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Metabolism and pharmacokinetics of pharmaceuticals in cats (*Felix sylvestris catus*) and implications for the risk assessment of feed additives and contaminants

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Graphical_abstract

Highlights

- Review of xenobiotic metabolising enzymes and transporters in cats.
- Pharmacokinetic data for 30 pharmaceuticals are compared between cats and rats.
- -Uncertainty factors for risk assessment of chemicals in cats are derived.
- -Future work to further characterise xenobiotic metabolism in cats is discussed.

Abstract

In animal health risk assessment, hazard characterisation of feed additives has been often using the default uncertainty factor (UF) of 100 to translate a no-observed-adverse-effect level in test species (rat, mouse, dog, rabbit) to a 'safe' level of chronic exposure in farm and companion animal species. Historically, both 10-fold factors have been further divided to include chemical-specific data in both dimensions when available. For cats (*Felis Sylvestris catus*), an extra default UF of 5 is applied due to the species' deficiency in particularly glucuronidation and glycine conjugation. This paper aims to assess the scientific basis and validity of the UF for inter-species differences in kinetics (4.0) and the extra UF applied for cats through a comparison of kinetic parameters between rats and cats for 30 substrates of phase I and phase II metabolism. When the parent compound undergoes glucuronidation the default factor of 4.0 is exceeded, with exceptions for zidovudine and S-carprofen. Compounds that were mainly renally excreted did not exceed the 4.0-fold default. Mixed results were obtained for chemicals which are metabolised by CYP3A in rats. When chemicals were administered intravenously the 4.0-fold default was not exceeded with the exception of clomipramine, lidocaine and alfentanil. The differences seen after oral administration might be due to differences in first-pass metabolism and bioavailability. Further work is needed to further characterise phase I, phase II enzymes and transporters in cats to support the development of databases and *in silico* models to support hazard characterisation of chemicals particularly for feed additives.

Keywords: cats; pharmacokinetics; rats; uncertainty factor; chemical risk assessment; feed additives, contaminants

1. Introduction

"I am what I am. I would tell you what you want to know if I could, for you have been kind to me. But I am a cat, and no cat anywhere ever gave anyone a straight answer." Peter. S. Beagle, The Last Unicorn.

Hazards associated with chemicals are considered to show a threshold dose or concentration below which no toxic effect would be observed. Agencies worldwide have estimated levels of exposure, at which the risk for human/animals is negligible, by dividing the no-observed-adverse-effect-level (NOAEL) by a standard default uncertainty factor (Dourson et al., 1996; Renwick, 1993; WHO, 1987). This default uncertainty factor is the product of two factors of 10-fold, one to account for interspecies differences and another 10-fold to account for variability within the human or animal population (EFSA FEEDAP Panel, 2017a; Lehman and Fitzhugh, 1954; WHO, 1987). Both 10-fold factors have been further divided into toxicokinetic and toxicodynamic aspects to include chemical-specific data in the risk assessment process when available. The inter-species 10-fold has been divided into 4.0-fold and 2.5-fold for toxicokinetics and toxicodynamics, respectively. The inter-individual 10-fold has been divided into two factors of 3.16 (WHO, 1999). Overall, these uncertainty factors are initially applied to animal-to-human extrapolations as well as for animal-to-animal extrapolation, especially for cats and dogs (EFSA FEEDAP Panel, 2016b; Walton et al., 2001a; Walton et al., 2001c). For domestic cats (*Felis sylvestris catus*), an additional uncertainty factor of 4-5 has been applied for chemicals which are known to be extensively glucuronidated since cats, as hypercarnivores, are known to have a low glucuronidation activity particularly for aromatic (phenolic) compounds (EFSA FEEDAP Panel, 2016b).

For feed additives as well as for undesirable chemicals in animal feed, limited data in cats is available. In order to derive safe intake levels in cats, in most cases toxicological studies in rats are used, applying a 100-fold factor to the derived NOAEL in rats (EFSA FEEDAP Panel, 2016a; EFSA FEEDAP Panel, 2016d; EFSA FEEDAP Panel, 2017b; EFSA FEEDAP Panel, 2019). According to this regulatory approach, for

thresholded toxicants the above default factors could be replaced by information on fundamental pharmacokinetic and mechanistic data. This would result in the derivation of more biologically defensible risk assessments. Pharmacokinetic data (such as clearance, area under curve (AUC), Cmax, and bioavailability) for a chemical could address interspecies extrapolations, inter-individual variability, and assist in identifying markers of actual target tissue dose. An interspecies default factor of 4.0 is used to allow for individuals of a given species to be exposed to a 4-fold higher level of a chemical compared to the test species for the same intake level. However, differences in the underlying physiological processes, such as blood flow, organ weight and cardiac output, can affect the internal concentration of a chemical (Walton et al., 2001b). Furthermore, biotransformation enzymes greatly determine absorption, bioavailability, metabolism and excretion of chemicals, affecting the internal concentration and the extent to which this may differ between species. Finally, the extent of the absorption, distribution, and excretion of a given xenobiotic may be also affected by transporters (Schrickx and Fink-Gremmels, 2008). Overall, including information of ADME properties and particularly metabolism in test species would allow for the characterisation of 'species- and pathway-related uncertainty factors. Historical examples include meta-comparative analysis of kinetic data for CYP1A2 metabolism, glucuronidation as well as renal excretion between test species (rat, mouse, dog, rabbit) and humans using markers of acute (Cmax) and chronic exposure (AUC, Clearance) (Walton et al., 2001b; Walton et al., 2001c; Walton et al., 2004).

This paper aims to provide 1. a comparative account for phase I, phase II xenobiotic metabolism and transporters between cats and rats 2. a comparative assessment of pharmacokinetic differences between rats and cats for available probe substrates of phase I and/or phase II metabolism to provide a scientific basis for the derivation of science-based UFs in cats. 3. a perspective on future work to support the development of databases and *in silico* tools for cats to support hazard characterisation of chemicals in this species. A graphical abstract is depicted in Figure 1.

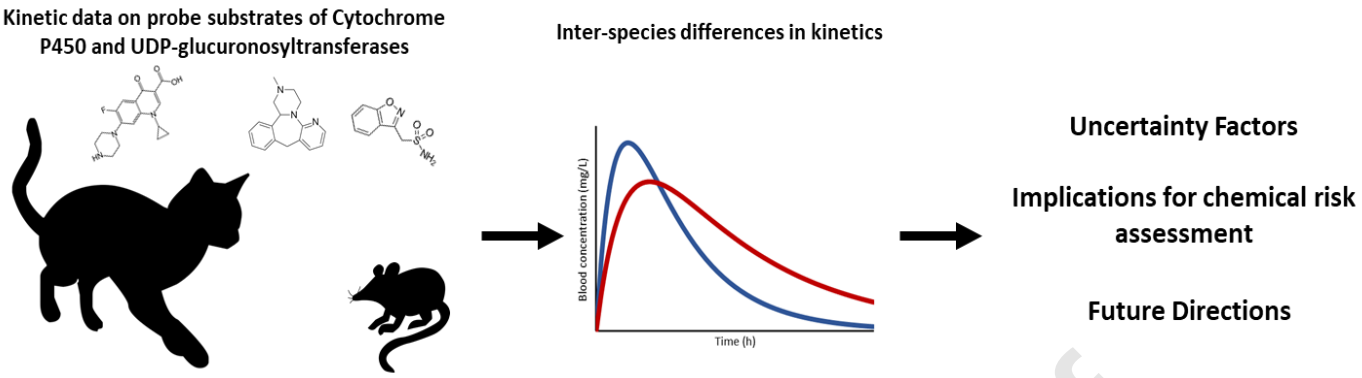

Figure 1. Comparative assessment of pharmacokinetics between cats and rats for various chemicals to derive science-based uncertainty factors and implications for chemical risk assessment.

2. Materials and Methods

2.1. Literature search

Literature searches were performed in PubMed and Scopus to identify 1. reviews on relevant information related to physiological parameters and phase I, phase II xenobiotic metabolism and transporters in cats and rats and. 2. Individual available *vivo* studies reporting PK parameters for probe substrates of phase I and phase II metabolism and transporters using a combination of the terms 'pharmacokinetic*' OR 'kinetic*' OR 'metabolism' AND 'cats' OR 'feline' AND 'name of compound' reporting *in vivo* parameters for markers of acute (Cmax) and chronic exposure (area under the plasma concentration curve (AUC) and clearance), were collected and computed in an excel database. All *in vivo* studies in cats were matched with the comparative rat data for each chemical through additional literature searches in rats, as the most common test species used in chemical risk assessment.

2.2. Standardisation and data analysis

PK parameters collected from the literature were standardised to quantify their comparative ratios between rats and cats on a normalised dose and body weight (BW) basis. AUCs and plasma clearance were normalised to the dose and body weight and expressed in ml/min/kg and µg.h/mL/kg BW

respectively and Cmax to µg/mL/kg BW. The oral route of exposure was preferred to the intravenous route (e.g. oral clearance (CL/F)) since it reflects the route of administration relevant to chronic exposure to feed additives and other xenobiotics such as contaminants and incorporates pre-systemic metabolism in the gut (bioavailability, F) and systemic clearance from the liver, both influencing internal dose and ADME processes of chemicals. However, data for the intravenous route was also collected since it is also an important route of exposure for veterinary drugs and provides a mean to quantify interspecies differences in liver metabolism while excluding differences in bioavailability and pre-systemic metabolism (oral route). Inter-species differences in pharmacokinetics as difference in internal dose between rats and cats were quantified as the ratio between weighted PK parameters for clearance (rats/ cats) and AUC and Cmax (cats/rats).

3. Results

3.1. Physiological differences between cats and rats

Physiological differences between rats and cats can be measured on BW basis (Table 1). While the variation in organ weight is relatively small, larger differences are observed for organ blood flow and cardiac output (2.2 to 2.5-fold) as well as in glomerular function rates (3-fold) between cats and rats. This is not unexpected, since for larger animal species physiological processes such as heart rate and cardiac output are slower, and metabolic and excretion rates lower (Nair and Jacob, 2016).

3.2. Xenobiotic metabolising enzymes and transporters activities

In the past century, aside from the adage “cats are not small dogs”, very little information was available on the biotransformation enzyme profile of feline species. A generic low glucuronidation ability has been long recognised as a feature of felines (Robinson and Williams, 1958) and rationalised by their dietary evolution as obligate carnivores greatly limiting the intake of natural xenobiotics such as plant toxins (Shrestha et al., 2011). With regards to phase I enzymes and renal excretion, no evidence was

found for slower clearance of drugs that are eliminated by oxidation or unchanged into urine or bile in cats. In addition, previous reviews have indicated that differences in plasma protein binding may explain observed PK differences in cats for highly bound compounds (Court, 2013). The section below provides a state of the knowledge on phase I, Phase II enzymes and transporters in feline species.

3.2.1 Phase I enzymes: Cytochrome P450

The limited information available for the major CYP isoforms involved in phase I biotransformation of xenobiotics in cats is summarised in Figure 2 while providing a comparison with rats and humans. (Sugiyama et al., 2019a). First of all, feline liver CYP content is reported to be relatively lower (one fifth) than that from rats (Tanaka et al., 2006) or dogs (one third) (Graham et al., 2002). With regards to CYP isoforms, CYP1A1 and 1A2 have been cloned and characterised, and found to share more than 72% homology with their rat and human counterparts (Tanaka et al., 2006). Both isoforms are able to bioactivate either benzo(a)pyrene or phenacetin with a relatively low Km (Tanaka et al., 2006). Accordingly, the intrinsic clearance of another prototypical CYP1A substrate, 7-ethoxyresorufin, was reported to be four-fold higher in cats compared to that in dogs (Shah et al., 2007). CYP1A1 mRNA transcript expression has been found in lung, stomach, small intestine and pancreas of cats while ,in contrast, CYP1A2 mRNA transcripts have only been detected in the liver similarly to rats and in most other mammalian species (Visser et al., 2019). *In vitro* kinetic studies using the CYP1A1 substrate theophylline revealed both a 3-demethylation as well as an 8-hydroxylation pathways; the rate of 3-demethylation in feline liver microsomes was higher than that of 8-hydroxylation, while the reverse was true in rat liver preparations (Tanaka et al., 2006). In addition, while Vmax of CYP1A2-mediated phenacetin O-demethylation were almost superimposable in cat and rat liver microsomes, the intrinsic clearance (Vmax/Km) was about one third in cat liver microsomes compared to rat, pointing to a higher sensitivity of the feline species to the generation of phenacetin toxic metabolites (Tanaka et al., 2006).

Cat liver microsomes have also been documented to biotransform a number of model fluorescent CYP2B substrates (van Beusekom et al., 2010). More recently, however, a feline CYP2B with a high degree of homology with the canine CYP2B-ortholog was found to be expressed in lung and small intestine but, unlike in rats, humans and dogs, not in liver. This evidence suggests a minor contribution of the CYP2B subfamily to the overall metabolism of CYP2B substrates such as barbiturates and several anaesthetics (e.g. medetomidine, ketamine, propofol) (Okamatsu et al., 2017). In humans, several CYP2C isoforms contribute to the biotransformation of ~20% of the most common prescribed drugs, including warfarin, tolbutamide and several NSAIDs (e.g. ibuprofen) whereas in cats, only one functional isoform (CYP2C41) has been identified so far (Ono et al., 2019) This is associated with a very low expression in the liver and small intestine and points to a negligible role also of CYP2C enzymes in systemic clearance of drugs for cat and is consistent with the very low amounts of hydroxylated metabolites of warfarin and tolbutamide detected under in vivo (Smith et al., 2000) and in vitro conditions (Shah et al., 2007). Feline CYP2D6 (Komatsu et al., 2010) and CYP2E (Tanaka et al., 2005) were found to share the highest homology with the respective canine orthologues and to be mostly expressed in liver. It is worth noting that in cats' liver, CYP2E is much more expressed compared to that in rats and humans, accounting for more than 40% of all CYPs (Figure 2). In this context, yeast microsomes expressing feline, human and canine CYP2E showed that the intrinsic clearance of the CYP2E probe substrate chlorzoxazone in cats exceeded by 3-fold the one measured in dogs and was within the same order of magnitude of that measured in humans (Tanaka et al., 2005), In line with its relative high expression (Figure 2), in humans, liver CYP3A mediates the metabolism of nearly half of all marketed drugs and feline CYP3A131 is ranked as the second CYP in cat liver (Figure 2) and is also expressed in the small intestine. Hence, likely to play a key role in the pre-systemic metabolism of several xenobiotic. Interestingly feline CYP3As are quite far from their rodent counterparts based on phylogenetic analysis and despite a high degree of homology with the canine CYP3As, both qualitative and quantitative differences have been reported in the CYP3A-

mediated metabolism of diazepam; these are thought to contribute to the hepatic injury often exhibited by cats upon the repeated exposure to the benzodiazepine (van Beusekom et al., 2015). Finally, recent studies using heterologous co-expression systems confirm the presence of CYP polymorphisms in cat liver and small intestine which may affect metabolism of drugs and other chemicals (i.e. CYP1A2, 2A, 2E and 3A), (Sugiyama et al., 2019a; Sugiyama et al., 2019b; Sugiyama et al., 2019c; Tanaka et al., 2005).

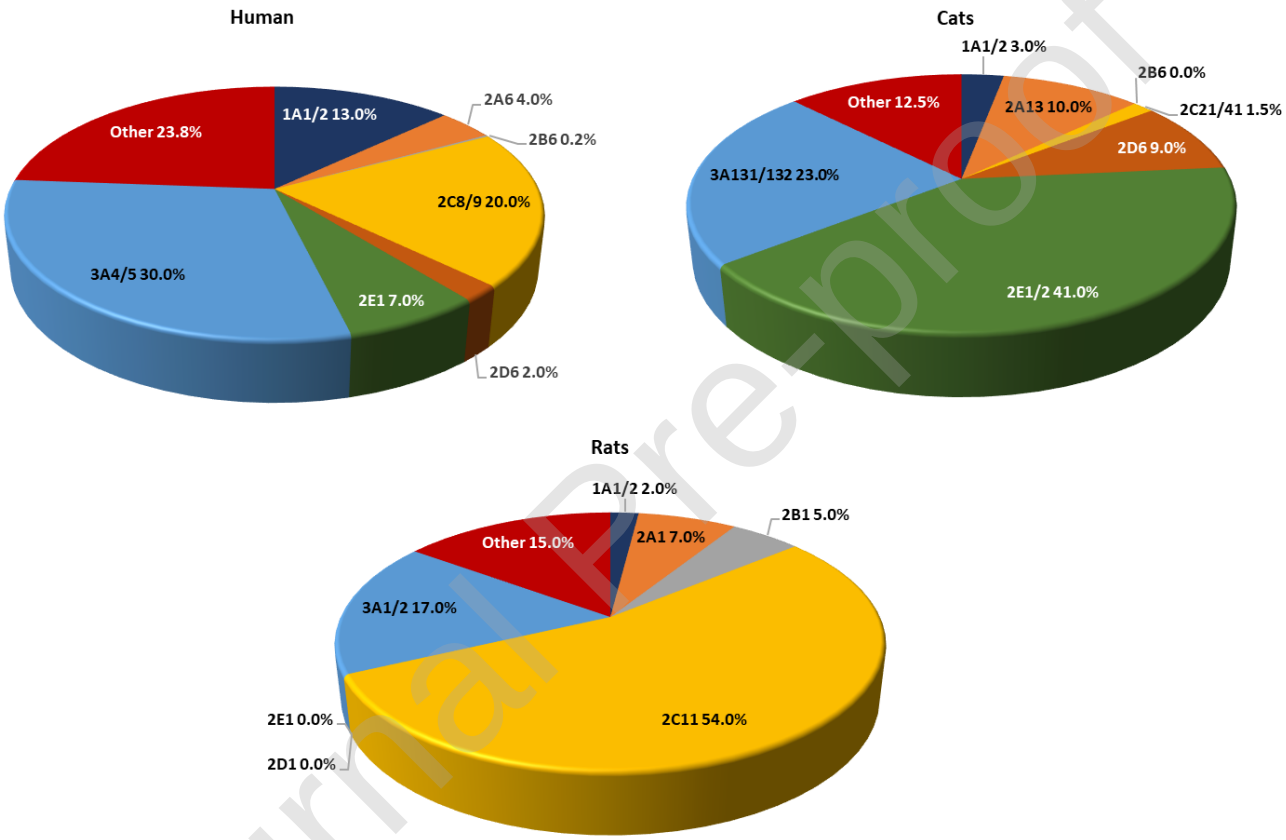

Figure 2. Major liver cytochrome P450 enzymes in rats (Walton et al., 2001c) and cats (Visser et al., 2019) compared to humans (Hewitt et al., 2007).

3.2.2 Phase II enzymes

The cat displays peculiar expressions and activities of several phase II enzymes, making it considerably different from rats, dogs and humans. Cats are long known as relatively inefficient in the glucuronidation of simple phenols and other aromatic substrates (Capel et al., 1974). The reason behind such low activity

lies in the fact that cats mostly lack functional UGT1A6 and UGT1A9, which results in the low clearance of several drugs (illustrated in Table 2), including chloramphenicol, carprofen, and propofol and many other phenolic derivatives and may explain the high sensitivity of felines to acetaminophen (APAP) (Court and Greenblatt, 2000). The intrinsic clearance of the UGT2B-mediated glucuronidation of 17β-oestradiol and several benzodiazepines has also been shown to be much lower in cats compared to that in dogs and provides a further possible rationale for the occurrence of adverse hepatic effects following the use of benzodiazepines (Kondo et al., 2017). However, other drugs, even of aromatic structure (e.g. salicylates, flurbiprofen, ibuprofen) seem to be efficiently glucuronidated (Court, 2013) and other pathways (e.g. glucosidation) may contribute to the overall clearance of drugs (Slovak et al., 2017). A single N-Acetyltransferase form (NAT-1) with limited activity toward arylamines is expressed in felines (Trepanier et al., 1998); the consequent reduction in *p*-aminophenol (PAP) conversion back to APAP coupled with the inability to form PAP glucuronides is believed to play a key role in the generation of APAP-mediated methemoglobinemia in cats (McConkey et al., 2009). Glycine conjugation, which is one of the major pathway in salicylate elimination, is a further defective pathway in cats, which is consistent with the slow clearance of aspirin (acetylsalicylic acid) in cats since cats excrete mostly salicylic glucuronides (60-80%) with some unchanged salicylate (12-23%) but only a minor amount of salicylurate (~5%) (Davis and Westfall, 1972). With regards to methyltransferases, genetic polymorphisms for erythrocyte thiopurine S-methyltransferase (TPMT) is present in cats and confers them with lower activities compared with several other species including humans (Court, 2013). Such S-Methylation is an important detoxification mechanism for several drugs used for treatment of anticancer drugs (6-mercaptopurine) and immunosuppressants (azathioprine) and may represent a factor of susceptibility in cats for thiopurine compounds (Court, 2013; Salavaggione et al., 2004). Information on isoforms of glutathione-S-transferases in cats is currently not available.

3.2.3 Transporters

Only in the last three decades, systematic investigations have been carried out on transporters in veterinary species and they have been the subject of recent reviews (Martinez et al., 2018; Virkel et al., 2019). Scant information is available for cats (Court, 2013; van Beusekom, 2015). No major differences in tissue distribution and cell localization of P-gp (MDR1) are known in cats, dogs and humans (Van Der Heyden et al., 2009). As regards ABCG2, a defective protein is known to be expressed in cats; this transporter is involved in the biliary excretion and is part of the blood-retina barrier in mammalian species so that drugs such as fluoroquinolones may accumulate in feline eyes leading to phototoxicity and eventually retinal damage (Ramirez et al., 2011). Also hepatic MRP2 (ABCC2), which participates in biliary excretion of chemicals, does not seem to be expressed in cats (Malekinejad et al., 2015). Overall, the above-mentioned deficiencies are expected to decrease the elimination rate of several chemicals possibly resulting in drug toxicity (Mealey, 2013). Further research is needed to assess the impact of transporters on the kinetics of pharmaceuticals and toxicants in cats and other feline species.

3.3. Comparative pharmacokinetics between cats and rats

Pharmacokinetics differences between cats and rats have been assessed for probe substrate pharmaceuticals of phase I, phase II and renal excretion. Pharmacokinetic data for probe substrate of specific transporters were not available. Mean ratios were calculated after normalisation to dose and body weight to quantify inter-species differences between cats and rats and major species-related kinetic features are illustrated below in Tables 2-7. A summary of the comparative pharmacokinetic features for these probe substrates of Phase I, Phase II metabolism and renal excretion between rats and cats for each pharmaceutical assessed in this study is provided below.

3.3.1 Probe substrates for Phase I enzymes

Table 2, 3 and 4 illustrate available data for phase I probe substrates for markers of chronic intravenous exposure (clearance and AUC, Table 2), markers of chronic oral exposure (clearance and AUC, table 3) and acute exposure (Cmax, table 4) respectively.

Alfentanil

Alfentanil is used as an analgesic and is extensively metabolised in rats with minor amounts excreted as the parent compound. Oxidative N-dealkylation is the primary metabolic route with further glucuronidation (Meuldermans et al., 1987). In cats, alfentanil is eliminated more slowly compared to other species and the metabolite have not been identified (Pascoe et al., 1993) (Table 2) However, evidence for glucuronidation in the rat suggest that alfentanil elimination may be reduced in the cat due to its lower hepatic glucuronidation activity.

Amantadine

Amantadine is an adjunct to NSAIDs for cats and dogs in the treatment of cancer-related pain and degenerative joint disease. The chemical is metabolised in rats, but the parent compound is also renally cleared (Goralski et al., 1999). Bioavailability of amantadine is about 90% in rats (Higashi et al., 2005). Oral bioavailability of a drug is defined as a fraction of its bioavailability after i.v. administration, which is assumed to be 100%. In cats, oral bioavailability of amantadine averaged about 130% (Siao et al., 2011). This artificial value might be due to a remarkable uptake of the drug by the lung upon i.v. administration, as it was previously reported in mice (Bleidner et al., 1965), thereby lowering the drug i.v. bioavailability. Metabolism has not been investigated (Siao et al., 2011).

Amitriptyline

Amitriptyline is a highly lipophilic belonging to the tricyclic antidepressant drug family such as clomipriamine and nortriptyline.. PK studies in rats have shown that around 50% of a radioactive dose of amitriptyline is excreted into the bile (Cassano et al., 1965). The main metabolic route for amitriptyline in rats is CYP-mediated hydroxylation and subsequent glucuronidation (Lee et al., 2015). Oral absorption of amitriptyline in cats is rapid, but information on metabolism were not available (Mealey et al., 2004). However, since cats are have lower glucuronidation activities, methyl hydroxylation or N-demethylation , as in humans and dogs, might be the predominant metabolic pathways in felines and metabolites may have longer half-lives compared to the parent compound (Boothe, 2011; Lee et al., 2015)

Atenolol

Atenolol is a beta-blocker widely used in veterinary medicine to treat hypertension and hypertrophic cardiomyopathy. In rat and humans the bioavailability of atenolol is around 50-60%, with limited generation of hydroxylated metabolites (10%) and predominant excretion of the unchanged compound via the kidney (Mehvar et al., 1990). By contrast, oral bioavailability of atenolol is near complete (90%) in cats and dogs and the elimination half-life is similar to that in humans (Khor et al., 2012). Intestinal absorption of atenolol has been reported to be strictly dependent on enteric drug transporters (Yu et al., 2017) and enteric pH (Tabacova and Kimmel, 2002). Differences in absorption might therefore explain the higher bioavailability in cats compared to that in rats and consequently differences in AUC and Cmax values .

Clomipramine

Clomipramine is a selective serotonin reuptake inhibitor with belongs to the tricyclic antidepressant drug family. In rats, clomipramine is rapidly absorbed with a low bioavailability (30%). Clomipramine is extensively metabolised via N-demethylation to desmethylclomipramine and hydroxylation by a range

of CYP isoforms and is then glucuronidated (Valoti et al., 1998; Yoo et al., 1999). In cats, the bioavailability is around 90%, which is much higher compared to humans (50%) and dogs (16%), and might reflect interspecies differences in first-pass metabolism (Lainesse et al., 2006). clomipramine metabolism in cats , shows differences in metabolite pattern formation, N-oxide representing the major metabolite (Lainesse et al., 2007). Intravenous and oral AUC values with a range of administered doses must be cautiously compared, as nonlinear pharmacokinetic studies have been reported in some humans and dogs at steady-state, and interpreted as potential saturation of hydroxylating hepatic CYP enzymes . Despite a relatively high bioavailability, clearance in the cat is much lower compared to that in the rat (Table 2 and 3) or the dog (Hewson et al., 1998). The rationale behind such such large interspecies variation may include higher plasma protein binding, as well as lower hydroxylation and glucuronidation activities in the cat (Lainesse et al., 2007; Lainesse et al., 2006).

Cyclosporine

Cyclosporine A (CsA) is an immunosuppressant and a substrate of P-glycoprotein and CYP3A in rats (Yang et al., 2017) and dogs (Boothe, 2011). The enteric absorption of CsA is also assumed to be dependent on the P-glycoprotein in cats and is associated with a bioavailability of around 29% (Colombo and Sartori, 2018). In several mammalian species, CsA is metabolised mainly in the liver by CYP3A enzymes to yield N-demethylated and hydroxylated derivatives; this oxidative pathway is reported to occur to a much lower extent in rats compared to that in humans, dogs, hamsters and rabbit based on microsome experiments (Robson, 2003). No major kinetic differences between rats and cats following iv or oral dosing have been reported (Table 2 and 3).

Flunixin

Flunixin is a nonsteroidal anti-inflammatory drug used in veterinary medicine only as flunixin meglumine. In rats, flunixin meglumine is eliminated via the liver and the kidney by active transport with

an i.v. elimination half-life of less than 2 hours (Hwang and Yun, 2011). In cats, flunixin meglumine displays high plasma protein binding, is largely taken up by the liver by means of an OATP-2-like transporter (Horii et al., 2004) and is mostly excreted via the biliary route with extensive enterohepatic circulation (Takata et al., 2011). This may account for the longer elimination half-life of the drug in cats vs. rats amounting to about 6 hr (Horii et al., 2004).

Fluoxetine

Fluoxetine is an antidepressant which acts as a selective serotonin reuptake inhibitor . In rats, oral fluoxetine bioavailability is approximately 38%, however first-pass metabolism has been shown to be dose dependent. Furthermore, the chemical is rapidly metabolised in the rat (Caccia et al., 1990). In cats, fluoxetine is extensively absorbed by the oral route (almost 100%,) (Papich, 2015) and N-demethylated into the equally active metabolite norfluoxetine, with a longer half-life compared to that of fluoxetine itself (Ciribassi et al., 2003; Boothe, 2012) The observed differences in AUC and Cmax between rats and cats (Table 3) might be due to differences in oral bioavailability and saturation of clearance pathways (CYP, transporters and transporters).

Itraconazole

Itraconazole is an antifungal drug administered by the oral route andits has been shown to be pH-dependent resulting in higher serum concentrations at lower (gastric) pH (Yoo et al., 2002). Bioavailability of itraconazole is low in rats (16%). Itraconazole is hydroxylated to hydroxyitraconazole by CYP3A in rats and dogs for which both forms are at the same time substrates and inhibitors (Peng et al., 2012; Yoo et al., 2000). In cats, bioavailability is around 52%; drug-drug interactions with cyclosporine have been documented, pointing at the involvement of CYP3A for itraconazole metabolism in cats (Colombo and Sartori, 2018).

Lidocaine

Lidocaine is used as local anaesthetic and antiarrhythmic drug. It is metabolised in rats and humans by CYP3A to several metabolites, including the active N-demethylated derivative monoethylglycinexylidide (Tang et al., 2009). In cats, lidocaine appears to be metabolised and cleared mainly through hepatic metabolism but no isoform-specific CYP has been identified. In addition, alterations in hepatic blood flow has been shown to influence internal concentrations of lidocaine (Thomasy et al., 2005). Pharmacokinetic differences in lidocaine observed between rats and cats might be due to differences in dose-dependent saturation of the enzymes involved in lidocaine's metabolism.

Mirtazapine

Mirtazapine is a tetracyclic antidepressant used as an appetite stimulator and an antiemetic in cats. In rats, bioavailability has been reported to be low (7%) (Liang et al., 2016; Rouini et al., 2014). Mirtazapine is a weakly basic drug (pKa 7.1) and may not be well absorbed in the stomach of fasting animals for which pH is low. In rats, only glucuronides have been detected, but it is suspected that mirtazapine is first metabolised by a range of CYP isoforms into 8-OH mirtazapine and then glucuronidated as it is observed in humans (Rouini et al., 2014). In cats, mirtazapine is primarily cleared by hepatic metabolism (Fitzpatrick et al., 2018) and hydroxylated to 8-OH mirtazapine and then glucuronidated (Quimby et al., 2011). Pharmacokinetic differences between rats and cats might be due to differences in bioavailability as well as to the limited glucuronidation capacity in cats.

Ondansetron

Ondansetron is a serotonin 5-HT3 receptor antagonist which is used to treat nausea and vomiting . Bioavailability of ondansetron is about 4% in rats (Yang and Lee, 2008). Hepatic oxidative metabolism accounts for nearly 95% of ondansetron clearance rats and <5% of the drug undergoes renal excretion. Species differences have been observed in the metabolism of ondansetron and in rats ondansetron is mainly metabolised by CYP2D and CYP3A (Yang and Lee, 2008). Bioavailability in cats is higher compared

to rats with 32% The significant differences in oral pharmacokinetic parameters between cats and rats can be explained by the poor oral bioavailability in rats, which is attributed to high first pass metabolism and consistently, such differences were not observed after iv administration (Quimby et al., 2014).

.Pioglitazone

Pioglitazone is used in veterinary medicine to treat Type 2 diabetes. Differences in bioavailability between rats (81%) and cats (55%) were reported, however, inter-individual variation in bioavailability up to 18% have been reported in cats (Clark et al., 2012). Although the extent of plasma protein binding of pioglitazone in cats has not been reported, its median volume of distribution suggests that it remains primarily in the plasma compartment in cats and may also be highly protein-bound. In rats, pioglitazone is metabolised by CYP3A (Umathe et al., 2008). According reports in rodents, dogs, and humans (Maeshiba et al., 1997), it is likely that hepatic metabolism is the predominant clearance and elimination route in cats, based on the PK evidence for troglitazone, which is structurally-related to pioglitazone. Overall, PK differences between cats and rats (Table 3) were minor (Clark et al., 2012).

Piroxicam

Piroxicam is a nonsteroidal anti-inflammatory drug which is metabolised mainly through oxidation via CYP2C and is rapidly eliminated in cats compared to dogs, humans, and rats (Bulman-Fleming et al., 2010; Court, 2013; Ogiso et al., 1999). Bioavailability of piroxicam is about 80% in cats (Heeb et al., 2003). Limited differences in absorption, intestinal or hepatic metabolism are expected between cats and rats for piroxicam.

Praziquantel

Praziquantel is used to treat parasitic worm infections. The chemical has a low solubility that results in a low oral bioavailability. In rats and humans, praziquantel is mainly metabolised by CYP3A yielding hydroxylated metabolites (Masimirembwa and Hasler, 1994). Available studies have shown that there

are large differences in the dose administered in cats compared to that in rats (8.5 mg/kg vs 40 mg/kg) and these may provide a rationale for the PK differences, observed between the two species (Arion et al., 2018; Masimirembwa et al., 1994). Furthermore, data suggest an important first-pass effect of praziquantel in cats that might contribute to the low bioavailability of the compound. However, it is noted that in this study praziquantel was co-administered with pyrantel which may have an impact on praziquantel bioavailability or first pass metabolism (Arion et al., 2018).

Quinidine

Quinidine belongs to the group of antiarrhythmics which also includes lidocaine. In rats, quinidine is metabolised by CYP3A (Izuwa et al., 2009). In cats, CYP2D is inhibited by quinidine *in vitro* (Perez Jimenez et al., 2016; Shah et al., 2007; van Beusekom et al., 2010). Multiple oral dosing with ketoconazole, a CYP3A inhibitor, prolonged t1/2 and decreased the total clearance of quinidine in cats suggesting that CYP3A may participate in the biotransformation of quinidine in the feline species (Shah et al., 2009). i

Ramipril

Ramipril is a prodrug and is converted in the liver to ramiprilat, which is an angiotensin-converting enzyme inhibitor used to treat hypertension. In humans and dogs, ramipril is converted to ramiprilat by de-esterification (hydrolysis) in the liver and it is likely that this may also occur in the rat and the cat (Desmoulins et al., 2008; Dubey and Ghosh, 2015). Currently. no major differences in the PK parameters of ramipril between rats and cats have been shown.

Tacrolimus

Tacrolimus is an immunosuppressive drug that is often used after organ transplantation. In rats, oral bioavailability is very low (5%), it is transported by P-glycoprotein,and also metabolised by CYP3A2 at both enteric and hepatic level (Zhou et al., 2013). In cats, the macrolide antibiotic clarithromycin (a CYP

3A-substrate) increased tacrolimus blood concentrations, through inhibition of CYP3A andP-glycoprotein first-pass metabolism and transport (Katayama et al., 2014). The large differences in PK parameters (AUC and Cmax) observed in cats compared to rats (Table 3) may be explained by a lower influence of the first pass effect for the PK of tacrolimus (CYP3A and drug transporters) resulting from lower activities of P-glycoprotein in cats .

Tramadol

Tramadol is an opioid analgesic and is used to treat acute and chronic pain. The mean bioavailability of tramadol is about 70% after a single oral dose in rats and about 18 metabolites have been identified (Wu et al., 2001; Zhang et al., 2014). Bioavailability of tramadol in cats is nearly complete (93%) (Pypendop and Ilkiw, 2008). In dogs, tramadol is metabolised by CYP2D into the active metabolite O-desmethyl tramadol (M1) which is also significantly produced in cats (Cagnardi et al., 2011; Shah et al., 2007). Remarkably, M1 is more persistent in cats compared to dogs which is mainly due to the higher amount of M1 produced in cats compared to dogs (Perez et al., 2016) and the likely lower glucuronidation activity in the cat (Cagnardi et al., 2011).

Overall, differences in internal dose between cats and rats for phase I probe substrates between cats and rats were heterogenous:

- For markers of chronic exposure, these ranged from 1.1-fold to 12.1-fold (clomipramine) for the intravenous route and for 1.4-fold to 120-fold (clomipramine) for the oral route. In addition, internal dose differences between cats and rats were much larger for the oral route compared to those for the intravenous route. For the oral route, compounds for which differences in internal doses were the largest for markers of chronic exposure included clomipramine (120-fold), tacrolimus (99-fold), fluoxetine (23-fold) and ondansetron (19.5-fold). The rationale behind this observation is likely to involve differences in absorption, CYP activities and phase II

enzymes involved in the conjugation of the CYP-generated metabolites, protein binding and drug transporter expression.For Cmax as a marker of acute exposure, these differences were also heterogenous and ranged from 0.55 to 40.4-fold (Clomipramine), although less striking compared to those observed for Clearances and AUCs (e.g. clormipramine (40.3-fold), fluoxetine (15.9-fold) and ondansetron (5.2-fold).

For Hydrolysis, ramipril clearance was 5-fold higher in the cat compared to that in rats but no differences in Cmax were noted.

3.3.2. Probe substrates for Phase II enzymes and renal excretion

Table 5 and 6 illustrate available data for phase II and renal excretion probe substrates for markers of chronic intravenous exposure (clearance and AUC, Table 5), markers of chronic and acute oral exposure (Table 6).

Probe substrates for phase II enzymes

Aspirin

Aspirin is a nonsteroidal anti-inflammatory drug. In rats, aspirin is hydrolysed to salicylic acid, which undergoes both glucuronidation and sulphation (Iwamoto et al., 1982). In contrast, aspirin in cats is eliminated much more slowly compared to rats, the limiting factor being a well-known deficiency in glycine conjugation to form salicylic acid in this species (Court, 2013). This explains the very large species differences in PK parameters between rats and cats (>1400-fold difference).

Carprofen

Carprofen belongs to the group of nonsteroidal anti-inflammatory drugs and is rapidly bio-transformed in rats through oxidation reactions followed by glucuronidation as major metabolic pathways. Biliary

excretion is about 70% in rats (Rubio et al., 1980). The S(+)-enantiomer is predominantly detected in plasma, while the R(-)-enantiomer is glucuronidated at a higher rate (Iwakawa et al., 1991). In cats, the R(-)-enantiomer predominated and its clearance is much slower than that in rats, humans and dogs (Court, 2013). Differences in carprofen clearance and proportion of enantiomers might be due to differences in metabolism (glucuronidation), excretion rates or in the extent of plasma protein binding (Taylor et al., 1996).

Propofol

Propofol is a phenolic derivative used in veterinary medicine to induce and maintain anaesthesia. Propofol is eliminated by glucuronidation (directly) and by CYP mediated oxidation to form 4-hydroxypropofol that is thereafter glucuronidated or sulphated and then excreted into the urine and the bile (Court, 2013). In dogs (Hay Kraus et al., 2000) and rats (Tai et al., 2015), CYP2B has been shown to be involved in propofol oxidation . Metabolism of propofol in cats is unknown, but the very low clearance compared to that in rats (Dutta and Ebling, 1998) and dogs (Court, 2013) might be related to the low glucuronidation capacity toward the phenolic derivative in cats as well as the very low CYP2B expression in the feline liver (Figure 2) (Court, 2013)

Zidovudine

Zidovudine is an antiretroviral medicine used to prevent HIV/AIDS and it is used in cats infected with the feline immunodeficiency virus. In rats, the compound is eliminated by glucuronidation (Mano et al., 2007). In cats zidovudine is rapidly and extensively absorbed; the slower clearance and prolonged elimination half-life reported in the cat compared to that in rats and other species, might be partially explained by the lower glucuronidation activity in cats (Zhang et al., 2004).

Zonisamide

Zonisamide is an antiepileptic drug which can be used for the treatment of epilepsy in cats which are refractory to phenobarbital. PK studies in humans, dogs and rats revealed that zonisamide is absorbed from the digestive tract, glucuronidated in the liver, and excreted mainly in the urine and to a minor extent in the faeces. Here, it is considered that zonisamide is similarly metabolised in cats, although the amount and rate of its excretion in the urine and faeces have not been measured. Elimination half-life in cats is longer compared to that in dogs which again reflects lower glucuronidation activity in felines (Hasegawa et al., 2008).

Renal excretion

Amoxicillin

Amoxicillin is a broad-spectrum antibiotic used against Gram-positive and Gram-negative bacteria often used in combination with clavulanic acid. In rats, bioavailability of amoxicillin is around 50% and is mainly excreted unchanged in urine (Chesa-Jimenez et al., 1994). Amoxicillin is well absorbed after oral administration in cats. In monogastrics, the chemical is reported to be excreted unchanged in the urine by glomerular filtration and active tubular secretion (Chicoine et al., 2007). Specific information for cats is not available.

Cefazolin

Cefazolin, a first-generation cephalosporin, is an antibiotic used to treat various infections. In rats, it is poorly absorbed via the oral route and eliminated via renal excretion with very minor hepatic metabolism, the majority of the drug (80-100%) being excreted unchanged in the urine (Nadai et al., 1993; Wiebe, 2015) . It is. In cats, cefazolin is also eliminated in the urine by glomerular filtration and no no major PK differences compared to rats have been observed after iv dosing (Albarellos et al., 2017).

Ceftazidime

Ceftazidime is an antibiotic and belongs to the third generation aminothiazolyl-cephalosporin. Ceftazidime is eliminated principally by renal excretion in rats and in cats (Albarellos et al., 2008; Granero et al., 1993).

Ciprofloxacin

Ciprofloxacin is a second-generation fluoroquinolone with a broad antibacterial spectrum. In rats, oral bioavailability is about 30% and the drug is mainly excreted unchanged in the urine (Siefert et al., 1986). Similar bioavailability has been reported in cats (about 22%); ciprofloxacin clearance in cats was 0.64 L/h/kg, which exceeded the glomerular filtration rate and indicates that tubular secretion or extra-renal excretion mechanisms may be involved (Albarellos et al., 2004).

Doxycycline

Doxycycline belongs to the tetracycline antimicrobial class and it is slowly absorbed in the gastrointestinal tract of rats and cats. The major elimination route of doxycycline is through intestinal secretions into the lumen with minor urinary and biliary excretion (Vargas-Estrada et al., 2008). Doxycycline is highly bound to plasma proteins, which impairs its tissue distribution (Hartmann et al., 2008). Due to the absence of metabolites in the urine, it is assumed that doxycycline is poorly metabolised and mainly excreted unchanged via kidneys in cats (Riond et al., 1990). The apparent higher bioavailability of the drug in cats compared to that in rat (Table 3) can be explained by differences in absorption and/or excretion rates.

Fluconazole

Fluconazole is an antifungal agent belonging to the same class as itraconazole. It is very effective in preventing allograft rejection and prolonging graft survival time in feline renal transplant recipients. It is poorly bio-transformed and eliminated principally by renal excretion in various species, because of its polarity, good water solubility, low molecular weight and high metabolic stability (Jezequel, 1994). Renal

excretion might be the main elimination route in cats, although kinetic studies are not available. Volume of distribution has been reported to be similar in a range of species; therefore, differences in half-lives of elimination are likely due to differences in renal clearance. Because the clearance of fluconazole islower that than what is expected from glomerular filtration alone, it is likely that tubular reabsorption of fluconazole occurs in cats (Vaden et al., 1997).

Overall, data for phase II probe substrates were much more limited:

- For aspirin, huge differences were observed for the intravenous clearance between cats and rats (>1400-fold) which reflect the very low glycine conjugation activity in cats. However, no data for the oral route were available as markers of chronic and acute exposure.
- For the limited glucuronidation probe substrates, internal dose differences between cats and rats ranged from 1.5-fold to 11.7-fold (propofol) for markers of chronic intravenous exposure and from 2.3-fold to 8.3-fold (zonidamide) for markers of chronic oral exposure. Comparison of the differences between the intravenous and oral route was only possible for zidovudine which showed respective differences in internal dose of 1.9 and 2.9-fold.

For compounds that are renally excreted, the limited data for the available probe substrates demonstrated consistent differences in internal dose between cats and rats which ranged from 1.5-fold to 3.1-fold for both markers of chronic intravenous and oral exposure and from 2 to 3-fold for markers of acute oral exposure.

4 Conclusions

Over the last decade, animal health has been the subject of increased attention particularly for risk assessment and welfare issues. Since the domestic cat (*Felis sylvestris catus*) is a major companion animal species, significant research efforts have supported the generation of information on xenobiotic metabolism and transporters and depicted the remarkable metabolic features displayed by cats compared to that in humans and dogs (Court, 2013). Of high relevance is the impairment of phase II enzymes in cats which have been relatively well-characterised, particularly glucuronidation for which several phenol derivatives and other chemicals have become an issue for the risk assessment of feed additives. In this context, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that 150 mg BHA/kg complete feed would be a safe dose for all animal species except for cats due to its known lower capacity for the glucuronidation of phenolic compounds (EFSA FEEDAP Panel, 2018). In the absence of data, FEEDAP has also drawn similar conclusions for a number of non-phenolic substrates such as, for instance, maltol (EFSA FEEDAP Panel, 2016c) and other flavourings, for which glucuronidation represents the main metabolic pathway. In practice, an additional uncertainty factor of 4 has been applied to identify a maximum safe feed concentration for cats compared to other target animal species, based on a NOEL derived from rat studies. The use of such a default uncertainty factor prompted us to review available information on activities of phase I, phase II xenobiotic metabolism and transporters in cats and compare available intravenous (clearance, AUC) and oral (AUC, Cmax) kinetic parameters for 30 pharmaceuticals between cats and rats.

This study highlights limitations in the analysis due to limited information available on key metabolic pathways and isoforms in cats for many pharmaceuticals let alone other xenobiotics. Overall, a default uncertainty factor of 4.0 was sufficient for approximately 60% of the probe pharmaceutical substrates. In situations under which the parent compound undergoes glucuronidation, the default factor of 4.0 would be exceeded, with the exception of zidovudine and S-carprofen. In general, mixed results were obtained for chemicals which are metabolised by CYP3A. When chemicals were administered

intravenously, in most cases, the 4.0-fold default uncertainty factor was not exceeded with the exception of clomipramine, lidocaine and alfentanil. For oral kinetics, the resulting uncertainty factors to allow for differences in internal dose were greater than 4 in almost 50% of the examined pharmaceuticals. Based on these results, some general conclusions can be drawn. First of all, the notable differences in oral kinetics between cats and rats can be rationalised by qualitative and quantitative differences in the expression and activities and xenobiotic-metabolising enzymes (pre-systemic metabolism). As a second line of evidence, with few exceptions, the most remarkable variations in such differences in internal dose is highlighted for those chemicals undergoing extensive phase II biotransformation (glucuronidation, glycine conjugation), while more limited differences were noticed for compounds mainly subjected to CYP-mediated oxidation or renal excretion, respectively. The same trend was also observed by Court (2013), who compared the elimination half-life of 25 drugs in cats, dogs and humans, thus confirming the taxa-specific trait of feline phase II reactions which is highly correlated with the hyper-carnivorous diet. For the limited database available for compounds that are mainly renally excreted, differences in internal dose between cats and rats showed consistent differences between 2-3-fold. This highlights that for such compounds, the 4-fold default uncertainty factor would cover such differences even though more data would further substantiate this conclusion.

According to the significant differences in oral PK parameters, rats as rodents, may not be a sound species for the prediction of phase I or phase II xenobiotic metabolism in cats. As a consequence, the extra default factor of 4 which is being applied to account for the relatively low glucuronidation ability of cats particularly for the risk assessment of feed additives may not cover all situations. Consequently, chemicals should be evaluated on a case by case basis using available information on physico-chemical properties, structural features, kinetic information including metabolism and toxicological evidence. Nevertheless, information on the metabolism of chemicals in feline species are still very limited. This is particularly relevant to the characterisation of specific CYP isoforms, phase II enzymes and transporters

in cats, for which information is more readily available for rats. These data gaps make the derivation of science-based uncertainty factors for cats, for a range of susbtances, a rather challenging task (i.e. chemical-specific adjustment factors, pathway-related uncertainty factors for phase I, phase II and transporters) .From such data gaps, *in vivo* pharmacokinetic studies are warranted investigating metabolism of pharmaceuticals including probe substrates for phase I, phase II enzymes and transporters and other xenobiotics of regulatory interest (feed additives, contaminants, etc) in cats are needed. These studies will allow to identify ADME profiles, generate PK parameters reflecting acute and chronic exposure (absorption, Cmax, AUC, Clearance, half-life etc) for these compounds. In parallel, the use of routine *in vitro* studies using liver preparations (nowadays commercially available), immortalised cell lines or enzymes/transporters expressed in heterologous systems is recommended to identify phase I, phase II enzymes, transporters and excretion pathways, ideally at the isoform level, for the metabolism and disposition of such relevant compounds. . It is foreseen that whole genome sequencing using next generation methods will allow the systematic identification of the expression of phase I, phase II enzymes and transporters at the isoform level (Kim et al., 2017; Li et al., 2016). Such data collection will provide a basis to develop a comprehensive database on comparative ADME properties of a broad range of compounds in feline species. In a second step, such information can be used to develop *in silico* models for cats such as QSARs, read-across tools and generic physiologically-based kinetic models for cats to predict isoform-specific metabolism, estimate PK parameters and characterise their sensitivity to xenobiotics compared to test species for hazard characterisation. In the longer term, the qualitative and quantitative information generated from such databases and models can be integrated to refine the risk assessment for feed additives and contaminants in domestic cats.These would also support environmental risk assessment of chemicals, including pesticides, contaminants and human pharmaceuticals, for wild feline species living close to human habitations and agricultural areas which may be exposed to a range of chemicals through prey and water consumption . A relevant example

includes the endangered Iberian lynx species (*Lynx pardinus*),inhabiting the Doñana national park and Sierra Morena which are close to important agriculture areas (Camacho-Muñoz et al., 2010; Mateo et al., 2012).

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Conflict of Interest

Ms. L. Lautz reports the grant EFSA/SCER/2014/06 from the European Food Safety Authority under which this study was funded and conducted. No conflicts of interests were identified. Dr. Jeddi worked as an EFSA trainee under the supervision of Dr. Dorne (full time employee) at the European Food Safety Authority. No conflicts of interests were identified. Drs. C. Nebbia and F.Girolami work at the University of Torino. No conflicts of interests were identified. The views expressed in this manuscript are the authors only and do not reflect the views of the European Food Safety Authority.

Authors' contribution

L. Lautz carried out the data collection, analysis of the results and drafted the manuscript. M. Jeddi carried out the data collection. J.L.C.M Dorne and C. Nebbia assisted in the design of the study, contributed to the section on xenobiotic metabolism in cats, the interpretation of the results, critical review, discussion and editing of the manuscript. F.Girolami contributed to the section on xenobiotic metabolism in cats All authors commented on previous versions of the manuscript and have read and approved the final version of this manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Average values of liver and kidney weights, organ blood flows, cardiac output and glomerular filtration rate in rats and cats

	Organ weight (g/kg)		**Blood flow (ml/min/kg)**				
	Liver	Kidney	Liver	Kidney	Gut	Cardiac output (ml/min/kg)	Glomerular filtration rate (ml/min/kg)
Cat (3 kg)	29[a]	7[a]	24[b]	17[b]	12[b]	120[c]	1.6[d]
Rat (0.25 kg)[e]	40	8	55	37	30	300	5.2
Ratio	1.4	1.1	2.3	2.2	2.5	2.5	3.0

a: (King et al., 2012);b: (Johnston and Owen, 1977); c: (Allen and Nymeyer, 1983; Baxter et al., 1952; Beaulieu et al., 2009; Groom and Rowlands, 1958; Johnston and Owen, 1977); d: (Braff et al., 2014); e: (Walton et al., 2004)

Table 2. Comparative assessment of phase I xenobiotic metabolism using markers of chronic exposure (AUC and Clearance) between rats and cats after intravenous administration

Parameter	Chemical	Cat	Rat	Ratio	Pathway Cats	Pathway Rats
Clearance	Alfentanil	11.58	53.00	**4.58**	Unknown	CYP3A
Clearance	Amantadine	8.20	35.50	**4.33**	Unknown	CYP/Renal excretion
Clearance	Clomipramine	6.55	79.32	**12.1**	Multiple CYPs	CYP3A
Clearance	Cyclosporine	3.04	3.38	1.11	CYP3A	CYP3A
Clearance	Flunixin	1.39	5.17	3.71	CYP	CYP
Clearance	Itraconazole	6.17	9.68	1.57	CYP3A	CYP3A
Clearance	Lidocaine	24.45	99.33	**4.06**	CYP3A	CYP3A
Clearance	Ondansetron	15.00	40.90	2.73	CYP	CYP2D/3A
Clearance	Pioglitazone	1.88	3.67	1.95	CYP	CYP3A
Clearance	Quinidine	17.18	52.33	3.05	CYP3A	CYP3A
AUC	Tramadol	1.11	0.73	1.53	CYP2D	CYP/Glucuronidation

Ratios of the pharmacokinetic parameters were calculated to quantify differences internal dose as follows: Rat Clearance/Cat Clearance; Cat (AUC/dose)/Rat (AUC/dose); Clearance (ml/min/kg); AUC ((h.ug/ml)/(mg/kg)); References are presented in supporting information.

Table 3. Comparative assessment of phase I xenobiotic metabolism using markers of chronic exposure (AUC and Clearance) between rats and cats after oral administration

Parameter	Chemical	Cat	Rat	Ratio	Phase I in Cats	Phase I in Rats
AUC	Amantadine	2.30	0.16	**14.02**	Unknown	CYP/Renal excretion
AUC	Amitriptyline	0.67	0.45	1.49	Unknown	CYP/Glucuronidation
AUC	Atenolol	3.81	0.71	**5.41**	Unknown	CYP/Renal excretion
Clearance	Clomipramine	4.35	522.10	**120.02**	CYP	CYP various
AUC	Cyclosporine	2.04	1.43	1.42	CYP3A	CYP3A
AUC	Fluoxetine	5.40	0.23	**23.55**	CYP	CYP
AUC	Itraconazole	1.59	0.52	3.07	CYP3A	CYP3A
Clearance	Mirtazapine	13.84	85.33	**6.16**	CYP/Glucuronidation	CYP/Glucuronidation
AUC	Ondansetron	0.35	0.02	**19.48**	CYP	CYP2D/3A
Clearance	Pioglitazone	3.70	8.50	2.30	CYP	CYP3A

AUC	Piroxicam	34.45	31.73	1.09	CYP	CYP2C
AUC	Praziquantel	0.29	0.02	**12.0**	CYP	CYP3A
AUC	Ramipril	0.08	0.44	0.19	Hydrolysis	Hydrolysis
AUC	Tacrolimus	0.99	0.01	**99.0**	CYP3A	CYP3A
AUC	Tramadol	0.85	0.27	3.19	CYP2D	CYP/Glucuronidation

Ratios of the pharmacokinetic parameters were calculated to quantify differences internal dose as follows: Rat Clearance/Cat Clearance; Cat (AUC/dose)/Rat (AUC/dose); Clearance (ml/min/kg); AUC ((h.ug/ml)/(mg/kg)); References are presented in supporting information.

Table 4. Comparative assessment of phase I xenobiotic metabolism using markers of acute exposure (Cmax) between rats and cats after oral administration

Parameter	Chemical	Cat	Rat	Ratio	Phase I in Cats	Phase I in Rats
Cmax	Amantadine	0.23	0.03	**7.26**	Unknown	CYP/Renal excretion
Cmax	Amitriptyline	0.05	0.11	0.39	Unknown	CYP/Glucuronidation
Cmax	Atenolol	0.67	0.08	**8.90**	Unknown	CYP/Renal excretion
Cmax	Clomipramine	0.17	0.01	**40.35**	CYP	CYP
Cmax	Cyclosporine	0.21	0.35	0.61	CYP3A	CYP3A
Cmax	Fluoxetine	0.09	0.01	**15.93**	CYP	CYP
Cmax	Itraconazole	0.14	0.03	**4.09**	CYP3A	CYP3A
Cmax	Mirtazapine	0.20	0.03	**6.80**	CYP/Glucuronidation	CYP/Glucuronidation
Cmax	Ondansetron	0.20	0.04	**5.21**	CYP	CYP2D/3A
Cmax	Pioglitazone	0.72	1.30	0.55	CYP	CYP3A
Cmax	Piroxicam	1.90	2.73	0.69	CYP	CYP2C
Cmax	Praziquantel	0.13	0.03	**4.13**	CYP	CYP3A
Cmax	Ramipril	0.07	0.06	1.07	Hydrolysis	Hydrolysis
Cmax	Tacrolimus	0.15	0.01	**37.40**	CYP3A	CYP3A
Cmax	Tramadol	0.18	0.06	3.12	CYP2D	CYP/Glucuronidation

Ratios of the pharmacokinetic parameters were calculated to quantify differences internal dose as follows: Cat (Cmax/dose)/Rat (Cmax/dose); Cmax (ng/ml)/(mg/kg); references are presented in supporting information.

Table 5. Comparative assessment of phase II xenobiotic metabolism and renal excretion using markers of chronic exposure (AUC and Clearance) between rats and cats after intravenous administration

Parameter	Chemical	Cat	Rat	Ratio	Pathway Cats	Pathway Rats
Clearance	Aspirin	0.09	130.33	**1472.7**	Glycine conjugation	Glucuronidation
Clearance	R-Carprofen	0.13	1.48	**11.7**	Glucuronidation	Glucuronidation
Clearance	S-Carprofen	0.29	0.49	1.71	Glucuronidation	Glucuronidation
Clearance	Propofol	24.93	264.04	**10.6**	Glucuronidation/CYP	Glucuronidation/CYP
Clearance	Zidovudine	6.83	13.00	1.90	Glucuronidation	Glucuronidation
Clearance	Cefazolin	3.50	5.52	1.58	Renal excretion	Renal excretion
Clearance	Ceftazidime	3.17	7.08	2.24	Renal excretion	Renal excretion
Clearance	Ciprofloxacin	10.67	33.00	3.09	Renal excretion	Renal excretion
Clearance	Fluconazole	0.90	1.58	1.76	Renal excretion	Renal excretion

Ratios of the pharmacokinetic parameters were calculated to quantify differences internal dose as follows: Rat Clearance/Cat Clearance; Cat (AUC/dose)/Rat (AUC/dose); Clearance (ml/min/kg); AUC ((h.ug/ml)/(mg/kg)); References are presented in supporting information.

Table 6. Comparative assessment of phase II xenobiotic metabolism and renal excretion using markers of chronic (AUC) and acute exposure (Cmax) between rats and cats after oral administration

Parameter	Chemical	Cat	Rat	Ratio	Pathway Cats	Pathway Rats
AUC	Zidovudine	2.42	0.82	2.95	Glucuronidation	Glucuronidation
AUC	Zonisamide	67.69	8.14	**8.32**	Glucuronidation	Glucuronidation
AUC	Ciprofloxacin	0.30	0.13	2.33	Renal excretion	Renal excretion
AUC	Doxycycline	6.67	1.76	3.79	Renal excretion	Renal excretion
Cmax	Zidovudine	1.15	0.45	2.58	Glucuronidation	Glucuronidation
Cmax	Zonisamide	1.27	0.54	2.37	Glucuronidation	Glucuronidation
Cmax	Amoxicillin	0.90	0.31	2.94	Unknown	Renal excretion
Cmax	Ciprofloxacin	0.07	0.04	1.97	Renal excretion	Renal excretion
Cmax	Doxycycline	0.80	0.32	2.49	Renal excretion	Renal excretion

Ratios of the pharmacokinetic parameters were calculated to quantify differences internal dose as follows: Cat (AUC/dose)/rat (AUC/dose); Cat (Cmax/dose)/rat (Cmax/dose); AUC ((h.ug/ml)/(mg/kg)); Cmax (ng/ml)/(mg/kg); references are presented in supporting information.