet owners may assume that acetaminophen can be safely applied in pets as well and subsequently administer this drug to their pet to reduce pain, fever or any sign of inconvenience.[10,21,22] Such well-intended administrations result in acute or chronic exposure of the animal to acetaminophen (single versus repeated administration).

Other pet owners use the internet as a source for pet health information. Dutch people increasingly search for health information online: in 2018 80% of the 25- to 45-year old people searched online for information concerning human health. Therefore, it is likely that a considerable proportion of the Dutch pet owners uses the internet to research pet health-related issues.[23] Studies have shown that a major part of the Australian and British pet owners used internet websites as a source of pet health information and that they do not always discuss the information found online with their vet.[24,25] The latter increases the chance of misinterpretation of online pet health information by the user. In addition, online sources may lack in quality and accuracy. Regarding to cats and acetaminophen, the online information is clear: never administer acetaminophen to your cat. For dogs, the information is less clear-cut. Some Dutch veterinary websites do not mention the dosage in which acetaminophen should be administered, or do not give notice of the maximum of five days during which acetaminophen can be administered, which may result in dog owners administer the drug to their dogs in a dose that that exceeds the therapeutic dose, or for a period longer than five days.[26,27] This may put dogs at risk for developing acetaminophen toxicosis.

Where there are benefits with using acetaminophen in dogs, these do not exist for using acetaminophen in cats, as this is contraindicated at any dose.[28,29] When veterinarians provide owners with acetaminophen to treat their dog at home, there is a risk they will also administer acetaminophen to their cat when it shows signs of illness, without first consulting their vet.

Acetaminophen toxicosis in dogs and cats

Ingestion of acetaminophen by both cats and dogs involves a risk of toxicosis. It primarily causes methemoglobinemia and haemolysis in cats and also in dogs at high dosages.[10,30] Especially cats are extremely sensitive to acetaminophen toxicosis, because of a deficiency in glucuronyl transferase.[12,21,31] In dogs, the first symptoms of toxicosis can be expected at a single dose from 200 mg/kg onward, whereas cats generally show clinical signs at a single dose of 50 mg/kg, see also Table 1 and Table 2.[12,32,33] The cat's extreme sensitivity is also reflected in the lethal dose: a dose of 120 mg/kg is considered to be a potentially life-threatening dose. This corresponds to one 500 mg tablet ingested by a cat weighing about four kg. For dogs, a dose from 500 mg/kg is fatal. It should be noted that the boundary values mentioned above and in Table 1 and Table 2 are just guidelines. The response to acetaminophen exposure may vary somewhat between individuals.

Table 1 Clinical signs observed in dogs following acute ingestion of acetaminophen. The dosage is given in mg/kg body weight.

Dosage of acetaminophen	Clinical signs and other comments
≤ 30 mg/kg	As a **well-tolerated dose to achieve analgesia** a dose of 10-15 mg/kg orally or rectally every eight hours for a maximum of five days has been mentioned.[28,34] The DPIC mentions a dose of 10 mg/kg orally every eight hours or 15 mg/kg orally twice a day.[29] The latter equates to a total dose of 30 mg/kg per day. (In the UK, a combination preparation of acetaminophen and codeine phosphate has even been registered, with the recommendation to administer the tablets at a dose of 33 mg/kg every eight hours (for a maximum of 5 days)).[35]
> 30 mg/kg	The **therapeutic dose** has been **exceeded**. However, clinical signs of acetaminophen intoxication generally occur after an single dose of ≥ 200 mg/kg. After a single dose of 100 mg/kg, no clinical effects have been observed in dogs.[12]
≥ 150 mg/kg	Dose at which the DPIC advises to **start treatment**.[29,32] At doses between 200 and 500 mg/kg, the development of liver failure causes signs of depression, vomiting and abdominal pain. Other clinical signs observed are anorexia, icterus, methemoglobinemia, hemoglobinemia and weight loss. Most dogs dosed exposed to < 500 mg/kg tend to recover.[32,34]
≥ 500 mg/kg	Is considered to be a **potentially life-threatening dose**. Other symptoms observed are vomiting, depression of the central nerve system, severe methemoglobinemia, haematuria and subcutaneous oedema of the face, paws and forelegs.[12,34] Doses of ≥ 1,000 mg/kg are reported to cause death, after the onset of unconsciousness and cyanosis.[36]

Table 2 Clinical signs observed in cats following acute ingestion of acetaminophen. The dosage is given in mg/kg body weight.

Dosage of acetaminophen	Clinical signs and other comments
> 0 mg/kg	Dose at which the DPIC advises to **start treatment**, because no dose can be classified as safe. The use of acetaminophen in cats is contraindicated at any dose.[28,29]
≥ 50 mg/kg	Dose at which **clinical signs** generally occur.[32,33] Although, a dosage of 10 mg/kg has shown to be fatal in a cat.[21] Another cat showed salivation after receiving acetaminophen in a dose of 20 mg/kg.[12]
≥ 60 mg/kg	Dose at which methemoglobinemia has been shown to occur. Other symptoms observed are slight depression of the central nerve system, haemoglobinuria and hematuria."[12,34]
≥ 120 mg/kg	Is considered to be a **potentially life-threatening dose**. Observed symptoms other than death are signs of depression, anorexia, severe methemoglobinemia, salivation, vomiting, dark-brown urine, facial oedema, vocalization, dyspnoea, cyanosis, and icterus.[12,34,37–39]

Dutch Poisons Information Center

Since humans and their pets share their living environment and pets depend on the well-intentioned care of humans, pets can be exposed to drugs used by humans. Therefore, this exposure, which mostly occurs unintentional, can lead to intoxications. In 2019, the Dutch

Poisons Information Center (DPIC) was consulted by telephone by veterinarians on no less than 1,675 animals possibly exposed to human drugs. 82% of the supposed veterinary exposures to human drugs occurred in dogs, followed by 17% in cats. The human drugs ibuprofen and acetaminophen (also known as paracetamol or N-acetyl-para-aminophenol) were responsible for the majority of the supposed exposures.[40] The same drugs were also seen at the top of the DPIC list of human drugs with the highest number of veterinary exposures in previous years.[40–45] Both acetaminophen and ibuprofen are OTC available and present in many households. This can increase the risk of animal exposure. In any case, exposures to the aforementioned drugs are relevant in veterinary medicine, as veterinarians have frequently contacted the DPIC in recent years.

Aim of the study

In case acetaminophen is more often used in pain management in dogs by veterinarians, this may lead to an increase in self-medication with acetaminophen by pet owners, whether or not after consulting websites of veterinary clinics. Therefore, an increase in dogs and cats exposed to acetaminophen about which the DPIC is consulted, is to be expected.
The aim of this study was to: 1) analyse the number of dogs and cats suspectedly exposed to acetaminophen about which the DPIC was consulted and 2) evaluate the circumstances of those exposures, specifically whether medication was given by veterinarian or pet owner, or 'stolen' by the pet.

Materials and methods

1. Data collection

Materials

The DPIC receives information requests concerning (suspected) exposures of both humans and animals. Those inquiries are stored in the DPIC database and can be used to identify trends in the frequency and circumstances of suspected exposures of animals with potentially toxic substances, such as acetaminophen. In this study two datasets provided by the DPIC were analysed; one concerning suspected exposures of dogs and cats to acetaminophen (n = 1,038 cases, n = 866 dogs, n = 196 cats), the other dataset concerning suspected exposures of dogs and cats to ibuprofen (n = 1,078 cases, n = 999 dogs, n = 115 cats). The documented cases specifically concerned consultations via the 24-hours info telephone of the DPIC.

In addition, the DPIC has provided more recent data, from the period September 1, 2020 to October 31, 2020. In this period the DPIC has specifically asked about the exposure scenario (medication stolen, administered or scenario unknown) during consultations. These data (n = 40 cases, n = 35 dogs, n = 10 cats) were also analysed.

Inclusion and exclusion criteria

Only cases involving suspected acetaminophen and ibuprofen ingestion by dogs and cats reported to the DPIC between January 1, 2010 and December 31, 2019 were included in this study. Both acute and chronic exposures were included, as well as cases in which there was an administration error. The same applies to both patients exposed to one substance (mono exposure) and to multiple substances (multi exposures).

The dataset consisted of initial records, but also of follow-up records. In follow-up records, the DPIC was called back about a previously reported case, for example, to pass on corrections or to ask additional questions. If there was a follow-up record, analysis was always based on the information in the most recent follow-up records.

Three patients were supposed to be exposed to acetaminophen via a route other than ingestion. It concerned one cat and two dogs presumably exposed to acetaminophen suppositories, where it has become clear in one dog that the pet owner has rectally administered, on his own initiative, two suppositories to his dog. Since the data on ibuprofen only relate to the route of ingestion, aforementioned three patients are excluded from the analysis to allow a fair comparison between patients likely exposed to acetaminophen and ibuprofen.

Additional exclusion criteria were applied when the circumstances of exposure were analysed. Furthermore, cases in which it was not known to how many tablets etc. an animal was exposed, or cases in which the body weight of an animal was unknown, were excluded in the context of exposure dose analysis.

Besides, the analyses only focused on the amount of acetaminophen or ibuprofen (in mg). Additions such as codeine have not been taken into account.

In addition, assumptions have been made with regard to the circumstances of exposure, unless the available data pointed in a different direction in a specific case. First, it was assumed that a veterinarian does not administer acetaminophen to a cat, or recommends to do this. After all, that would imply a gross medication error. Acetaminophen will therefore only be stolen by the cat, or administered by the owner on his own initiative. Besides, some cases have been classified as 'chronic intoxication' or 'repeated exposure'. In such cases, it is unlikely that, for example an animal has stolen medication for several days in a row. Therefore, it was assumed that medication was administered to patients in such cases. At last, in cases in which the number of tablets to which the animal is supposedly exposed is unknown, or is expressed as a range, it is unlikely that a person has administered the tablets, since the person who administered tablets could have given an indication of the amount of tablets. In such cases, it was assumed that an animal has stolen the medication.

In general, it is important to mention that the analysis was based on worst case scenarios. For example, when the dataset has mentioned a range of the amount of missing tablet, it was assumed that the highest number of tablets is missing. And when a range was mentioned concerning body weight, the lowest weight was considered to be the reference point. When several animals were supposedly exposed, the analysis was based on the situation in which the lightest animal was exposed to the entire amount of missing tablets. The analysis based on worst case scenario also assumed that missing tablets have been ingested by the animal. However, this does not mean that the animal has actually ingested this (amount of) tablets. Therefore, when "exposed" is mentioned from now on, it should be read "supposedly exposed", because it cannot be said with certainty in every case that an animal has actually ingested the medication. During consultations, the DPIC also uses the worst case scenario as basis for a risk analysis.

2. Study setup

Trend analysis

The data provided by the DPIC were processed and interpreted to investigate whether there was a trend in occurrence of exposures to acetaminophen in dogs and cats in the past ten years. The results concerning acetaminophen exposures have been compared to ibuprofen; another human drug that has been at the top of DPIC's list of suspected veterinary exposures to human drugs along with acetaminophen for years. By analyzing ibuprofen as a second OTC available analgesic, an increase in the number of dogs or cats exposed to acetaminophen about which the DPIC was consulted, could be distinguished from an increase in the number of dogs or cats exposed to OTC analgesics in general. After all, if the hypothesis were true, there would be no increase in the number of dogs exposed to ibuprofen. In addition, the absolute numbers of animals exposed to acetaminophen or ibuprofen have been corrected for any change in the number of animals exposed to potentially toxic substances, on which the DPIC has been consulted in the past ten years. Therefore, the absolute number of animals exposed to

acetaminophen or ibuprofen in a given year was expressed as a proportion of the number of animals exposed to potentially toxic substances in that year.

Circumstances of Exposure analysis

Further, the circumstances of the exposures were evaluated to gain insight in factors involved in the occurrence of exposures to acetaminophen, such as: 1) the source of exposure (administered or stolen), 2) the exposure dose (mg/kg), 3) the number of tablets, capsules etc. to which the animal is exposed and 4) the dose (mg) of the tablets, capsules etc. in question.

For the purpose of exposure dose analysis, patients were divided into categories based on symptomatology. For an elaboration of those categories concerning acetaminophen, please refer to Table 1 and Table 2 in the Background of the study. For the tables regarding ibuprofen, see Table 4 and Table 5 in the Appendix. In 2012, the DPIC started documenting the symptoms that the dogs and cats showed, in the acetaminophen dataset, and in the ibuprofen dataset from 2013. These symptoms were also included in the analysis.

For the purpose of the analysis concerning the number of tablets, the patients has been divided into categories based on the number of tablets to which patients has been exposed. These categories differ per substance type and species.

3. Statistical analysis

Descriptive statistics were performed for several variables in Microsoft Excel. Simple linear regression, as well as multiple linear regression, was used to describe the relationship between different variables. Since the data consisted of counts, Poisson regression was used. The strength of those relationships was determined using the Spearman rank correlation coefficient. The significance level was set at $P < 0.05$. An overview of the results of the statistical analyses can be found in the Appendix. The statistical software used was RStudio with R software version 3.5.2.

Results

1. Information requests to the DPIC

From 2010 to 2019, the DPIC was consulted about an exponential growing amount of veterinary patients exposed to potentially toxic substances, as shown in Figure 1. This increase was partly due to an exponential increase in both the number of dogs and the number of cats exposed to potentially toxic substances during the past ten years.

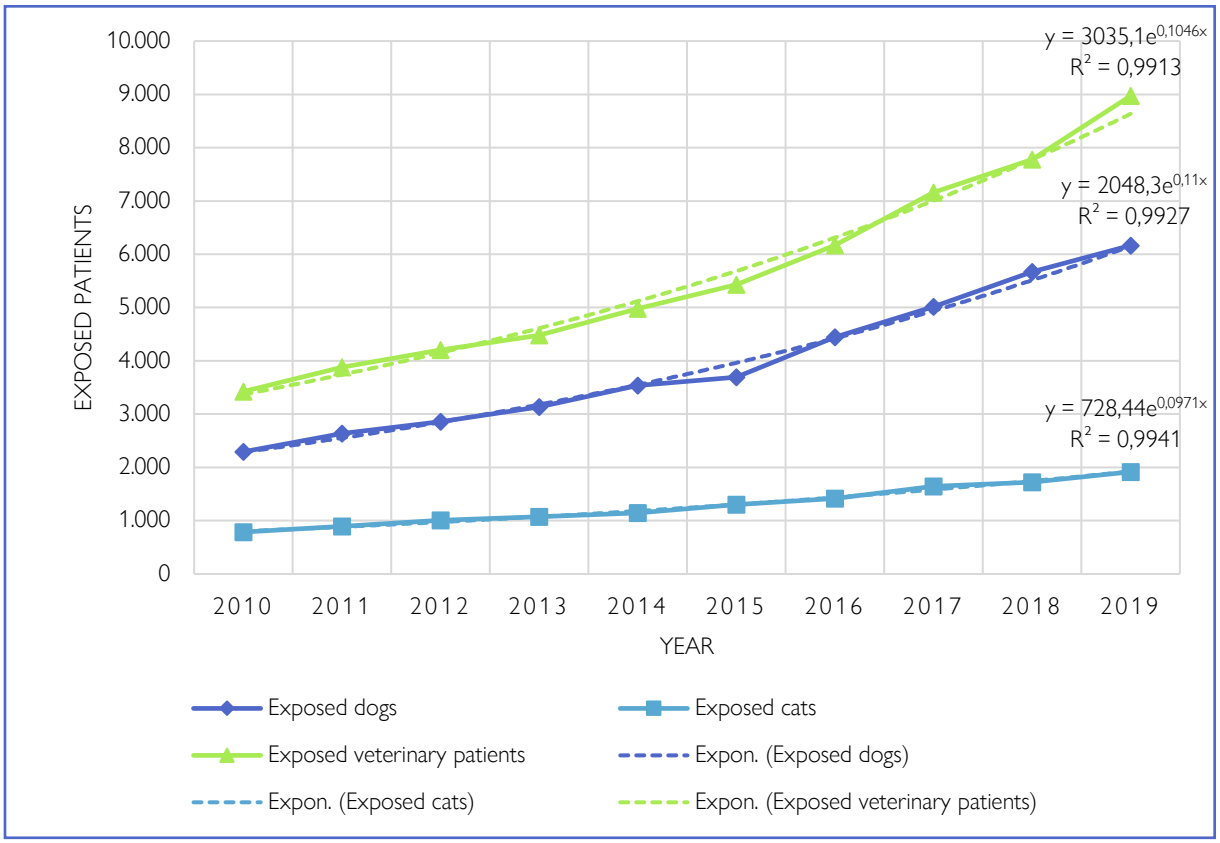

Figure 1 Veterinary patients, including dogs and cats, exposed to potentially toxic substances from 1 January 2010 to 31 December 2019. Broken lines show exponential growth curves. The number of veterinary patients, dogs and cats about which the DPIC has been consulted, has increased exponentially in the last ten years.

A relationship between the number of dogs and cats kept by Dutch households and the number of dogs and cats exposed to potentially toxic substances could not reliably be demonstrated, due to lack of data on the number of dogs and cats in multiple years between 2010 and 2019, see Table 3 in the Appendix. In addition, the available data are based on annual test samples among a limited number of 7,500 households. Therefore, the number of dogs and cats kept by more than seven million Dutch households in the past ten years is only an estimate, not exact data.[46]

2. Information request concerning exposure to acetaminophen and ibuprofen

As shown in Figure 2, an increase in exposed patients can also be seen in the number of dogs exposed to both acetaminophen and ibuprofen. These numbers have increased exponentially during the past ten years. For cats, it is less clear whether there has been an increase in patients exposed to acetaminophen and ibuprofen about which the DPIC has been consulted. Therefore, linear regression was used to determine the mean increase (*b*) per year with 95% confidence intervals (*CI*) for the 10-year period. There has been a significant mean annual growth of 9.2% in the absolute number of cats exposed to acetaminophen[A], as well as a mean annual increase of 12.3% in the number of cats exposed to ibuprofen.[B]

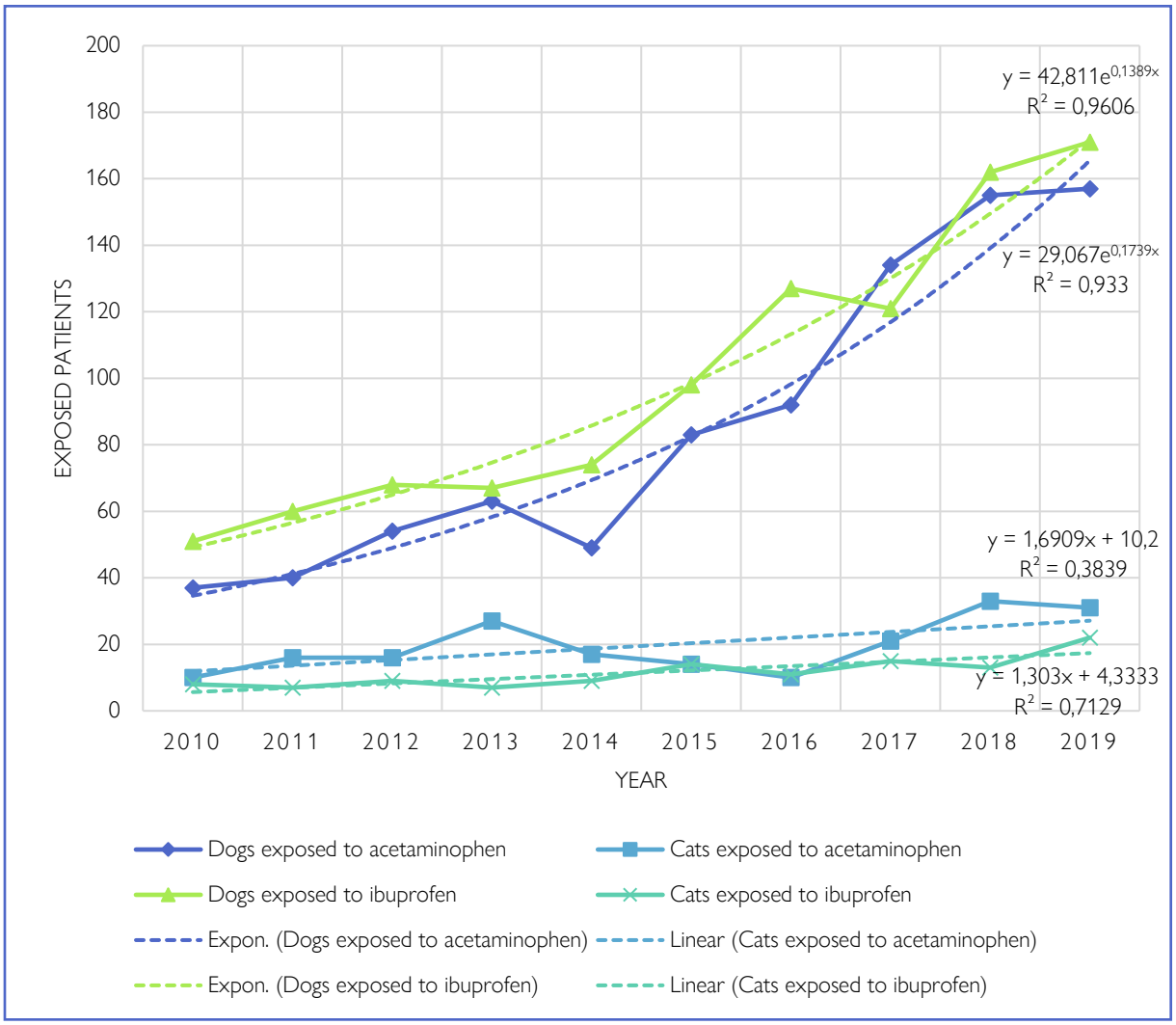

Figure 2 Dogs and cats exposed to acetaminophen and ibuprofen respectively, from 1 January 2010 to 31 December 2019. Broken lines concerning dogs show exponential growth curves. Broken lines concerning cats show linear regressions for the exposed cats per year for that category. The number of dogs exposed to acetaminophen and ibuprofen has increased exponentially, with a linear increase in the number of cats exposed to acetaminophen and ibuprofen respectively.

[A] b = 1.092, P = 0.047, 95% CI: 1.015 – 1.176.

[B] b = 1.123, P = 7.15· 10^{-4}, 95% CI: 1.076 - 1.172.

3. Relation between the increase in animals exposed to potentially toxic substances and the increase in animals exposed to acetaminophen and ibuprofen

3.1 Expressed in absolute numbers

A linear relationship has been demonstrated between the number of dogs exposed to potentially toxic substances and the number of dogs exposed to acetaminophen when using linear regression.[C] To determine the strength of this relationship, correlation was performed using the Spearman correlations. This has also been done for species cat and substance type ibuprofen. A significant positive (Spearman's rank) correlation was found between the number of dogs presumably exposed to potentially toxic substances and the number of dogs exposed to acetaminophen.[D]

Also, a linear relationship was demonstrated between the number of dogs exposed to potentially toxic substances and the number of dogs exposed to ibuprofen[E], as well as a significant positive correlation between these two variables.[F]

Focussing on the cats that were exposed to acetaminophen, no significant correlation was found between the number of cats exposed to potentially toxic substances and the number of cats exposed to acetaminophen.[G] However, a linear relationship has been demonstrated between these two variables when using linear regression.[H]

In contrast, the number of cats exposed to potentially toxic substances and the number of cats exposed to ibuprofen were significantly correlated.[I] In addition, a linear relationship has been demonstrated between these two variables when using linear regression.[J]

3.2 As a proportion of the number of dogs and cats exposed to potentially toxic substances respectively

The number of dogs exposed to acetaminophen is expressed as proportion of the number of dogs exposed to potentially toxic substances in a given year, in order to reduce the influence of an increasing number of patients about which the DPIC was consulted. The same has been done for species cat and substance type ibuprofen. The changes in proportions are described in Figure 3.

[C] $b = 1.0004$, $P = 6.41e^{-6}$, 95% CI: 1.0003 - 1.0004.

[D] $r = 0.964$, $r^2 = 0.929$, $P < 2.2e^{-16}$ (r: correlation coefficient; r^2 = square of the correlation coefficient)

[E] $b = 1.0003$, $P = 1.68e^{-6}$, 95% CI: 1.0003 - 1.0004.

[F] $r = 0.976$, $r^2 = 0.952$, $P < 2.2e^{-16}$.

[G] $r = 0.585$, $r^2 = 0.343$, $P = 0.075$.

[H] $b = 1.001$, $P = 0.042$, 95% CI: 1.000 - 1.001.

[I] $r = 0.860$, $r^2 = 0.739$, $P = 1.423 \cdot 10^{-3}$.

[J] $b = 1.0009$, $P = 2.38 \cdot 10^{-4}$, 95% CI: 1.0006 - 1.0012.

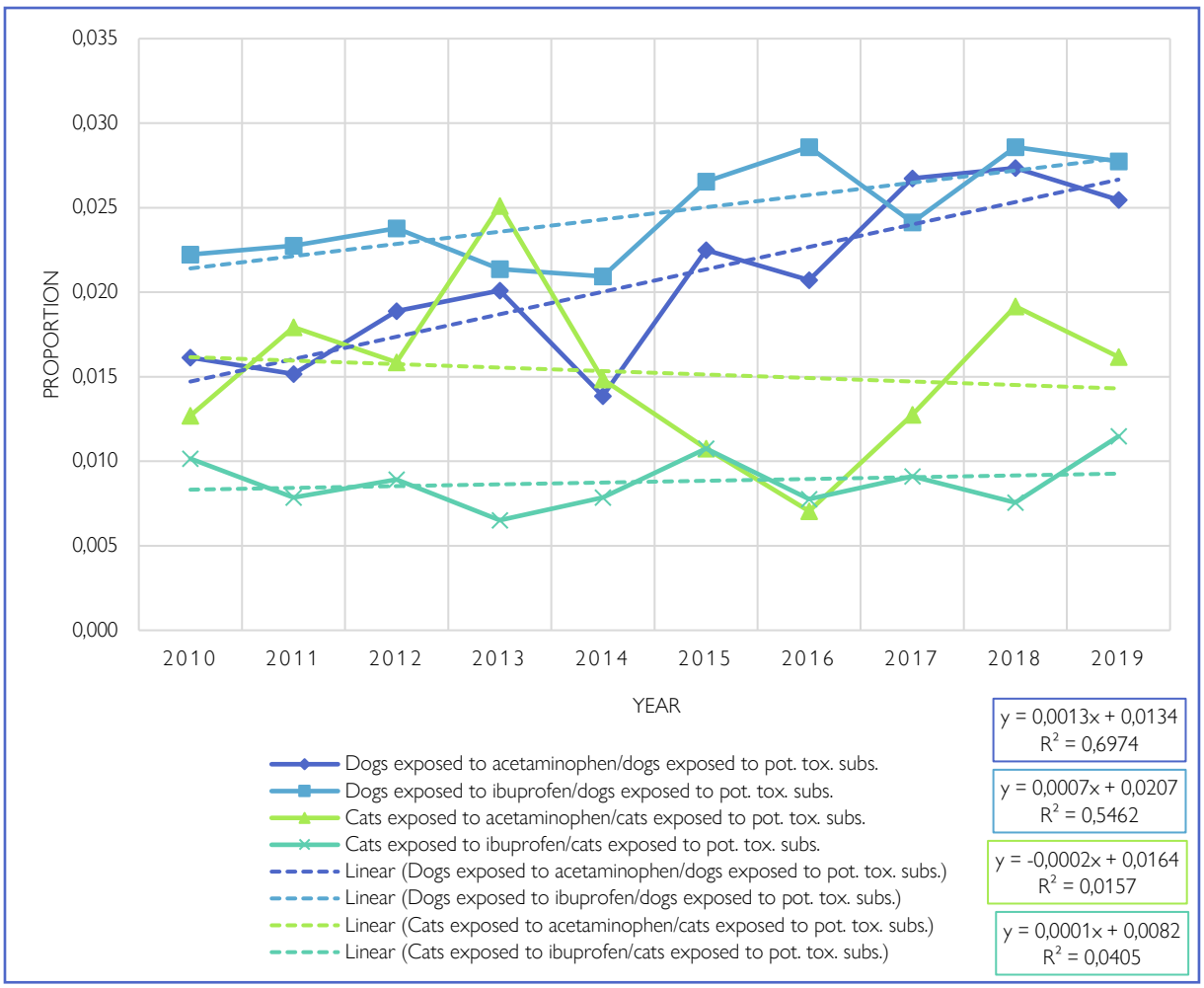

Figure 3 Dogs and cats exposed to acetaminophen and ibuprofen respectively, expressed as proportion of the number of dogs and cats exposed to potentially toxic substances respectively, from 1 January 2010 to 31 December 2019. Broken lines show linear regressions for the proportion per year for that category. Concerning dogs, a significant increase in proportion is demonstrated, where the increase relating to acetaminophen is stronger than ibuprofen. No trends can be identified for cats.

The number of dogs exposed to acetaminophen, as well as the number of dogs exposed to ibuprofen, as a proportion of the total number of dogs exposed to potentially toxic substances, showed a significant annual increase in the past ten years. In case of acetaminophen, the mean annual growth was 6.7%.[K] The proportion of ibuprofen rose less rapidly, in particular 3.0% per year.[L]

In contrast to dogs, the number of cats exposed to acetaminophen, as well as the number of cats exposed to ibuprofen, as a proportion of the total number of cats exposed to potentially toxic substances, showed no significant annual change in the past ten years. Therefore, there is no question of rising or falling trends with regard to the species cat.

[K] b = 1.067, P = 0.002, 95% CI: 1.067 - 1.098.
[L] b = 1.030, P = 0.014, 95% CI: 1.011 - 1.049.

3.3 As a proportion of the number of the sum of dogs and cats exposed to potentially toxic substances

The number of dogs exposed to acetaminophen was also expressed as proportion of the sum of the number of dogs and cats exposed to potentially toxic substances in a given year, for the purpose of a multiple regression analysis. The same was done for species cat and substance type ibuprofen. The changes in proportions are described in Figure 4.

Figure 4 Dogs and cats exposed to acetaminophen and ibuprofen respectively, expressed as proportion of the number of the sum of dogs and cats exposed to potentially toxic substances, from 1 January 2010 to 31 December 2019. Broken lines show linear regressions for the proportion per year for that category. The mean number of dogs exposed ibuprofen (per total amount of dogs and cats exposed to potential toxic substances) increased significantly with 10.5% each year, and the mean number of cats exposed to ibuprofen was 24.0% lower than the mean number of dogs exposed to ibuprofen.

Again, only the changes in proportions with regard to species 'dog' were significant, shown by simple regression analysis.[M] Multiple quasipoisson regression analysis with independent variables

[M] Acetaminophen: b = 1.070, P = 0.002, 95% CI: 1.041 - 1.101.
Ibuprofen: b = 1.033, P = 0.008, 95% CI: 1.014 - 1.053.

"Year", "Species" and "Substance type", taking into account interactions between variables, indicated that the mean number of dogs exposed to ibuprofen (per total amount of dogs and cats exposed to potential toxic substances) increased with 10.5% each year.[N] The multiple regression analysis also showed that the mean number of cats exposed to ibuprofen was 24.0% lower than the mean number of dogs exposed to ibuprofen (per total amount of dogs and cats exposed to potential toxic substances).[O] The difference between the mean number of dogs exposed to acetaminophen and the mean number of dogs exposed to ibuprofen (per total amount of dogs and cats exposed to potential toxic substances), as well as the difference between the mean number of cats exposed to acetaminophen and the mean number of cats exposed to ibuprofen (per total amount of dogs and cats exposed to potential toxic substances), was not significant.

4. Circumstances of exposure

4.1 Exposure scenario

As can be concluded from Figure 5, it was not possible to determine retrospectively in many canine patients whether they had been exposed to acetaminophen because the medication had been administered, or because the dogs themselves had stolen the acetaminophen. The exposure scenario was unknown in a considerable proportion (74.8%) of the patients. In cases where the scenario was known or could be deduced by making assumptions, 79.8% of the dogs had stolen acetaminophen, and to the remaining 20.2% of the dogs acetaminophen was administered.

When the number of dogs exposed to stolen and administered acetaminophen respectively, was expressed as proportion of the total number of dogs exposed to acetaminophen for each year, there were no significant increases over the period 2010-2019. In short, it cannot be said that dogs stole acetaminophen relatively more often, or that acetaminophen was administered relatively more often to dogs during the past ten years.

Concerning ibuprofen, in 71.7% of the patients the scenario was unknown. Regarding the remaining dogs: 94.7% of the dogs had stolen this drug, and to 5.3% of the dogs ibuprofen had been administered during the past ten years. The finding that medication was more often stolen by the dogs than administered, was also observed for acetaminophen. However, the percentage 'stolen' was clearly higher for ibuprofen than for acetaminophen (94.7% vs. 79.8%). Besides, people seemed to administer acetaminophen more often to a dog than ibuprofen (20.2% vs. 5.3%).

When the number of dogs exposed to stolen and administered ibuprofen respectively, was expressed as proportion of the total number of dogs exposed to ibuprofen for each year, there were no significant changes over the period 2010-2019. In short, it cannot be said that dogs stole ibuprofen relatively more often, or that ibuprofen was administered relatively more often to dogs during the past ten years, which finding is comparable to acetaminophen.

[N] b = 1.105, P = $1.25e^{-5}$, 95% CI: 1.064 - 1.149.
[O] b = 0.760, P = $3.28e^{-10}$, 95% CI: 0.712 - 0.806.

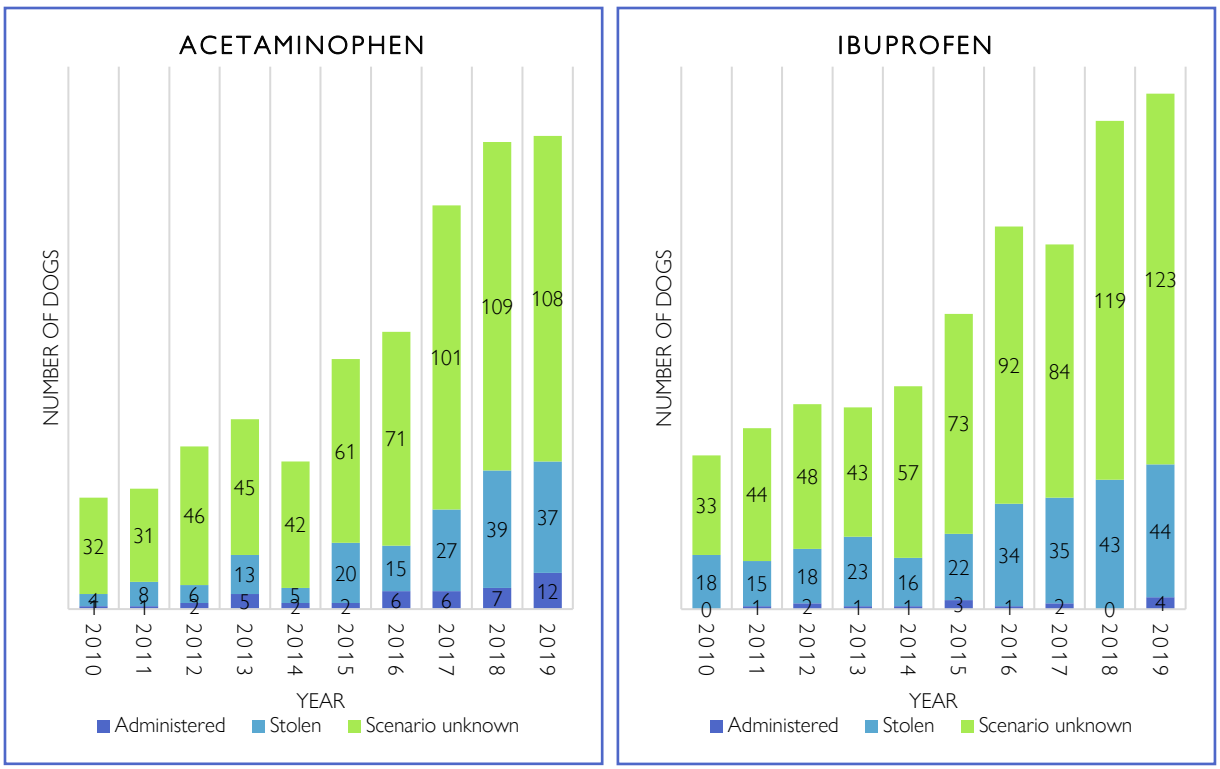

Figure 5 Left: number of **dogs** supposedly exposed to **acetaminophen** divided into categories based on exposure scenario, from 2010 to 2019. The number of dogs exposed to stolen acetaminophen as well as administered acetaminophen has increased significantly (with 27.7% and 28.2% respectively). Right: number of **dogs** supposedly exposed to **ibuprofen** divided into categories based on exposure scenario, from 2010 to 2019. There was only a significant increase of 13.7% observed in the number of dogs exposed to stolen ibuprofen.

As regards the feline patients, in 72.3% of the cases the scenario was unknown. In cases where the scenario was known or could be deduced by making assumptions, 79.6% of the cats had stolen acetaminophen, and to the remaining 20.4% of the cats acetaminophen had been administered. In terms of percentage, cats stole acetaminophen about as often as dogs (79.8% vs. 79.6%). In addition, the percentage of cats exposed to administered acetaminophen was comparable to dogs (20.4% vs. 20.2%).

When the number of cats exposed to stolen and administered acetaminophen respectively, was expressed as proportion of the total number of cats exposed to acetaminophen for each year, there were no significant changes over the period 2010-2019, what is comparable to dogs exposed to acetaminophen. Therefore, it cannot be said that cats stole acetaminophen relatively more often, or that acetaminophen was administered relatively more often to cats during the past ten years.

In 66.1% of the cats exposed to ibuprofen, the exposure scenario could not be determined. In the cases where the scenario was known or could be deduced by making assumptions, 92.3% of the cats had stolen ibuprofen, and to the remaining 7.7% of the cats ibuprofen had been administered during the past ten years.

In general, dogs and cats have stolen medication relatively more often than they have been given medication during the past ten years. In addition, the percentage 'stolen' was clearly higher

for ibuprofen than for acetaminophen (92.3% vs. 79.6%), what is comparable to dogs. Also, people seemed to administer acetaminophen more often to cats than ibuprofen (20.4% vs. 7.7%).

When the number of cats exposed to stolen and administered ibuprofen, was expressed as proportion of the total number of cats exposed to ibuprofen for each year, there were no significant changes over the period 2010-2019. Consequently, it cannot be said that cats stole ibuprofen relatively more often, or that acetaminophen was administered relatively more often to cats during the past ten years.

In addition, data of a two-month period, from September 1, 2020 to October 31, 2020, were analysed. During this period, the DPIC has specifically asked callers about the exposure scenario, when they requested information regarding acetaminophen and ibuprofen exposures. Usually, the DPIC does not ask about the scenario in every consultation. As can be observed in Figure 6, the vast majority of the animals (82.2%) involved dogs and cats that had stolen the medication. Medication was administered by the pet owner on his own initiative in the minority of the dogs and cats (11.1%). In 14.3% of the canine patients exposed to acetaminophen, the drug was administered by the pet owner. The latter percentage was slightly lower than the 20.2% concerning dogs exposed to administered acetaminophen following from the 2010-2019 dataset. Also noteworthy was the considerable percentage of cats (42.9%) exposed to acetaminophen by the owner administering the drug to the cat on his own initiative. This percentage was higher than the 20.4% concerning cats that have been administered acetaminophen following from the 2010-2019 dataset.

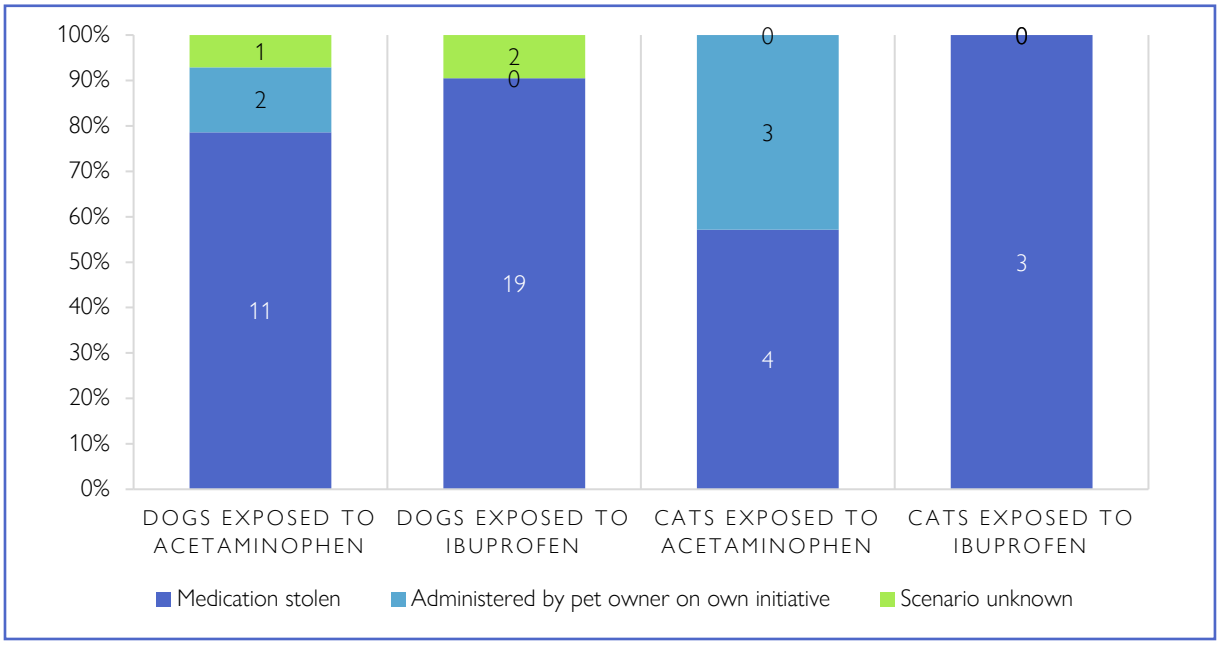

Figure 6 The distribution of exposure scenarios per species and substance type, for the period September 1 to October 31, 2020.

4.2 Exposure dose

Over the past ten years, most of the dogs (49.6% of 827 dogs) were exposed to a dose of 30 to 150 mg/kg acetaminophen. With this dose, the therapeutic dose is exceeded, but there is no need to start treatment yet. In 85.9% of the 311 dogs exposed to a dose of 30 to 150 mg/kg for which information about observed symptoms was recorded, no symptoms of toxicosis were observed at the time the report was made. Symptoms were observed in the other 14.1% (of the 311 dogs) at the time the report was made. This concerned, for example, the occurrence of vomiting, diarrhoea, tremors, and sleepiness.

When the number of dogs exposed to acetaminophen in each exposure dose category was expressed as proportion of the total number of dogs exposed to acetaminophen for each year, as demonstrated in Figure 7, there were no significant increases over the period 2010-2019. Therefore, it cannot be stated that dogs have been exposed to a relatively higher dose of acetaminophen during the past ten years.

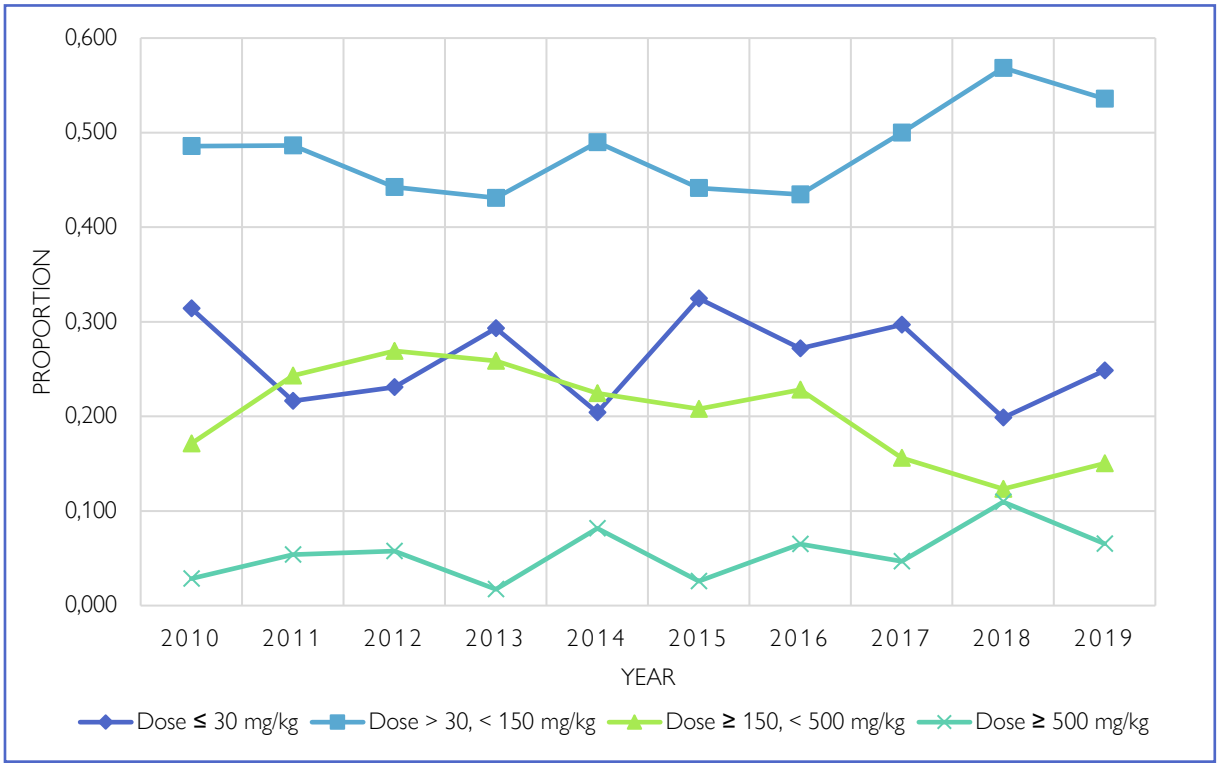

Figure 7 The number of **dogs** exposed to **acetaminophen** divided into exposure dose categories based on symptomatology, expressed as proportion of the total number of dogs exposed to acetaminophen for each year, from 2010 – 2019. There were no significant changes in proportions observed in this period.

The majority of dogs (31.5% of 943 dogs) was exposed to a dose of 50 - 150 mg/kg ibuprofen, followed by a dose of 20 - 50 mg/kg (18.9% of 943 dogs). In these patients, treatment will be indicated and toxic effects on the gastrointestinal tract can be expected. No symptoms of toxicosis were observed in 77.9% of a total of 339 dogs for which information about observed symptoms was recorded and that were exposed to a dose of 20 to 150 mg/kg ibuprofen, at the moment the DPIC was consulted. When clinical signs did occur, they usually consisted of vomiting

(88.0% of 75 dogs) and diarrhea, in accordance with the expected toxic effects on the gastrointestinal tract.

In contrast to dogs exposed to acetaminophen, the number of dogs exposed to ibuprofen expressed as proportion of the total number of dogs exposed to ibuprofen for each year, see Figure 8, has changed in several exposure dose categories. A significant increase was observed in the category 5 - 20 mg/kg.[P] At this dose, usually no clinical signs are expected and no treatment has to be initiated. There even was a significant decrease in the number of dogs exposed to ibuprofen in each year, corrected for the total number of dogs exposed to ibuprofen in each year, in the higher exposure dose categories (300 - 500 mg/kg and ≥ 500 mg/kg).[Q]

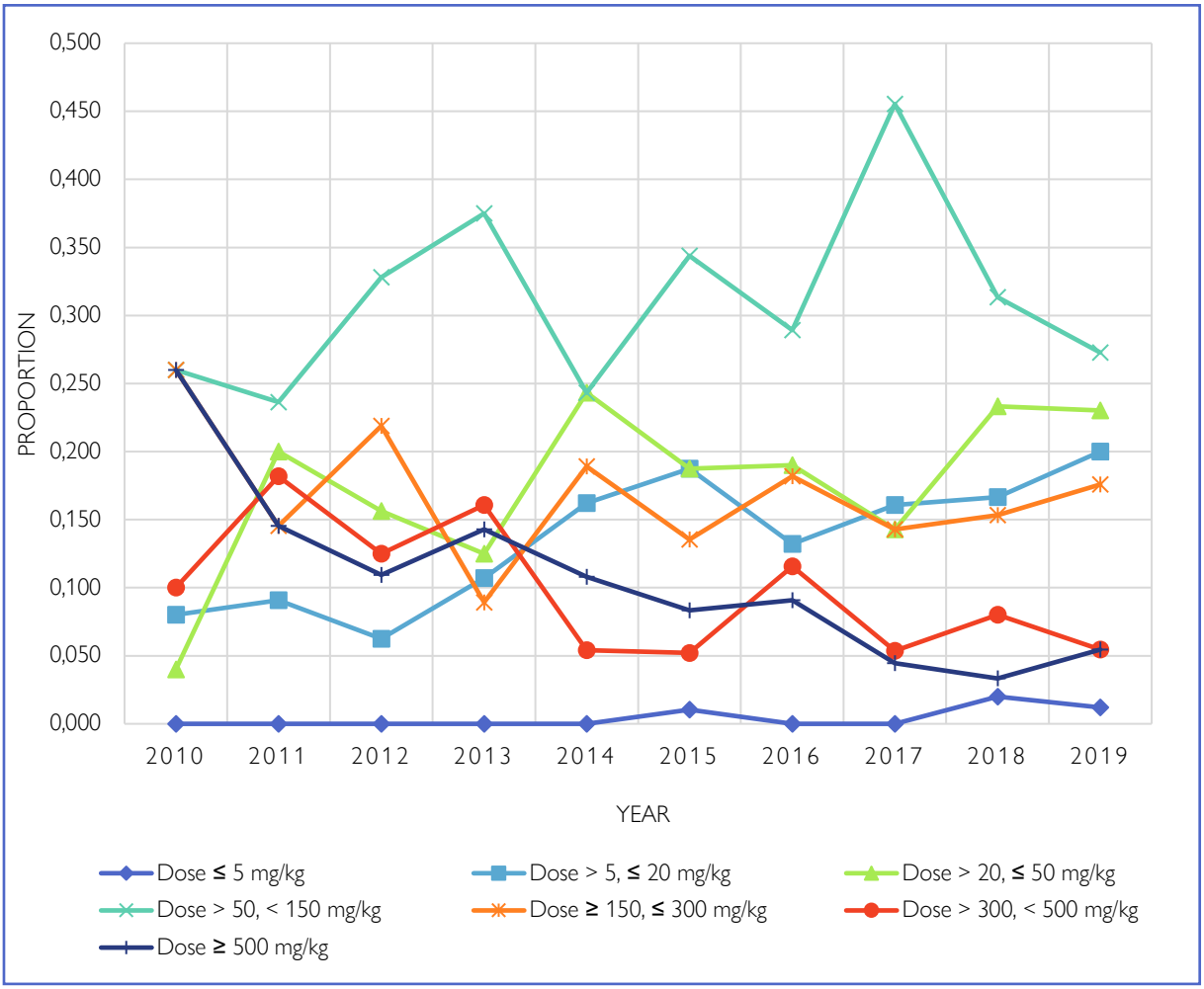

Figure 8 The number of **dogs** exposed to **ibuprofen** divided into exposure dose categories based on symptomatology, expressed as proportion of the total number of dogs exposed to acetaminophen for each year, from 2010 to 2019. There was a significant increase observed in the category 5 - 20 mg/kg, and a significant decrease in the higher exposure dose categories (300 - 500 mg/kg and ≥ 500 mg/kg).

[P] b = 1.106, P = 0.003, 95% CI: 1.054 - 1.161.

[Q] > 300 mg/kg, < 500 mg/kg: b = 0.903, P = 0.048, 95% CI: 0.828 - 0.983.
≥ 500 mg/kg: b = 0.829, P = 0.0002, 95% CI: 0.783 - 0.876.

Most of the cats (38.3% of 175 cats) were exposed to a dose less than 50 mg/kg acetaminophen in the period 2010-2019. These patients need to be treated, however, clinical signs generally occur at a dose of ≥ 50 mg/kg. Nevertheless, symptoms of toxicosis were observed in the analysed feline patients that were exposed to a dose less than 50 mg/kg, at the moment a request for information was made to the DPIC. This concerned 28.6% of 41 cats for which information about observed symptoms was recorded. Clinical signs observed were, for example, incontinence, vomiting and sleepiness.

There were no significant changes observed over the past ten years when the number of cats exposed to acetaminophen in each exposure dose category was expressed as proportion of the total number of cats exposed to acetaminophen. This finding is similar to that concerning dogs exposed to acetaminophen.

As for ibuprofen, the majority of the cats (52.3% of 107 cats) was exposed to a dose of 50 - 200 mg/kg, followed by a dose of 8 - 50 mg/kg (29.9% of 107 cats). For both categories, treatment must be started when ingestion of ibuprofen is suspected. Also, toxic effects on the gastrointestinal tract can be expected. 56.7% of 61 cats for which information about observed symptoms was recorded and that were exposed to a dose of 8-200 mg/kg, showed no clinical signs of toxicosis at the moment of consultation. In the remaining 27 cats that did show symptoms, vomiting occurred in 81.5% of the patients.

When the number of cats exposed to ibuprofen for each exposure dose category was corrected for the total number of cats exposed to ibuprofen, no trends have been demonstrated over the past ten years, what is comparable to the results of exposure dose analysis concerning cats exposed to acetaminophen.

4.3 Number of tablets

Over the past ten years, most of the dogs (48.4% of 779 dogs) were exposed to an amount of 0 up to and including 1 tablet, capsules etc. of acetaminophen.

When the number of dogs exposed to acetaminophen in each tablet amount category was expressed as proportion of the total number of dogs exposed to acetaminophen for each year, there were no significant increases over the period 2010-2019. In short, no trends were observed concerning the amount of acetaminophen tablets to which dogs has been exposed in the past ten years.

Regarding ibuprofen, the majority of the dogs (38.9% of 913) was exposed to an amount of > 1 up to and including 6 tablets, capsules etc.

When the number of dogs exposed to ibuprofen for each tablet amount category was corrected for total number of dogs exposed to ibuprofen for each year, as described in Figure 9, there was a significant increase over the past ten years in the category 0 - 1 tablet. Besides, a significant decrease could be seen in category > 8 tablets of ibuprofen.[R]

[R] 0 - 1 tablet: b = 1.101, P = 0.007, 95% CI: 1.044 - 1.161.
> 8 tablets: b = 0.915, P = 0.004, 95% CI: 0.876 - 0.954.

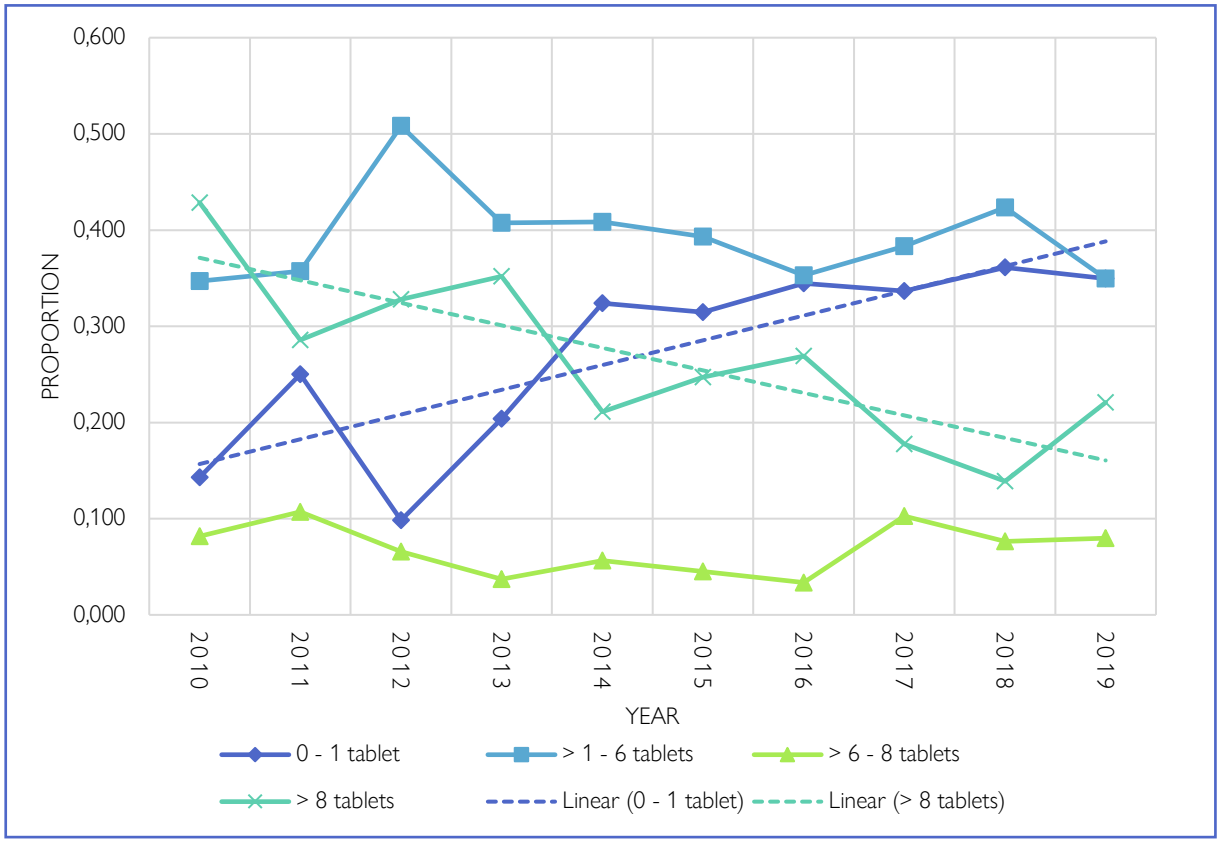

Figure 9 The number of **dogs** exposed to **ibuprofen** divided into categories based on amount of tablet, capsules etc., expressed as proportion of the total number of dogs exposed to ibuprofen, for each year from 2010 - 2019. Broken lines show linear regressions. An upward trend is demonstrated in the category 0 -1 tablet, while a downward trend was seen in category > 8 tablet of ibuprofen.

The majority of the cats (41.6% of 149 cats) was exposed to an amount of > 0,75 - 1 tablet of acetaminophen in the period 2010-2019, which does not differ much from the number of tablets of acetaminophen the majority of the dogs were exposed to.

There was no significant increase or decrease over the past ten years, when the number of cats exposed to acetaminophen for each category of amount of tablets was expressed as proportion of the total number of cats exposed to acetaminophen for each year, which was also seen in the dogs exposed to acetaminophen

Concerning ibuprofen, most of the cats (80.4% of 102 cats) were exposed to 0 to 1 tablet.

In contrast to dogs exposed to ibuprofen, there were no significant changes over the period 2010-2019, when the number of cats exposed to ibuprofen in each tablet amount category was expressed as proportion of the total number of cats exposed to ibuprofen for each year. In short, it cannot be said that cats were exposed to increasing or decreasing amounts of tablets of ibuprofen or acetaminophen during the past ten years.

4.4 Dose of tablets

During the past ten years, a majority of the dogs (83.3% of 783) was exposed to acetaminophen tablets with a dose of 500 mg. When the number of dogs exposed to acetaminophen in each "tablet dose category" was corrected for the total number of dogs exposed to acetaminophen for

each year, there were no significant changes in the number of dogs exposed to tablets with a certain dose of acetaminophen over the period 2010-2019.

Comparable to acetaminophen, there were also no significant changes in the number of dogs exposed to tablets with a certain dose of ibuprofen over the period 2010-2019. With regard to ibuprofen, most of the dogs (63.9% of 913 dogs) were exposed to ibuprofen tablets with a dose of 400 mg.

Similar to what has been observed in the dog, the majority of the cats (72.4% of 156 cats) was exposed to acetaminophen tablets with a dose of 500 mg in the period 2010-2019. When the number of cats exposed to acetaminophen in each tablet dose category was expressed as proportion of the total number of cats exposed to acetaminophen for each year, there were no significant changes in the number of cats exposed to tablets with a particular dose of acetaminophen over the period 2010-2019.

Also comparable to what has been observed in the dog, most of the cats (70.3% of 101 cats) were exposed to ibuprofen tablets with a dose of 400 mg.

Unlike dogs, and cats exposed to acetaminophen, there has been demonstrated a significant increase in the number of cats exposed to tablets with a certain dose of substance, when the number of cats exposed to ibuprofen in each category was corrected for the total number of cats exposed to ibuprofen for each year, as shown in Figure 10. There was a mean increase of 23.0% in the numbers of cats exposed to tablets with 200 mg of ibuprofen during the past ten years.[S]

[S] b = 1.230, P = 0.031, 95% CI: 1.059 - 1.451.

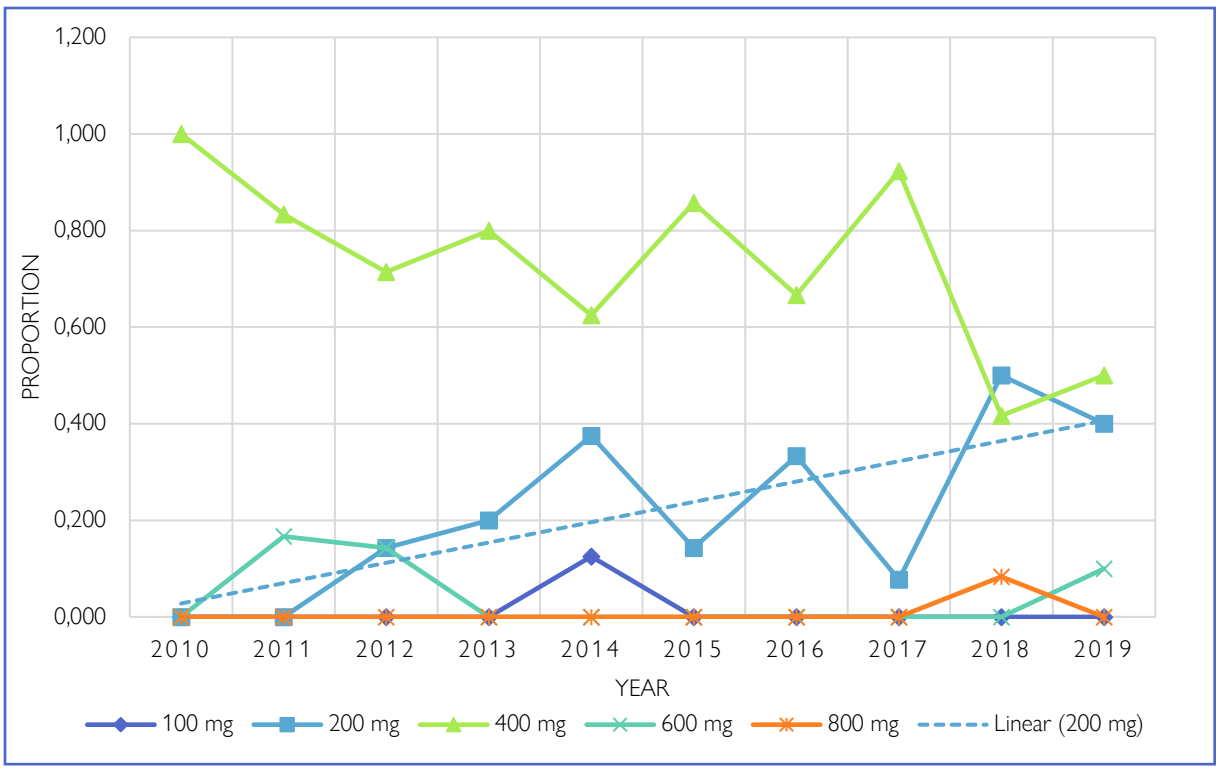

Figure 10 The number of **cats** presumably exposed to **ibuprofen** divided into categories based on the dose of tablets, capsules etc., expressed as proportion of the total number of cats presumably exposed to ibuprofen for each year from 2010 to 2019. The broken line shows linear regressions for the exposed cats per year in category 200 mg. A significant, upward trend had been demonstrated for cats exposed to tablets containing 200 mg of ibuprofen.

Discussion

The aim of this study was to elucidate whether the number of dogs and cats suspected of being exposed to acetaminophen about which the DPIC was consulted, has increased.

1. Dogs

The absolute increase in number of dogs exposed to acetaminophen in the past ten years may be due to an increased awareness of the DPIC and their services, and not due to an increase in self-medication with acetaminophen by pet owners as a result of veterinarians using acetaminophen more often in pain management in dogs. Results derived from this study suggested that there was an exponentially increasing number of dogs exposed to acetaminophen over the period 2010-2019. However, from 2010 to 2019 the DPIC was consulted about an exponential growing amount of dogs exposed to potentially toxic substances. The latter result may indicate increased awareness of the DPIC and their services among veterinarians, or may be a result of an increased number of dogs kept by Dutch households. Whether the latter was the case, cannot be demonstrated due to a lack of data, also with regards to cats, which is a limitation of this study. The study has shown that there is a strong association between the number of dogs exposed to potentially toxic substances and the number of dogs exposed to acetaminophen. Hence, to reduce the influence of the overall growing amount of dogs exposed to potentially toxic substances reported to the DPIC, it was of increased value to investigate whether the ratio of the number of dogs exposed to acetaminophen compared with the number of dogs exposed to potentially toxic substances has increased from 2010 to 2019.

This research has shown that also the aforementioned ratio has increased over the years. Possible explanations would be an increasing amount of dogs suspected of stealing acetaminophen, an increasing amount of dogs to which acetaminophen was administered and/or a decrease in the number of dogs exposed to potentially toxic substances over the past ten years. However, the latter is out of the question. A reason why acetaminophen was stolen more often could be that this self-help medication was increasingly present in Dutch households. Unfortunately, it was not possible to trace sales figures concerning acetaminophen (or concerning ibuprofen). Determining these sales figures will be an extensive task, as this drug is available "on every street corner". Another possible explanation that acetaminophen was stolen more often, is contained in the behaviour of pet owners: they may have been increasingly careless with the storage of acetaminophen during the past ten years. An increasing amount of dogs to which acetaminophen was administered, could be due to a growing belief among pet owners that acetaminophen can be used safely as a therapeutic in dogs. Such a perception of pet owners could be boosted by online information or by positive advice from a veterinarian to use acetaminophen in their dogs.

Indeed, there was an increase in absolute numbers of dogs suspected of having stolen acetaminophen and dogs to which acetaminophen was administered as a therapeutic, but when the data were analysed in the form of a ratio, no significant differences were observed. Therefore,

it could not be concluded from the data that pet owners have been administered acetaminophen to their dog more often, which was initially expected.

This study also demonstrated that there was an exponentially increasing number of dogs exposed to ibuprofen, another OTC drug, in The Netherlands over the period 2010-2019, which was associated to the number of dogs exposed to potentially toxic substances. Since the same rise and association was seen in dogs exposed to acetaminophen, a common cause may be found. The absolute increase in number of dogs exposed to ibuprofen may also be a result of an increased awareness of the DPIC and their services.

The ratio of the number of dogs exposed to ibuprofen compared with the number of dogs exposed to potentially toxic substances was increased from 2010 to 2019, but less rapidly than the ratio of the number of dogs exposed to acetaminophen. Similar to acetaminophen, possible explanations would be an increasing amount of dogs suspected of stealing ibuprofen and/or an increasing amount of dogs to which ibuprofen was administered. The results suggested there was an only an increase in absolute numbers of dogs suspected of having stolen ibuprofen, but when the data were analysed in the form of a ratio, no significant differences were observed. This outcome is similar to dogs exposed to acetaminophen. For ibuprofen, it was difficult to explain the results based on the analysed scenarios too, because of the assumptions made in the analysis. Given the increased ratio of the number of dogs exposed to ibuprofen, it is therefore unlikely that the increasing number of dogs exposed to acetaminophen was caused by an increase in self-medication of pet owners as a result of veterinarians using acetaminophen more often in pain management in dogs.

Concerning the circumstances under which the assumed exposures took place, the following can be said.

In percentage terms, during the past ten years the DPIC was consulted more often about dogs that had stolen acetaminophen than about dogs to which acetaminophen was administered. The same phenomenon was seen in dogs exposed to ibuprofen, although dogs stole ibuprofen relatively more often than acetaminophen. The dog's taste perception could play an important role in this. The flavour of sugar and other sweet flavours are considered to be highly palatable in dogs, while the bitter flavour of drugs is considered to be little palatable.[47] On the other hand, people were relatively more likely to administer acetaminophen to a dog than ibuprofen. The exact reason is not known, but probably people consider acetaminophen to be safer than ibuprofen. For example, because their veterinarian also uses acetaminophen in pain management in dogs.

In terms of exposure dose (mg/kg), the majority of dogs was exposed to relatively low doses. Despite of the increasing number of dogs exposed to acetaminophen over the past ten years, the cases did not appear to be increasing in severity (looking at exposure dose). In the case of ibuprofen, a large portion of the dogs were exposed to a dose that causes toxic effects, although these are usually only effects on the gastrointestinal tract. Remarkable was the relatively increasing number of dogs that were exposed to a low dose (5 - 20 mg/kg), while the relative number of dogs exposed to the higher exposure doses (300 - 500 mg/kg and ≥ 500 mg/kg) has decreased over the past ten years. Possible explanations are people now administer less tablets of

ibuprofen to their dogs than before, ibuprofen is less present in households (or in smaller packages) and people are tidier when it comes to storing ibuprofen. However, the latter is not consistent with a possible explanation given for the increasing number of dogs exposed to acetaminophen. It does not make sense that people have become more cautious about storing ibuprofen, while they may have become more careless about storing acetaminophen.

2. Cats

Similar to dogs, there was an annual growth in number of cats exposed to acetaminophen in The Netherlands over the period 2010-2019, as well as a an exponential growing amount of cats exposed to potentially toxic substances about which the DPIC was consulted. Even though there was an association between these variables, they were not significantly correlated. Also concerning cats, it was useful to investigate whether ratio of the number of cats exposed to acetaminophen compared with the number of cats exposed to potentially toxic substances has increased from 2010 to 2019, in this way reducing the influence of a growing amount of cats exposed to potentially toxic substances reported to the DPIC. However, this study has demonstrated that there was no question of an upward or downward trend. Therefore, it cannot be said whether the number of cats exposed to acetaminophen in The Netherlands remained the same or changed during the past ten years. The small sample size for cats probably influenced these results, as a small sample size lowers the significance level of the findings. Thus, the results concerning cats must be interpreted with caution.

A comparable finding was found in cats exposed to ibuprofen: an annual growth in number of cats exposed to ibuprofen from 2010 to 2019, but highly correlated to the number of cats exposed to potentially toxic substances about which the DPIC was consulted. However, there was no trend here either when looking at the ratio of the number of cats exposed to ibuprofen compared with the number of cats exposed to potentially toxic substances.

Analysis of the circumstances of exposure indicated that cats regularly steal tablets, even though cats are generally not known as animals that steal tablets. In addition, the administration of tablets to cats is often seen as problematic by owners. Therefore, it is all the more remarkable that cats ingest tablets on their own initiative to such an extent. Similar to dogs, cats also seem to prefer stealing ibuprofen over acetaminophen. Again, the explanation may be a matter of taste. Also cats do not like bitter-tasting drugs.[47] However, it should be noted that cats, unlike dogs, do not appear to be able to taste sugars, which are sweet stimuli.[48] Furthermore, people still have administered acetaminophen tablets to cats during the past ten years. This suggests that not every cat owner is aware of the dangers of administering acetaminophen to a cat. After all, it can be assumed that administration is not advised by a veterinarian. Also, online information seems to be unambiguous, so that will not be the cause of people administering acetaminophen to their cat.

3. Research limitations

In what has been reported above, some limitations of this study have already been mentioned. However, several aspects of this research have their limitations.

First, it should be noted that the exposure scenario data were considerably based on assumptions made by the researcher, because the scenario was not explicitly mentioned in many cases. This creates an uncertainty factor, which makes it difficult to explain results based on the analysed scenarios. Therefore, the results with regard to the exposure scenarios can give an indication of reasons why animals have been exposed to the drugs, but is not possible to make firm conclusions based on this results. The results are not objective enough for that.

In general, it can be said that the information requests that the DPIC has received concerning exposures of both humans and animals, reflect what has happened in the Dutch population of dogs and cats during the past ten years. But it is not clear to what extent this reflection is reliable; the number of patients exposed to potentially toxic substances about which the DPIC is consulted, may be just the tip of the iceberg. After all, not every veterinarian will report a suspected case of exposure or a proven intoxication with a human drug to the DPIC. At this point, the data were biased: the requests received by the DPIC mainly related to veterinarians having questions about an acetaminophen exposure or about the therapy to be applied. Probably these veterinarians were not aware of protocols concerning acetaminophen exposures, because they never had to deal with such exposures in their work environment. Veterinarians in a different work environment may have been aware of this, because they were more experienced. Therefore, the data in this study will not have been fully representative of the prevalence of acetaminophen exposures in Dutch veterinary practices. In addition, the fact that the available data consisted only of information request by telephone, further influenced the reliability of the reflection. Requests via the DPIC website were not included in the datasets, with the result that possible cases have been missed.

Furthermore, it cannot be prevented that the datasets partially consist of indirectly obtained information. It is conceivable that veterinarians contact the DPIC, after they or their para-veterinarians have spoken to the pet owner. It is not necessary that the exposed animal was already examined by a veterinarian. The information provided by the animal owner may contain inconsistencies. If a veterinarian does not call the DPIC back later to pass on corrections based on anamnesis and clinical examination, inconsistencies will remain in the datasets.

Further, in this study the number of exposed patients was repeatedly counted instead of the number of cases, resulting in a "clouded view". After all, in a case where, for example, an empty strip of acetaminophen is found in the basket of one of the three dogs, this does not mean that all three dogs have ingested acetaminophen. In fact, if no one has seen the actual ingestion, it cannot be said with certainty that all three dogs have been exposed. Counting three exposed dogs in such a case may overestimate the true exposure. If the number of cases had been counted, there would have been less risk of overestimating of the situation. The fact that the analysis is based on the worst case scenario, can also lead to overestimation of the situation.

From a clinical point of view, it only is interesting when the dog or cat has actually ingested acetaminophen, because only then a risk of intoxication arises. The available information per case did not always answer the question whether ingestion has taken place or not. In addition,

emesis was induced in some of the patients for early decontamination, if vomiting did not occur spontaneously already. In such cases, despite exposure to a toxic dose, the clinical symptoms may be moderate or even absent. Hence, an increase in the number of dogs exposed to acetaminophen does not have to be problematic, as long as pet owners and veterinarians take timely and adequate measures. Therefore, this study did not provide any information on the extent of the problem of actual acetaminophen intoxications in dogs and cats in the period 2010 – 2019.

Final conclusions and future perspectives

In conclusion, this study has demonstrated that the number of dogs suspected of being exposed to acetaminophen about which the DPIC was consulted, both absolutely and relatively, has increased over the years 2010 - 2019. However, no trend could be demonstrated regarding the relative number of cats exposed to acetaminophen in the same period. There is uncertainty about the cause of the increase with regard to the dog. A likely reason for the increase could be an increased awareness of the DPIC and their services among veterinarians, as there was also an absolute and relative increase in case of ibuprofen. The increase concerning acetaminophen is less likely to be due to an increase in self-medication with acetaminophen by pet owners resulting from an increased use of the drug by veterinarians in pain management in dogs, or resulting from consultation of websites of veterinary clinics with inadequate information by pet owners.

As a consequence, further investigations are required. First, a future study should preferably be conducted prospectively, and not retrospectively as happened in this study. In this way, for example, specific questions can be asked about the exposure scenario in each consultation concerning an acetaminophen exposure. In addition, a random survey among Dutch veterinary practices can be used to gather more information about the circumstances of acetaminophen exposure in dogs and cats (assuming that veterinarians will honestly admit when they have administered acetaminophen to an animal or have advised to administer acetaminophen). Such a random survey could also provide a better picture of the prevalence of exposures in The Netherlands.

Furthermore, an a priori power analysis can be performed to determine a sufficient sample size to achieve adequate power. This is especially important with regard to cats; as the number of cats about which the DPIC is consulted has proven to be relatively low over the past ten years.

Moreover, it would be of added value to investigate whether the clinical signs and time for onset of signs are consistent with acetaminophen-induced toxicosis. If so, it can be said with more certainty that the patient has ingested acetaminophen in a particular case.

At last, data on the number of dogs and cats kept by Dutch households, as well as sales figures of acetaminophen and ibuprofen in The Netherlands, would be a welcome addition to future research. In these data, an explanation could be found for changes in the number of patients exposed to acetaminophen and ibuprofen, respectively.

Finally, considering that acetaminophen and ibuprofen have been at the top of the list of human medications on which the DPIC is consulted for many years, it remains important to create awareness among the pet owner that such medications cannot be left lying around unpunished (even among cat owners), or cannot be administered to their pet without consequences. In this, the veterinarians have an important role to play.

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Appendix

1. Table concerning number of dogs and cats kept by Dutch households

The data in Table 3 are based on an annual survey conducted among households on behalf of the trade organisations 'Dieren, benodigdheden en voeders' (Dibevo) and 'Nederlandse Voedingsindustrie Gezelschapsdieren' (NVG), and based on a reports compiled on behalf of the Ministry of Economic Affairs, Agriculture and Innovation.[49–52]

Table 3 The number of dogs and cats kept by Dutch households, from 2010 to 2019. For several years, no data are available and available data are rough estimates.

Year	Dogs	Cats
2010	1,493,000	2,877,000
2011	-	-
2012	1,570,000	2,724,000
2013	-	-
2014	1,500,000	2,615,000
2015	-	-
2016	1,500,000	2,600,000
2017	1,500,000	2,600,000
2018	1,500,000	2,600,000
2019	1,690,000	2,940,000

2. Tables concerning exposure dose

For the purpose of the analysis concerning exposure dose, patients were divided into categories based on symptomatology. For ibuprofen, the categories have been determined based on the information below. These boundary values are just broad guidelines, due to the variation in response to ibuprofen exposure between individuals.[53]

Table 4 Clinical signs observed in dogs following acute ingestion of ibuprofen. The dosage is given in mg/kg body weight.

Dosage of ibuprofen	Clinical signs and other comments
≤ 5 mg/kg	In the past, a dosage of 4-5 mg/kg per day orally was recommended in the dog.[32,34,54]
> 5 mg/kg	The dose previously considered to be **therapeutic** has been **exceeded**. (Chronic exposure (30 day period) to a dose of 8 mg/kg/day has been shown to result in the development of gastric ulcers and erosion).[55]
>20 mg/kg	Dose at which the NVIC advises to start treatment, based on a single intake.[53] A single dose of 20 mg/kg has been shown to cause no ill effects.[55]
> 50 mg/kg	Dose at which toxic effects on the gastrointestinal tract has been shown to occur.[33,53] At a dose range of 100 - 125 mg/kg vomiting, diarrhea, nausea, abdominal pain and anorexia have been observed.[34] At a single dose of 125 mg/kg vomiting, fecal blood loss and gastric erosions have been observed.[55]
≥ 150 mg/kg	Dose at which a risk of renal dysfunction emerges. The DPIC utilises a range of 100 – 175 mg/kg, in which signs of renal failure will arise.[53] Signs of renal dysfunction, for example polyuria and polydipsia, oliguria and uremia, have been observed at a dose of 175 - 200 mg/kg.[34]
> 300 mg/kg	Dose at which neurological effects has been shown to occur.[53] Seizures, coma and other signs of neurological function disorders has been observed at a dose range of 400 - 500 mg/kg.[34]
≥ 500 mg/kg	Is considered to be a **potentially life-threatening dose**. [34,56]

Table 5 Clinical signs observed in cats following acute ingestion of ibuprofen. The dosage is given in mg/kg body weight.

Dosage of ibuprofen	Clinical signs and other comments
> 0 mg/kg	Ibuprofen has never been available for therapeutic use in cats. Safety probably cannot be guaranteed in this species.
> 8 mg/kg	Dose at which the NVIC advises to **start treatment**, based on a single intake.[53]
> 50 mg/kg	Dose at which toxic effects on the gastrointestinal tract has been shown to occur. Clinical signs observed are gastrointestinal haemorrhage and irritation.[33,57]
> 200 mg/kg	Dose at which a risk of renal dysfunction emerges.[33]
> 600 mg/kg	Is considered to be a **potentially life-threatening dose**.[33,57]

3. Additional line and bar charts related to the analysis of exposure circumstances

3.1 Exposure scenario related

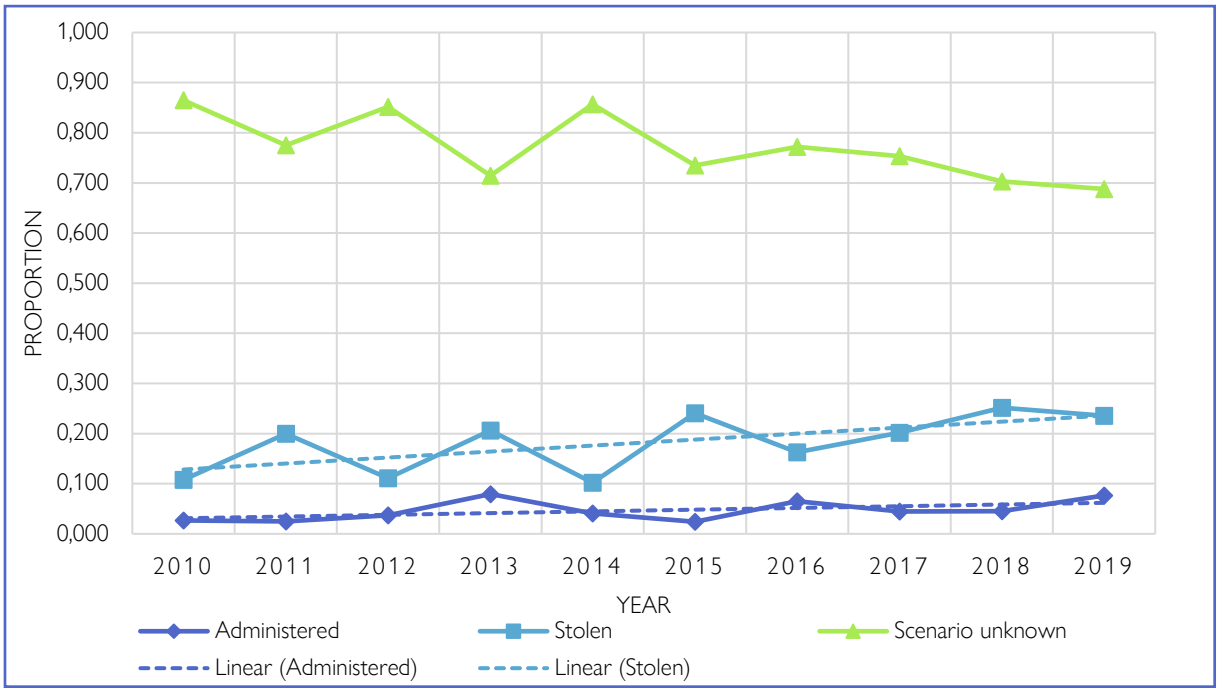

Figure 11 The number of **dogs** exposed to stolen and administered **acetaminophen** in **each category**, expressed as proportion of the total number of dogs exposed to acetaminophen for each year. There were no significant increases in dogs exposed to stolen and administered acetaminophen respectively over the period 2010 – 2019.

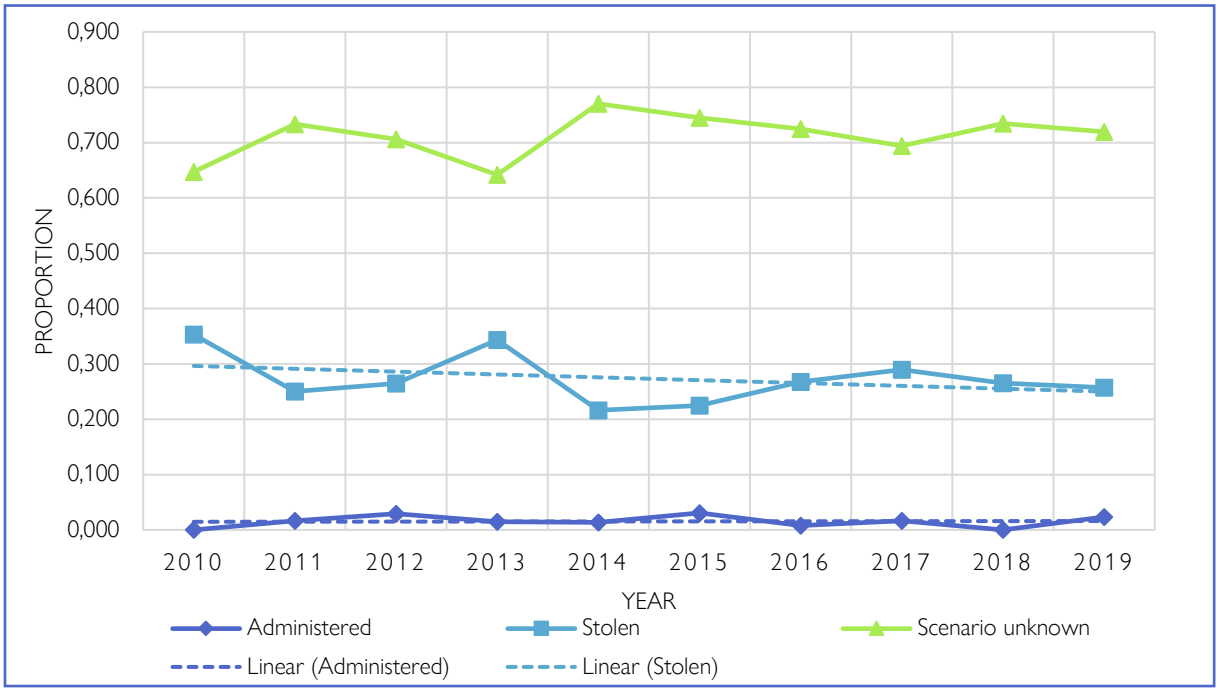

Figure 12 The number of **dogs** exposed to **ibuprofen** in **each category**, expressed as proportion of the total number of dogs exposed to ibuprofen for each year, from 2010 to 2019. There were no significant changes in dogs exposed to stolen and administered ibuprofen respectively.

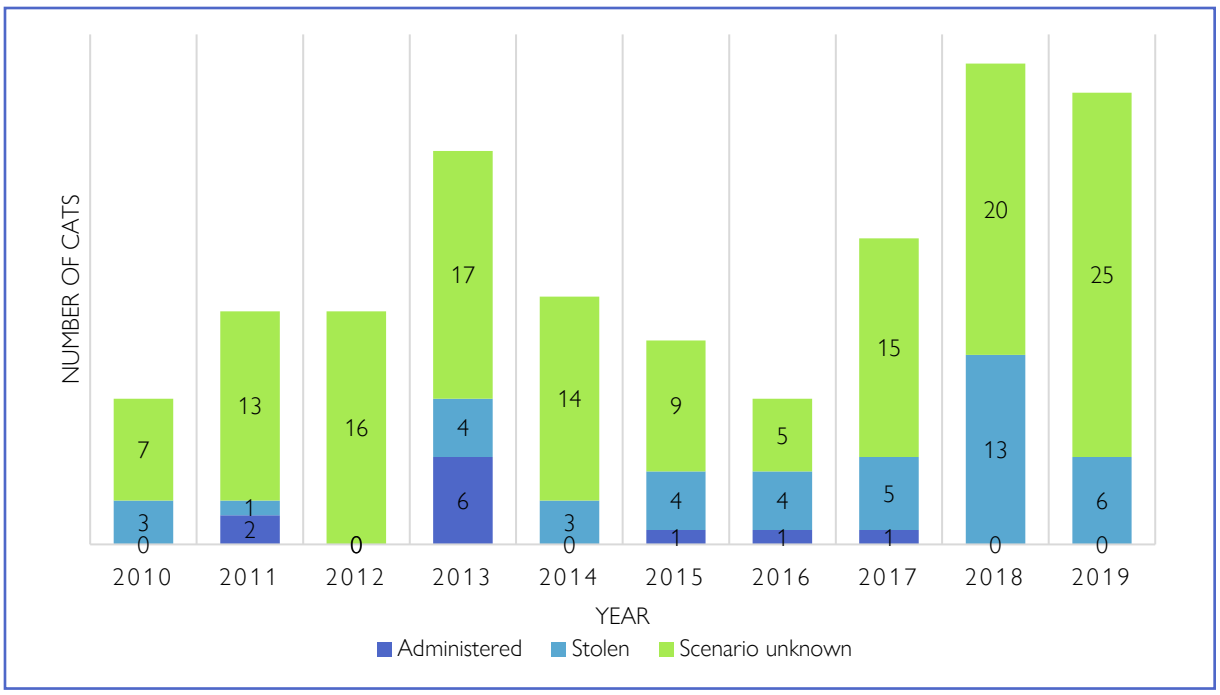

Figure 13 The number of **cats** supposedly exposed to **acetaminophen** divided into categories based on exposure scenario, from 2010 to 2019 There was a significant increase of 22.9% in the number of cats exposed to stolen ibuprofen.

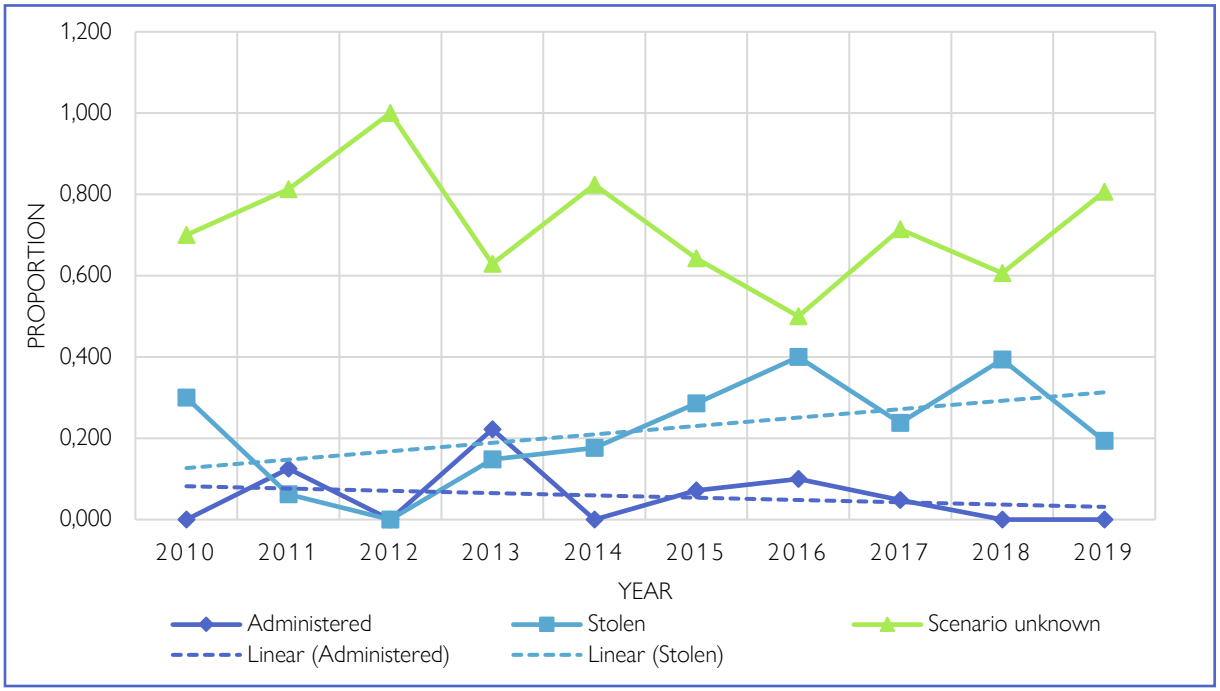

Figure 14 The number of **cats** supposedly exposed to **acetaminophen** in each category, expressed as proportion of the total number of cats exposed to acetaminophen for each year, from 2010 to 2019. There were no significant changes in the number of cats exposed to stolen and administered acetaminophen respectively.

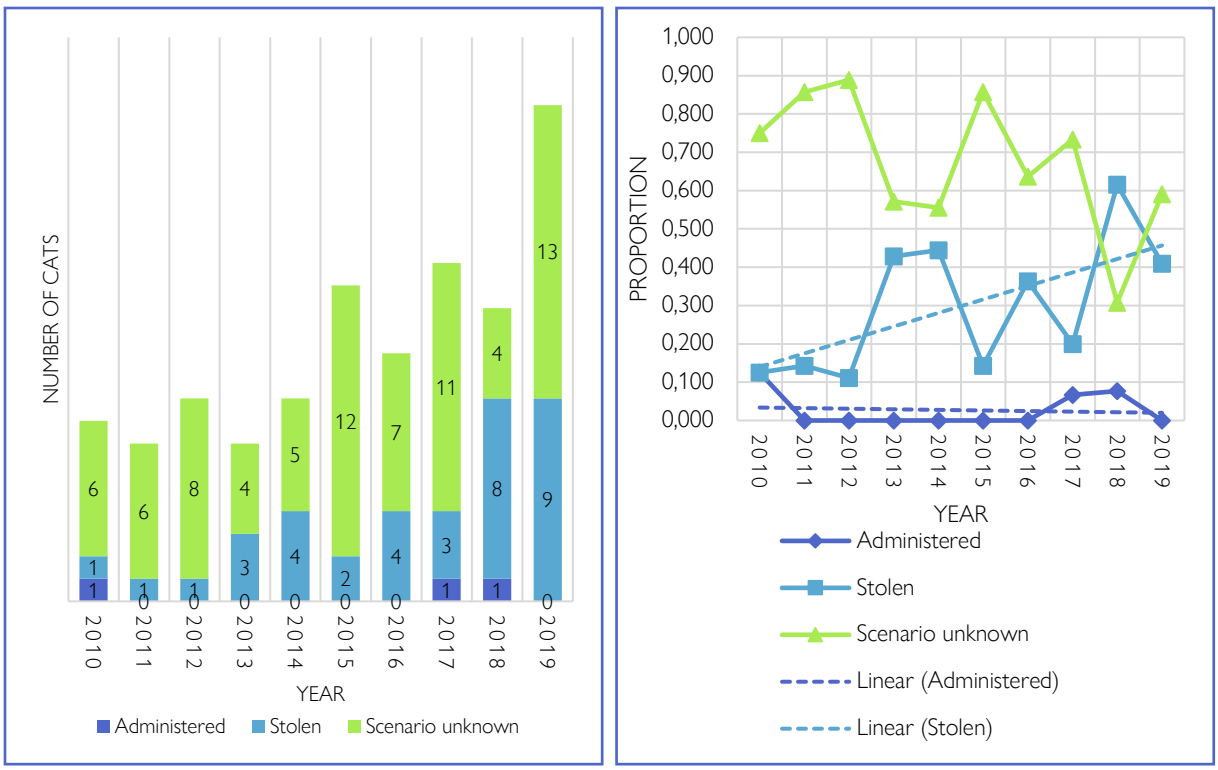

Figure 15 Left: the number of **cats** exposed to **ibuprofen** divided into categories based on exposure scenario, from 2010 to 2019. There was as significant mean increase of 27.6% in the number of cats exposed to stolen ibuprofen. Right: the number of cats exposed to ibuprofen in **each category**, expressed as proportion of the total number of cats exposed to ibuprofen for each year. There were no significant changes over the period 2010 – 2019.

3.2 Exposure dose related

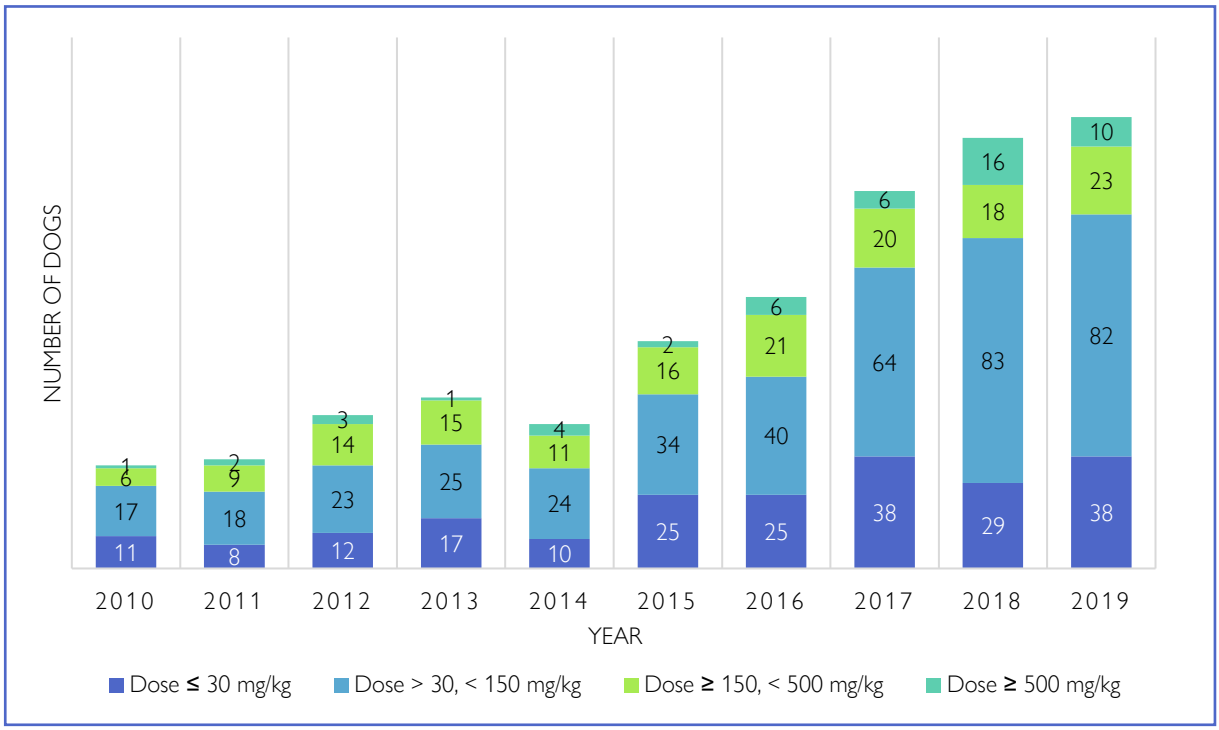

Figure 16 The number of **dogs** exposed to **acetaminophen** divided into exposure dose categories based on symptomatology, from 2010 to 2019. In each category a significant increase could be observed, with the strongest mean increase in category ≥ 500 mg/kg, considered to be a potentially life-threatening dose.

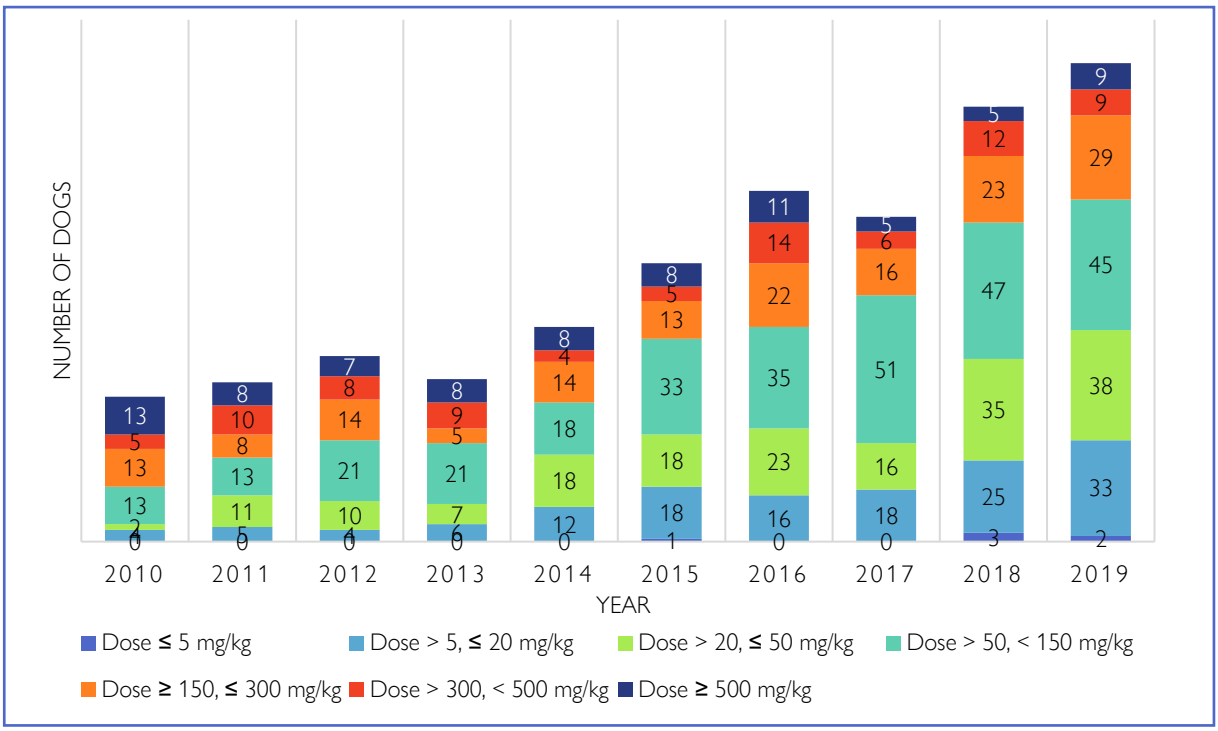

Figure 17 The number of **dogs** exposed to **ibuprofen** divided into exposure dose categories based on symptomatology, from 2010 to 2019. A significant increase can be seen in the categories covering a dose from 0 to 300 mg/kg, with the strongest growth (84.1%) in category ≤ 5 mg/kg.

Figure 18 Left: the number of **cats** exposed to **acetaminophen** divided into exposure dose categories based on symptomatology, from 2010 to 2019. There were no significant changes observed in absolute numbers of cats exposed to acetaminophen in each exposure dose category. Right: the number of cats exposed to acetaminophen in each exposure dose category, expressed as proportion of the total number of cats exposed to acetaminophen for each year. No trends have been demonstrated here either.

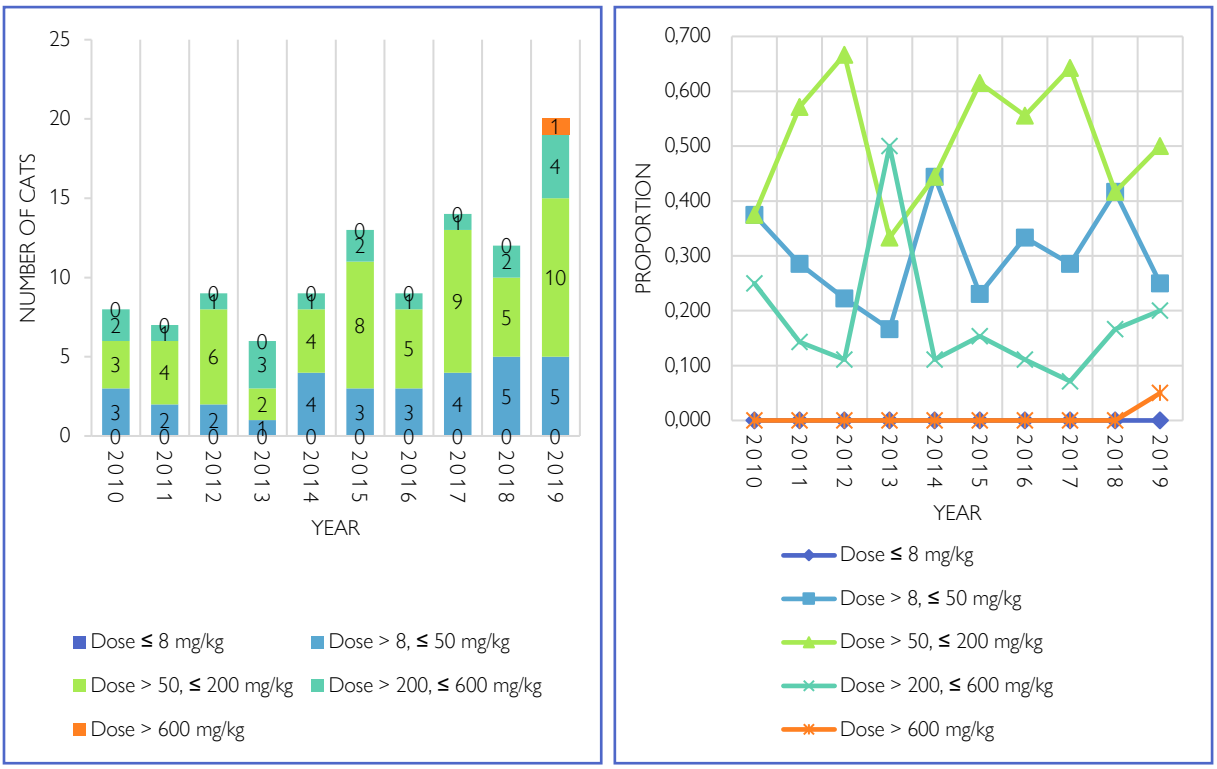

Figure 19 Left: the number of **cats** exposed **ibuprofen** divided into exposure dose categories based on symptomatology, from 2010 to 2019. The only significant changes in absolute numbers of cats exposed to ibuprofen were observed in exposure dose categories covering an exposure dose from 8 to 200 mg/kg, with the strongest growth (11.4%) in category 50 - 200 mg/kg . Right: the number of cats exposed to ibuprofen in each exposure dose category, expressed as proportion of the total number of cats exposed to ibuprofen for each year. No trends have been demonstrated here.

3.3 Related to the amount of tablets

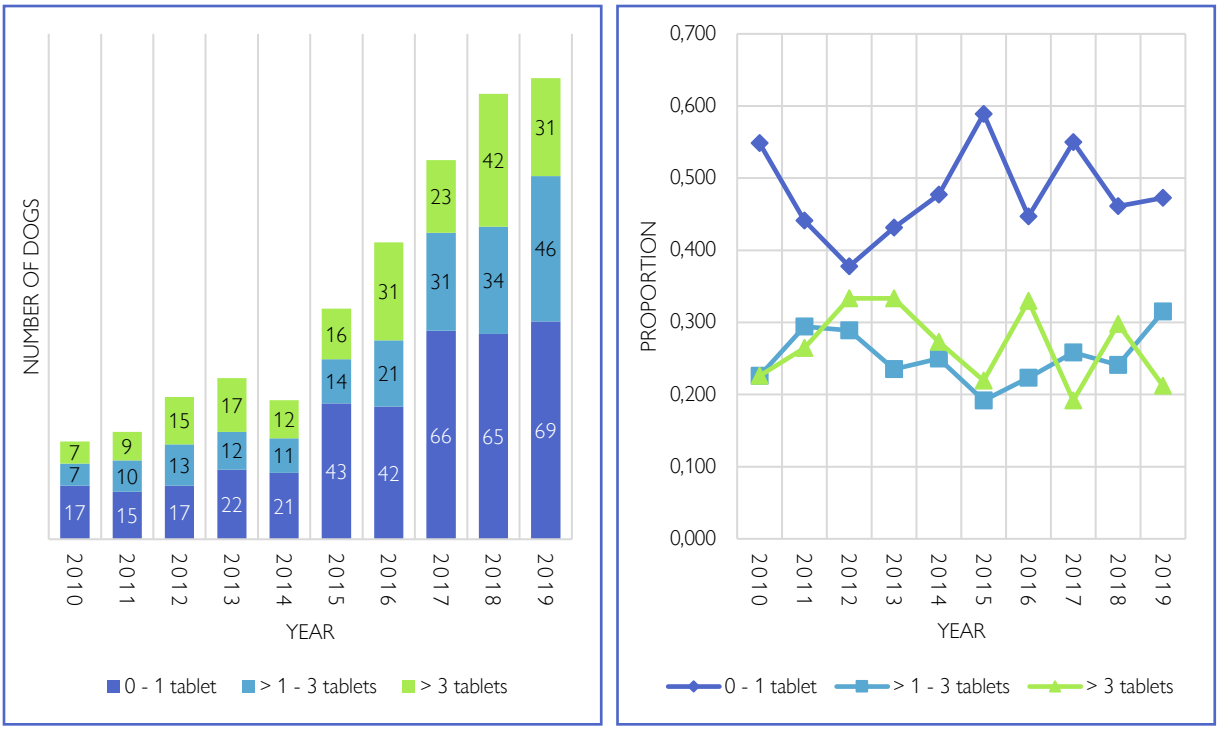

Figure 20 Left: the number of **dogs** exposed to **acetaminophen** divided into categories based on amount of tablet, capsules etc. to which the dogs have been exposed, from 2010 to 2019. A significant increase was observed in each tablet amount category, with the strongest mean increase (23.2%) in number of dogs in category >1 – 3 tablets. Right: the number of **dogs** exposed to **acetaminophen** in each tablet amount category, expressed as proportion of the total number of dogs exposed to acetaminophen for each year. No trends have been demonstrated in the period 2010 – 2019.

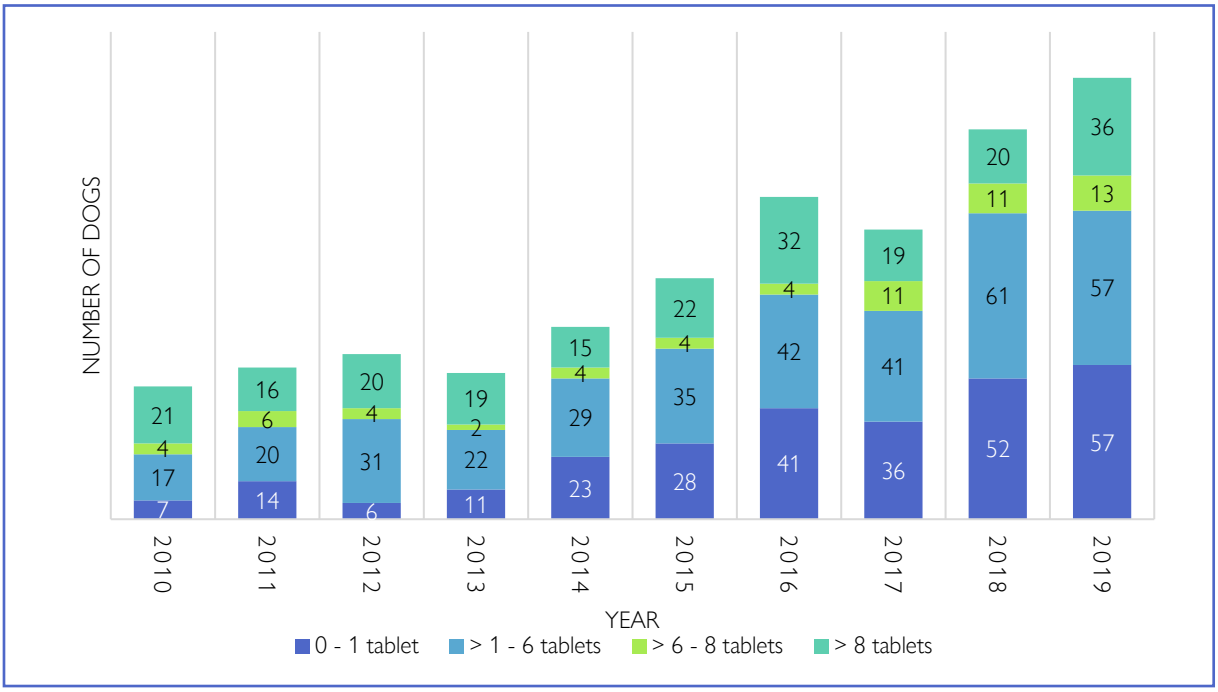

Figure 21 The number of **dogs** exposed to **ibuprofen** divided into categories based on amount of tablet, capsules etc., to which the dogs were exposed, for each year from 2010 to 2019. A significant increase could be seen in the categories covering an amount of 0 up to 8 tablets, with the strongest growth (25.9%) in category 0 – 1 tablet.

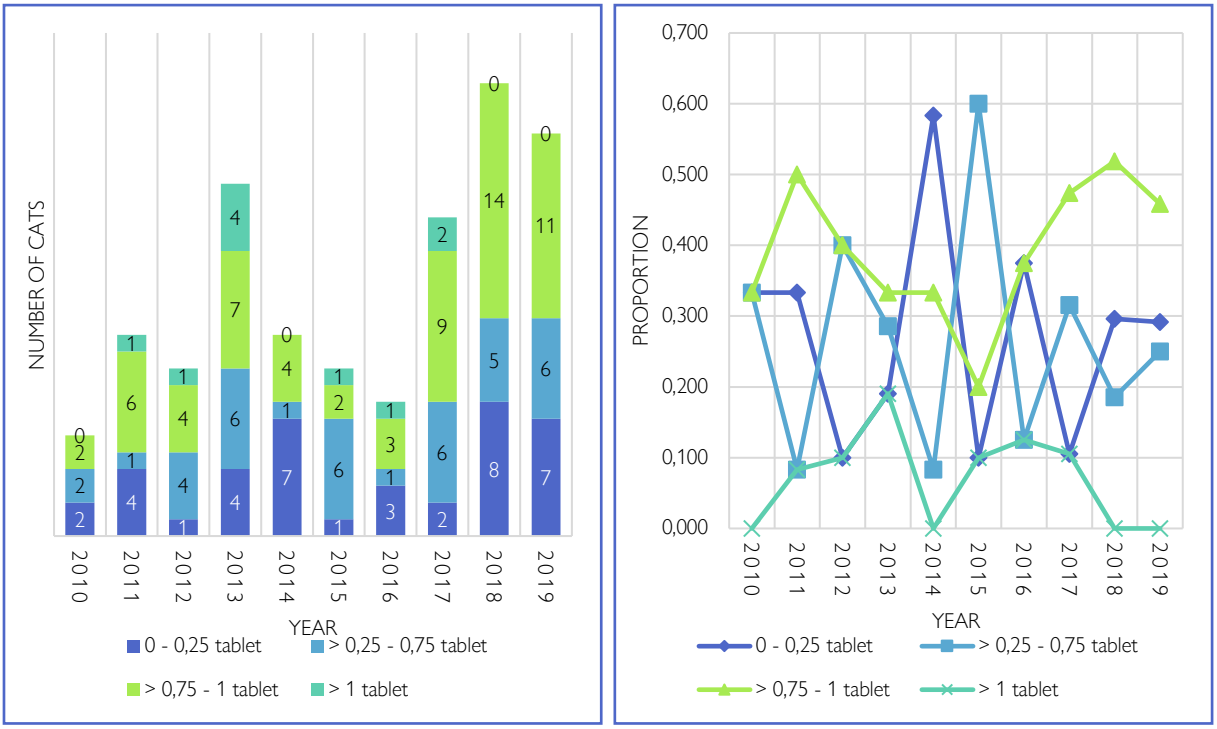

Figure 22 Left: the number of **cats** exposed to **acetaminophen** divided into categories based on amount of tablet, capsules etc., from 2010 to 2019. A significant mean increase of 16.2% was observed in the category >0,75 – 1 tablet over the past ten years. Right: the number of **cats** exposed to **acetaminophen** in **each category**, expressed as proportion of the total number of cats exposed to acetaminophen for each year. No trends have been observed in the period 2010 - 2019.

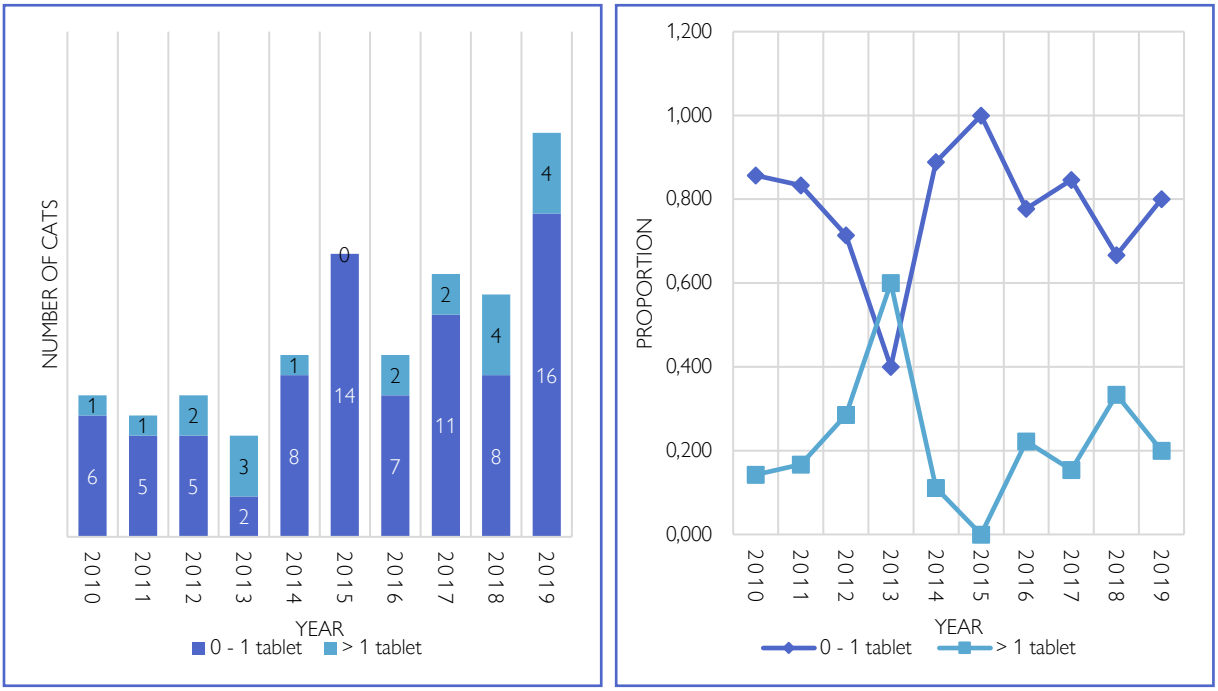

Figure 23 Left: the number of **cats** exposed to **ibuprofen** divided into categories based on amount of tablet, capsules etc., for each year from 2010 to 2019. For the number of cats exposed to 0 – 1 tablet a significant increase of 13.1% cats per year could be observed. Right: the number of **cats** exposed to **ibuprofen** in **each** tablet amount **category**, expressed as proportion of the total number of cats exposed to ibuprofen for each year. No trends have been observed in the period 2010 - 2019.

3.4 Related to the dose of tablets

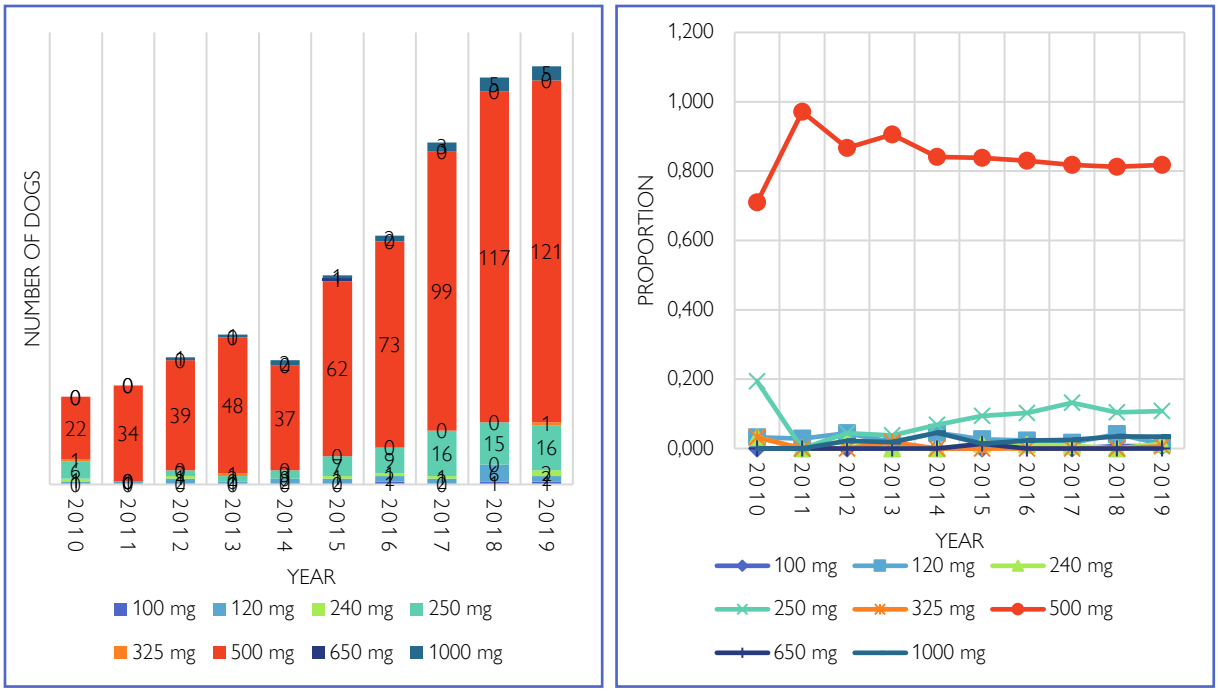

Figure 24 Left: the number of **dogs** exposed to **acetaminophen** divided into categories based on the dose of tablets, capsules etc., from 2010 to 2019. A significant mean increase in the number of dogs exposed to acetaminophen could be observed in the categories 100, 120, 250, 500 and 1,000 mg. Right: the number of **dogs** exposed to **acetaminophen** in **each tablet dose category**, expressed as proportion of the total number of dogs exposed to acetaminophen for each year from 2010 to 2019. No trends were demonstrated in this period.

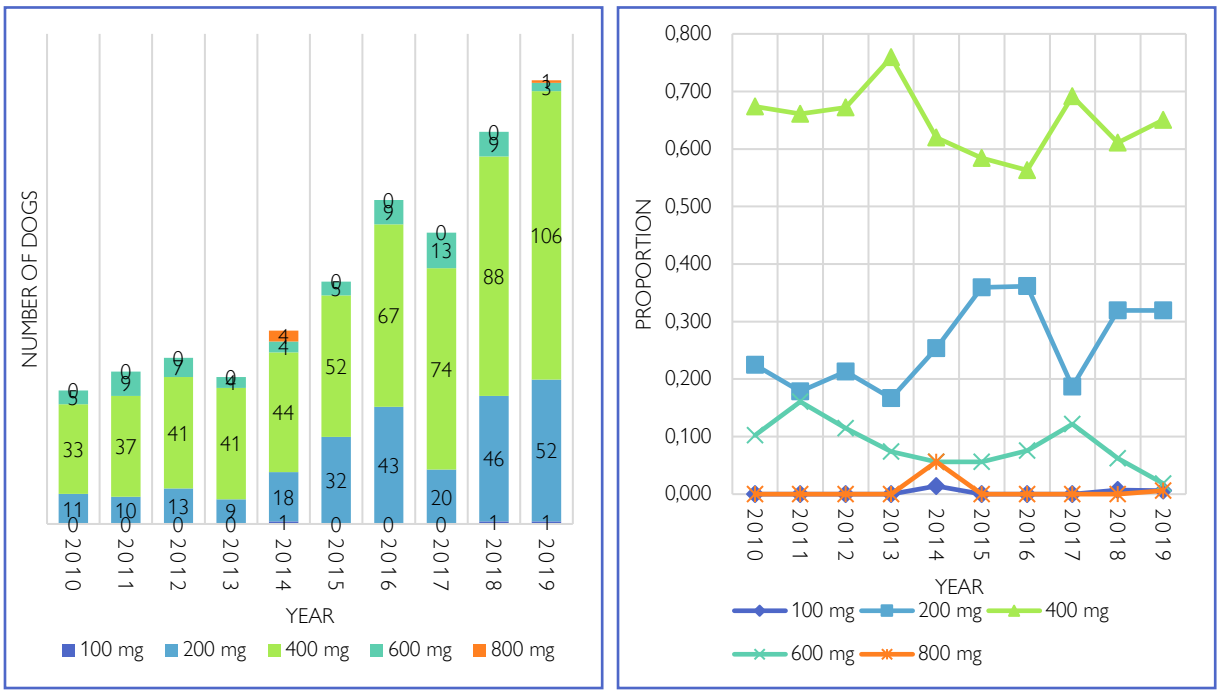

Figure 25 Left: the number of **dogs** exposed to **ibuprofen** divided into categories based on the dose of tablets, capsules etc., from 2010 to 2019. A significant mean increase could be observed in the number of dogs exposed to tablets containing 200 and 400 mg ibuprofen Right: the number of **dogs** exposed to **ibuprofen** in **each tablet dose category**, expressed as proportion of the total number of dogs exposed to ibuprofen for each year from 2010 to 2019. No trends were observed in this period.

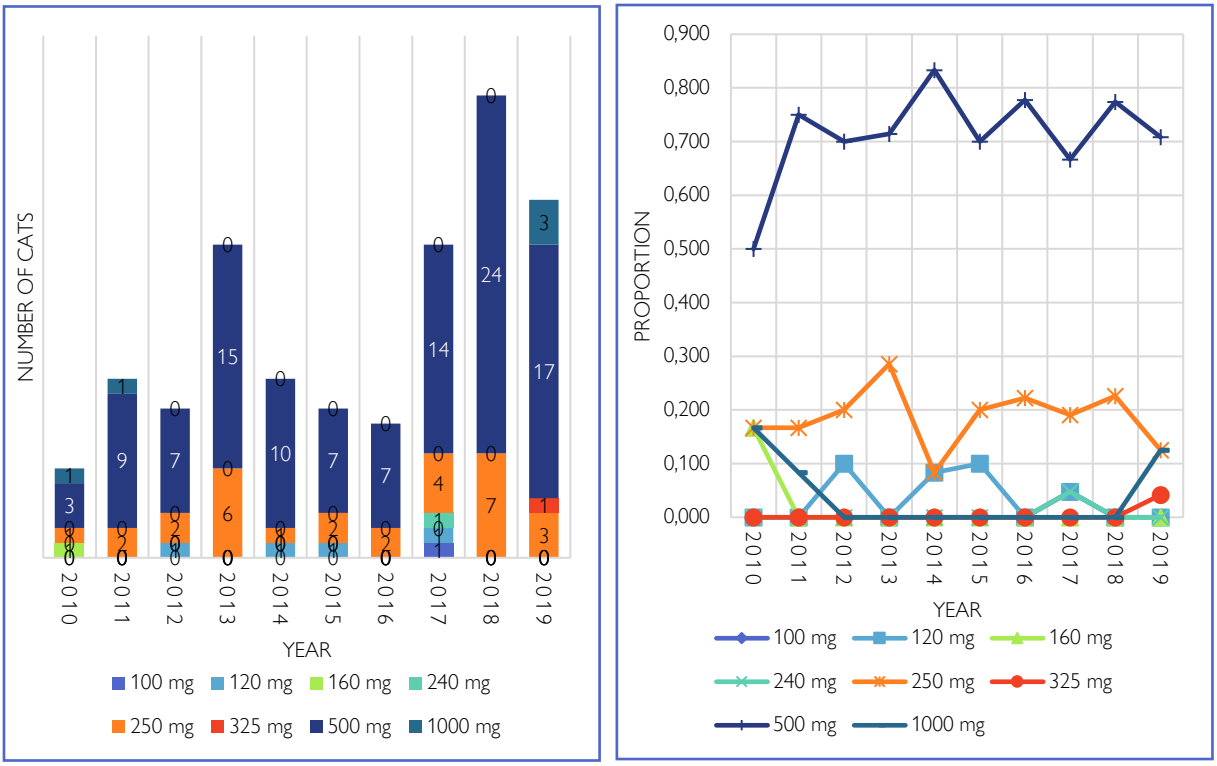

Figure 26 Left: the number of **cats** exposed to **acetaminophen** divided into categories based on the dose of tablets, capsules etc., from 2010 to 2019. Right: the number of **cats** exposed to **acetaminophen** in each tablet dose category, expressed as proportion of the total number of cats exposed to acetaminophen for each year. No significant increases or decreases in the number of cats exposed to tablets with a particular dose of acetaminophen could be demonstrated over the period 2010 – 2019.

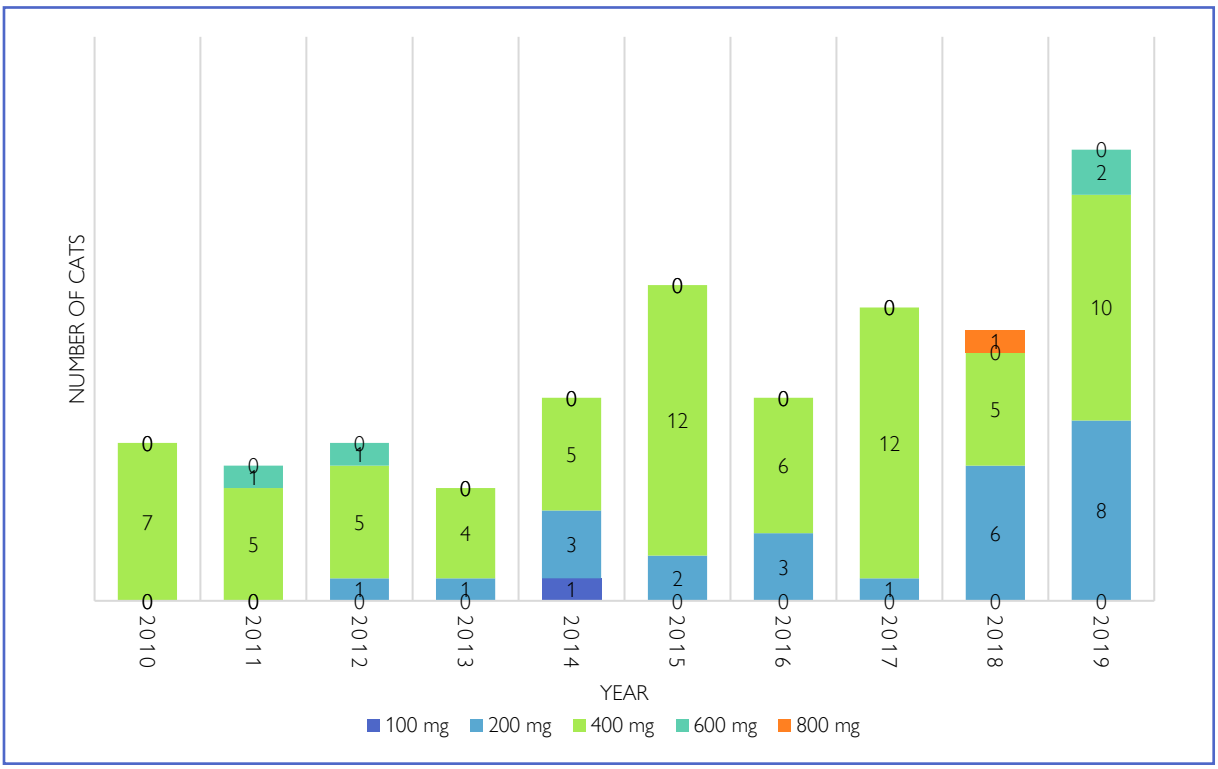

Figure 27 The number of **cats** presumably exposed to **ibuprofen** divided into categories based on the dose of tablets, capsules etc., from 2010 to 2019. A significant mean increase of 40.6% could be observed in the number of cats exposed to tablets containing 200 mg ibuprofen.

4. Tables concerning results of statistical analysis

Table 6 Results of Spearman rank correlation.

Variables	Correlation coefficient (r)	Square of the correlation coefficient (r^2)	P-value (P)
A. Absolute number of dogs exposed to acetaminophen B. Absolute number of dogs exposed to potential toxic substances	0.964	0.929	$< 2.2e^{-16}$*
A. Absolute number of cats exposed to acetaminophen B. Absolute number of cats exposed to potential toxic substances	0.585	0.343	0.075
A. Sum of the absolute number of dogs and cats exposed to acetaminophen B. Sum of the absolute number of dogs and cats exposed to potential toxic substances	0.960	0.923	$1.016e^{-5}$*
A. Absolute number of dogs exposed to ibuprofen B. Absolute number of dogs exposed to potential toxic substances	0.976	0.952	$< 2.2e^{-16}$*
A. Absolute number of cats exposed to ibuprofen B. Absolute number of cats exposed to potential toxic substances	0.860	0.739	0.001*
A. Sum of the absolute number of dogs and cats exposed to ibuprofen B. Sum of the absolute number of dogs and cats exposed to potential toxic substances	0.976	0.952	$< 2.2e^{-16}$*

Table 7 Results of (quasi)poisson regression analysis. The mean change is resulting from the regression coefficient (b).

Variables	Mean change	P-value (P)	95% Confidence interval (CI)
Dependent variable: Absolute number of cats exposed to acetaminophen *Independent variable:* Year (2010 – 2019)	+9.2%	0.047*	+1.5% – +17.6%
Dependent: Absolute number of cats exposed to ibuprofen *Independent:* Year (2010 – 2019)	+12.3%	0.001*	+7.6% – +17.2%
Dependent: Absolute number of dogs exposed to acetaminophen *Independent:* Absolute number of dogs exposed to potential toxic substances	+0.04%	$6.41e^{-6}$*	+0.03% – +0.04%

Dependent: Absolute number of cats exposed to acetaminophen *Independent:* Absolute number of cats exposed to potential toxic substances	+0.07%	0.04152*	+0.01% – 0.13%
Dependent: Sum of the absolute number of dogs and cats exposed to acetaminophen *Independent:* Sum of the absolute number of dogs and cats exposed to potential toxic substances	+0.03%	$5.77e^{-6}$*	+0.02% – +0.03%
Dependent: Absolute number of dogs exposed to ibuprofen *Independent:* Absolute number of dogs exposed to potential toxic substances	+0.03%	$1.68e^{-6}$*	+0.03% – +0.04%
Dependent: Absolute number of cats exposed to ibuprofen *Independent:* Absolute number of cats exposed to potential toxic substances	+0.09%	0.0002*	+0.06% – +0.12%
Dependent: Sum of the absolute number of dogs and cats exposed to ibuprofen *Independent:* Sum of the absolute number of dogs and cats exposed to potential toxic substances	+0.02%	$8.85e^{-7}$*	+0.02% – +0.03%
Dependent: Number of dogs exposed to acetaminophen / number of dogs exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	+6.7%	0.002*	+6.7% – +9.8%
Dependent: Number of dogs exposed to ibuprofen / number of dogs exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	+3,0%	0.014*	+1.1% – +4.9%
Dependent: Number of cats exposed to acetaminophen / number of cats exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	-1.3%	0.73	-8.4% – +6.2%
Dependent: Number of cats exposed to ibuprofen / number of cats exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	+1.2%	0.576	-2.8% – +5.4%
Dependent: Number of dogs exposed to acetaminophen / sum of the number of dogs and cats exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	+7.0%	0.002*	+4.1% – +10.1%
Dependent: Number of dogs exposed to ibuprofen / sum of the number of dogs and cats exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	+3.3%	0.008*	+1.4% – +5.3%

Dependent: Number of cats exposed to acetaminophen / sum of the number of dogs and cats exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	-2.4%	0.54	-9.3% – +5.1%
Dependent: Number of cats exposed to ibuprofen / sum of the number of dogs and cats exposed to potential toxic substances (→ proportion) *Independent:* Year (2010 – 2019)	+0.2%	0.93	-0.04% – +4.6%
Multiple regression analysis	**Mean change**	**P-value (P)**	**95% Confidence interval (CI)**
Dependent: Number of patients (with substance type ibuprofen, species dog and year 2010 as a reference) *Independent:* A. Year B. Substance type acetaminophen C. Year : Species cat D. Substance type acetaminophen : Species cat	 A. +10.5% B. -3.1% C. -24.0% D. -9.4%	 A. $1.25e^{-5}$* B. 0.783 C. $3.28e^{-10}$* D.0.682	 A. +6.4% – +14.9% B. -22.6% – +21.2% C. -28.8% – -19.4% D. -43.9% – +43.6%
Analysis of exposure scenario	**Mean change**	**P-value (P)**	**95% Confidence interval (CI)**
Dependent: Number of dogs exposed to administered acetaminophen *Independent:* Year (2010 – 2019)	+28.2%	0.0008*	+17.1% – +41.2%
Dependent: Number of dogs exposed to administered acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+7.7%	0.147	-1.6% – +18.1%
Dependent: Number of dogs exposed to stolen acetaminophen *Independent:* Year (2010 – 2019)	+27.7%	0.0001*	+19.3% – +37.2%
Dependent: Number of dogs exposed to stolen acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+6.8%	0.06	+0.7% – +13.4%

Dependent: Number of dogs exposed to administered ibuprofen *Independent:* Year (2010 – 2019)	+13.7%	0.173	-3.5% – +35.7%
Dependent: Number of dogs exposed to administered ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+1.0%	0.905	-14.0% – +18.8%
Dependent: Number of dogs exposed to stolen ibuprofen *Independent:* Year (2010 – 2019)	+13.7%	0.0001	+9.8% – +17.9%
Dependent: Number of dogs exposed to stolen ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-1.9%	0.318	-5.2% – +1.6%
Dependent: Number of cats exposed to administered acetaminophen *Independent:* Year (2010 – 2019)	-12.2%	0.510	-57.7% – +26.1%
Dependent: Number of cats exposed to administered acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-9.7%	0.514	-34.1% – +20.4%
Dependent: Number of cats exposed to stolen acetaminophen *Independent:* Year (2010 – 2019)	+22.9%	0.015*	+8.3% – +41.1%
Dependent: Number of cats exposed to stolen acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+10.0%	0.193	-3.4% – +26.0%
Dependent: Number of cats exposed to administered ibuprofen *Independent:* Year (2010 – 2019)	+6.3%	0.758	-27.4% – +60.3%
Dependent: Number of cats exposed to administered ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-5.6%	0.77421	-37.7% – +39.2%
Dependent: Number of cats exposed to stolen ibuprofen *Independent:* Year (2010 – 2019)	+27.6%	0.0005*	+17.5% – +39.2%
Dependent: Number of cats exposed to stolen ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+12.9%	0.069	+1.0% – +26.7%

Analysis of exposure dose	Mean change	P-value (P)	95% Confidence interval (CI)
Dependent: Number of dogs exposed to a dose of < 30 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+18.1%	0.0003*	+12.0% – +24.8%
Dependent: Number of dogs exposed to a dose of < 30 mg/kg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-0.8%	0.721	-4.7% – +3.4%
Dependent: Number of dogs exposed to a dose of >30, < 150 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+22.8%	3.41e^{6}*	+18.5% – 27.3%
Dependent: Number of dogs exposed to a dose of >30, < 150 mg/kg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+1.6%	0.126	-0.2% – +3.5%
Dependent: Number of dogs exposed to a dose of **≥** 150, < 500 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+11.5%	0.001*	+6.9% – +16.3%
Dependent: Number of dogs exposed to a dose of **≥** 150, < 500 mg/kg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-5.0%	0.055	-9.1% – -0.7%
Dependent: Number of dogs exposed to a dose of **≥** 500 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+31.8%	0.001*	+18.2% – 48.4%
Dependent: Number of dogs exposed to a dose of **≥** 500 mg/kg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+8.7%	0.14	-1.5% – +20.4%
Dependent: Number of dogs exposed to a dose of **≤** 5 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+84.1%	0.026*	+28.0% – +214.9%
Dependent: Number of dogs exposed to a dose of **≤** 5 mg/kg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+66.1%	0.052	+15.2% – +185.9%

Dependent: Number of dogs exposed to a dose of > 5, **≤** 20 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+26.9%	$9.64e^{-6}$*	+21.1% – +33.1%
Dependent: Number of dogs exposed to a dose of > 5, **≤** 20 mg/kg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+10.6%	0.003*	+5.4% – 16.1%
Dependent: Number of dogs exposed to a dose of > 20, **≤** 50 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+23.1%	0.0004*	+15.0% – +32.1%
Dependent: Number of dogs exposed to a dose of > 20, **≤** 50 mg/kg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+7.3%	0.093	-0.1% – +15.5%
Dependent: Number of dogs exposed to a dose of > 50, < 150 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+16.8%	$9.17e^{-5}$*	+12.0% – +21.9%
Dependent: Number of dogs exposed to a dose of > 50, < 150 mg/kg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+2.2%	0.384	-2.4% – +7.1%
Dependent: Number of dogs exposed to a dose of **≥** 150, **≤** 300 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+13.0%	0.006*	+6.0% – +20.7%
Dependent: Number of dogs exposed to a dose of **≥** 150, **≤** 300 mg/kg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-3.0%	0.334	-8,6% – +2.8%
Dependent: Number of dogs exposed to a dose of > 300, < 500 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+4.2%	0.373	-4.3% – +13.7%
Dependent: Number of dogs exposed to a dose of > 300, < 500 mg/kg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-9.7%	0.048*	-17.2% – -1.7%
Dependent: Number of dogs exposed to a dose of **≥** 500 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	-4.2%	0.209	-10.0% – +1.9%

Dependent: Number of dogs exposed to a dose of **≥** 500 mg/kg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-17.1%	0.0002*	-21.7% – -12.4%
Dependent: Number of cats exposed to a dose of < 50 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+3.8%	0.401	-4.4% – +12.7%
Dependent: Number of cats exposed to a dose of < 50 mg/kg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-6.2%	0.112	-12.6% – +0.6%
Dependent: Number of cats exposed to a dose of **≥** 50, < 60 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+11.8%	0.408	-12.5% – +46.1%
Dependent: Number of cats exposed to a dose of **≥** 50, < 60 mg/kg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+9.9%	0.340	-8.2% – +33.1%
Dependent: Number of cats exposed to a dose of **≥** 60, < 120 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+12.9%	0.173	-3.4% – +33.2%
Dependent: Number of cats exposed to a dose of **≥** 60, < 120 mg/kg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+5.6%	0.472	-8.3% – +22.0%
Dependent: Number of cats exposed to a dose of **≥** 120 mg/kg acetaminophen *Independent:* Year (2010 – 2019)	+11.5%	0.080	+0.4% – +24.2%
Dependent: Number of cats exposed to a dose of **≥** 120 mg/kg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+2.5%	0.481	-4.0% – +9.5%
Dependent: Number of cats exposed to a dose of > 8, **≤** 50 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+11.0%	0.015*	+3.9% – +18.7%
Dependent: Number of cats exposed to a dose of > 8, **≤** 50 mg/kg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+0.8%	0.825	-5.9% – +7.9%

Dependent: Number of cats exposed to a dose of > 50, ≤ 200 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+11.4%	0.028*	+3.1% – +20.7%
Dependent: Number of cats exposed to a dose of > 50, ≤ 200 mg/kg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+0.9%	0.742	-4.2% – +6.3%
Dependent: Number of cats exposed to a dose of > 200, ≤ 600 mg/kg ibuprofen *Independent:* Year (2010 – 2019)	+7.0%	0.299	+5.0% – +20.9%
Dependent: Number of cats exposed to a dose of > 200, ≤ 600 mg/kg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-5.2%	0.496	-18.5% – +9.8%
Analysis of amount of tablets	**Mean change**	**P-value (P)**	**95% Confidence interval (CI)**
Dependent: Number of dogs exposed to 0 – 1 tablets of acetaminophen *Independent:* Year (2010 – 2019)	+21.6%	$1.97e^{-5}$*	+16.6% – +27.0%
Dependent: Number of dogs exposed to 0 – 1 tablets of acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+0.6%	0.71	-2.4% – +3.7%
Dependent: Number of dogs exposed to > 1 – 3 tablets of acetaminophen *Independent:* Year (2010 – 2019)	+.23.2%	$6.76e^{-6}$*	+18.4 – +28.2
Dependent: Number of dogs exposed to > 1 – 3 tablets of acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+0.4%	0.803	-2.9% – +3.9%
Dependent: Number of dogs exposed to > 3 tablets of acetaminophen *Independent:* Year (2010 – 2019)	+18.1%	0.0007*	+11.2% – +25.6%
Dependent: Number of dogs exposed to > 3 tablets of acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-1.5%	0.535	-5.8% – +3.1%

Dependent: Number of dogs exposed to 0 – 1 tablet of ibuprofen *Independent:* Year (2010 – 2019)	+25.9%	$3.82e^{-5}$*	+19.2% – +33.2%
Dependent: Number of dogs exposed to 0 – 1 tablet of ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+10.1%	0.007*	+4.4% – +16.1%
Dependent: Number of dogs exposed to > 1 – 6 tablets of ibuprofen *Independent:* Year (2010 – 2019)	+14.4%	$3.23e^{-5}$*	+10.8% – +18.0%
Dependent: Number of dogs exposed to > 1 – 6 tablets of ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-0.5%	0.746	-3.3% – +2.4%
Dependent: Number of dogs exposed to > 6 – 8 tablets of ibuprofen *Independent:* Year (2010 – 2019)	+17.0%	0.009*	+7.2% – +28.3%
Dependent: Number of dogs exposed to > 6 – 8 tablets of ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-0.6%	0.895	-8.8% – +8.3%
Dependent: Number of dogs exposed to > 8 tablets of ibuprofen *Independent:* Year (2010 – 2019)	+5.8%	0.080	+0.1% – +11.9%
Dependent: Number of dogs exposed to > 8 tablets of ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-8.5%	0.004*	-12.4% – -4.6%
Dependent: Number of cats exposed to 0 – 0,25 tablet of acetaminophen *Independent:* Year (2010 – 2019)	+11.6%	0.149	-2.2% – +28.1%
Dependent: Number of cats exposed to 0 – 0,25 tablet of acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-1.2%	0.859	-13.2% – +12.4%
Dependent: Number of cats exposed to > 0,25 - 0,75 tablet of acetaminophen *Independent:* Year (2010 – 2019)	+11.0%	0.147	-2.1% – +26.4%
Dependent: Number of cats exposed to > 0,25 - 0,75 tablet of acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-1.0%	0.894	-13.8% – +13.7%
Dependent: Number of cats exposed to > 0,75 - 1 tablet of acetaminophen *Independent:* Year (2010 – 2019)	+16.2%	0.027*	+4.5% – 30.0%

Dependent: Number of cats exposed to > 0,75 - 1 tablet of acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+2.5%	0.396	-2.9% – +8.3%
Dependent: Number of cats exposed to > 1 tablet of acetaminophen *Independent:* Year (2010 – 2019)	-5.9%	0.683	-30.3% – +24.9%
Dependent: Number of cats exposed to > 1 tablet of acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-5.5%	0.623	-24.6% – +17.3%
Dependent: Number of cats exposed to 0 – 1 tablet of ibuprofen *Independent:* Year (2010 – 2019)	+13.1%	0.026*	+3.6% – +23.7%
Dependent: Number of cats exposed to 0 – 1 tablet of ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+0.2%	0.945	-4.5% – +5.1%
Dependent: Number of cats exposed to > 1 tablet of ibuprofen *Independent:* Year (2010 – 2019)	+14.7%	0.060	+1.7% – +30.3%
Dependent: Number of cats exposed to > 1 tablet of ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-0.6%	0.945	-16.0% – +17.6%
Analysis of tablet dose	**Mean change**	**P-value (P)**	**95% Confidence interval (CI)**
Dependent: Number of dogs exposed to tablet(s) containing 100 mg acetaminophen *Independent:* Year (2010 – 2019)	+72.7%	0.036*	+20.9% – +191.5%
Dependent: Number of dogs exposed to tablet(s) containing 100 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+57.3%	0.096	+6.1 – +185.44%
Dependent: Number of dogs exposed to tablet(s) containing 120 mg acetaminophen *Independent:* Year (2010 – 2019)	+15.0%	0.040*	+3.1% – +29.1%
Dependent: Number of dogs exposed to tablet(s) containing 120 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion)	-4.6%	0.333	-12.8% – -4.3%

Independent: Year (2010 – 2019)			
Dependent: Number of dogs exposed to tablet(s) containing 240 mg acetaminophen *Independent:* Year (2010 – 2019)	+12.2%	0.314	-8.6% – +40.1
Dependent: Number of dogs exposed to tablet(s) containing 240 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+11.0%	0.331	-29.7% – +10.5%
Dependent: Number of dogs exposed to tablet(s) containing 250 mg acetaminophen *Independent:* Year (2010 – 2019)	+29.1%	0.005*	+13.9% – +48.2%
Dependent: Number of dogs exposed to tablet(s) containing 250 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+4.3%	0.591	-10.1% – +21.4%
Dependent: Number of dogs exposed to tablet(s) containing 325 mg acetaminophen *Independent:* Year (2010 – 2019)	-5.9%	0.758	-37.6% – +37.9%
Dependent: Number of dogs exposed to tablet(s) containing 325 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-30.2%	0.167	-61.1% – +4.1%
Dependent: Number of dogs exposed to tablet(s) containing 500 mg acetaminophen *Independent:* Year (2010 – 2019)	+20.2%	$1.85e^{-6}$*	+16.7% – +23.8%
Dependent: Number of dogs exposed to tablet(s) containing 500 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-0.4%	0.642	-2.2% – +1.4%
Dependent: Number of dogs exposed to tablet(s) containing 650 mg acetaminophen *Independent:* Year (2010 – 2019)	+6.3%	0.873	-53.0% – +168.2%
Dependent: Number of dogs exposed to tablet(s) containing 650 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+6.3%	0.873	-53.0% – +168.2%
Dependent: Number of dogs exposed to tablet(s) containing 1,000 mg acetaminophen *Independent:* Year (2010 – 2019)	+38.4%	0.0002	+25.6% – +53.8%

Dependent: Number of dogs exposed to tablet(s) containing 1,000 mg acetaminophen / number of dogs exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+17.1%	0.073	+1.2% – +36.9%
Dependent: Number of dogs exposed to tablet(s) containing 100 mg ibuprofen *Independent:* Year (2010 – 2019)	+44.2%	0.158	-3.0% – +157.6
Dependent: Number of dogs exposed to tablet(s) containing 100 mg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+24.0%	0.407	-20.8% – +125.4%
Dependent: Number of dogs exposed to tablet(s) containing 200 mg ibuprofen *Independent:* Year (2010 – 2019)	+21.6%	0.0009*	+13.1% – +31.2%
Dependent: Number of dogs exposed to tablet(s) containing 200 mg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+5.8%	0.076	+0.2% – +11.8%
Dependent: Number of dogs exposed to tablet(s) containing 400 mg ibuprofen *Independent:* Year (2010 – 2019)	+14.5%	$5.11e^{-7}$*	+12.4% – +16.6%
Dependent: Number of dogs exposed to tablet(s) containing 400 mg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-1.0%	0.323	-2.9% – +0.9%
Dependent: Number of dogs exposed to tablet(s) containing 600 mg ibuprofen *Independent:* Year (2010 – 2019)	+2.5%	0.647	-7.5% – +13.8%
Dependent: Number of dogs exposed to tablet(s) containing 600 mg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-9.8%	0.065	-18.0% – -1.0%
Dependent: Number of dogs exposed to tablet(s) containing 800 mg ibuprofen *Independent:* Year (2010 – 2019)	+6.3%	0.846	-44.2% – +118.0%
Dependent: Number of dogs exposed to tablet(s) containing 800 mg ibuprofen / number of dogs exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-0.1%	0.998	-53.2% – +112.7%

Dependent: Number of cats exposed to tablet(s) containing 100 mg acetaminophen *Independent:* Year (2010 – 2019)	+44.2%	0.373	-23.2% – +343.7%
Dependent: Number of cats exposed to tablet(s) containing 100 mg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+44.2%	0.373	-23.2% – +343.7%
Dependent: Number of cats exposed to tablet(s) containing 120 mg acetaminophen *Independent:* Year (2010 – 2019)	0%	1.000	-26.4% – +35.8%
Dependent: Number of cats exposed to tablet(s) containing 120 mg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-4.4%	0.782	-31.2% – +30.8%
Dependent: Number of cats exposed to tablet(s) containing 240 mg acetaminophen *Independent:* Year (2010 – 2019)	+44.2%	0.373	-23.2% – +343.7%
Dependent: Number of cats exposed to tablet(s) containing 240 mg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+44.2%	0.373	-23.2% – +343.7%
Dependent: Number of cats exposed to tablet(s) containing 250 mg acetaminophen *Independent:* Year (2010 – 2019)	+11.3%	0.182	-3.4% – +29.1%
Dependent: Number of cats exposed to tablet(s) containing 250 mg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-0.3%	0.941	-6.9% – +6.8%
Dependent: Number of cats exposed to tablet(s) containing 500 mg acetaminophen *Independent:* Year (2010 – 2019)	+14.1%	0.021*	+4.4% – +25.2%
Dependent: Number of cats exposed to tablet(s) containing 500 mg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	+1.7%	0.264	-1.0% – +4.4%
Dependent: Number of cats exposed to tablet(s) containing 1,000 mg acetaminophen *Independent:* Year (2010 – 2019)	+14.7%	0.527	-22.9% – +83.7%

Dependent: Number of cats exposed to tablet(s) containing 1,000 mg acetaminophen / number of cats exposed to acetaminophen (→ proportion) *Independent:* Year (2010 – 2019)	-14.9%	0.492	-49.5% – +29.9%
Dependent: Number of cats exposed to tablet(s) containing 100 mg ibuprofen *Independent:* Year (2010 – 2019)	-14.3%	0.721	-71.9% – +99.0%
Dependent: Number of cats exposed to tablet(s) containing 100 mg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-14.3%	0.721	-71.9% – +99.0%
Dependent: Number of cats exposed to tablet(s) containing 200 mg ibuprofen *Independent:* Year (2010 – 2019)	+40.6%	0.001*	+23.0% – +63.5%
Dependent: Number of cats exposed to tablet(s) containing 200 mg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+23.0%	0.031*	+5.9% – +45.1%
Dependent: Number of cats exposed to tablet(s) containing 400 mg ibuprofen *Independent:* Year (2010 – 2019)	+6.7%	0.186	-2.2% – +16.5%
Dependent: Number of cats exposed to tablet(s) containing 400 mg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-5.3%	0.053	-9.6% – -0.8%
Dependent: Number of cats exposed to tablet(s) containing 600 mg ibuprofen *Independent:* Year (2010 – 2019)	+9.7%	0.650	-25.3% – +68.3%
Dependent: Number of cats exposed to tablet(s) containing 600 mg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	-14.0%	0.465	-44.7% – +24.7%
Dependent: Number of cats exposed to tablet(s) containing 800 mg ibuprofen *Independent:* Year (2010 – 2019)	+99.0%	0.157	+6.3% – +604.1%
Dependent: Number of cats exposed to tablet(s) containing 800 mg ibuprofen / number of cats exposed to ibuprofen (→ proportion) *Independent:* Year (2010 – 2019)	+99.0%	0.157	+6.3% – +604.0%