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# An Analysis of the Use of Dogs in Predicting Human Toxicology and Drug Safety

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**Summary** — Dogs remain the main non-rodent species in preclinical drug development. Despite the current dearth of new drug approvals and meagre pipelines, this continues, with little supportive evidence of its value or necessity. To estimate the evidential weight provided by canine data to the probability that a new drug may be toxic to humans, we have calculated Likelihood Ratios (LRs) for an extensive dataset of 2,366 drugs with both animal and human data, including tissue-level effects and Medical Dictionary for Regulatory Activities (MedDRA) Level 1–4 biomedical observations. The resulting LRs show that the absence of toxicity in dogs provides virtually no evidence that adverse drug reactions (ADRs) will also be absent in humans. While the LRs suggest that the presence of toxic effects in dogs can provide considerable evidential weight for a risk of potential ADRs in humans, this is highly inconsistent, varying by over two orders of magnitude for different classes of compounds and their effects. Our results therefore have important implications for the value of the dog in predicting human toxicity, and suggest that alternative methods are urgently required.

**Key words:** *canine, dog, drug development, preclinical testing, toxicology.*

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## Introduction

It is generally assumed that testing new pharmaceuticals on animals helps to ensure human safety and efficacy. Regulatory agencies worldwide require preclinical trials (e.g. 1, 2), which involve at least two species — typically one rodent and one non-rodent species — to determine toxicity and pharmacokinetics. The expectation is that additional data from the non-rodent will detect adverse effects not detected by rodent tests. Despite the current dearth of new drug approvals and meagre pipelines (e.g. 3, 4), this practice continues, with little supportive evidence of its value or necessity (5).

Dogs are used in significant numbers in science — approximately 90,000 are used per annum across the EU and the USA, according to the latest available figures (6–8). About 80% of this use is as the non-rodent species in the evaluation of pharmaceutical safety and efficacy (6). However, only limited evaluations of the reliability of the canine model for this purpose have been conducted, chiefly due to the difficulty of accessing relevant data, most of which are unpublished and proprietary to pharmaceutical companies. Those evaluations that have been conducted have usually employed 'concordance' metrics (e.g. 9), which various authors have interpreted as the true positive rate ('sensitivity') or the Positive Predictive Value (PPV). While these metrics are appropriate for assessing the reliability of a diagnostic test for a specific disorder (e.g. HIV infection), the insights they provide depend critically on the question being asked of the diagnostic test. However, they are not appropriate for assessing the salient question at issue with animal models, which is *whether or not they contribute significant weight to the evidence for or against the toxicity of a given compound in humans*. Overcoming this key problem — almost entirely overlooked by previous authors — requires a precise specification of the various terms used (see *Methods*). Briefly, the appropriate metrics are Likelihood Ratios (LRs; 10): the Positive Likelihood Ratio (PLR) and the inverse Negative Likelihood Ratio (iNLR). Therefore, there is clearly a need for the kind of statistically-appropriate critical analysis that we provide here. The dataset we have used is unique, in that it is large and allows the conditional probabilities required for the LRs (PLR/iNLR) to be calculated.

## Methods

Animal models are widely used to assess the risk that a given compound will prove toxic in humans. As with any diagnostic test, their reliability can only be assessed by performing tests in which the same compound is given to both animals and humans, and the presence or absence of toxicity recorded. This leads to a 2 × 2 matrix of results, as shown in Figure 1 (11).

**Figure 1: A 2 × 2 matrix of results**

| | Compound toxic in humans | Compound not toxic in humans |
|---|---|---|
| **Compound toxic in animal model** | a: true positives (TPs) | b: false positives (FPs) |
| **Compound not toxic in animal model** | c: false negatives (FNs) | d: true negatives (TNs) |

The basis of this matrix is that the human data are correct, and the dog data are true/false, if they do/do not match them. The various cells in this matrix allow a variety of diagnostic metrics to be deduced, of which the most familiar and widely used are the true positive rate for the test (or 'sensitivity' = a/[a + c]), and the true negative rate (or 'specificity' = d/[d + b]). In previous research into the reliability of animal models as predictors of toxicity in humans, some authors (e.g. 9) have focused on the sensitivity, expressed as the 'true positive concordance rate', or the so-called Positive Predictive Value (PPV), given by a/(a+b), which reflects the probability that human toxicity was correctly identified by the animal model, given that toxicity was observed in the animal model (e.g. 12). However, neither of these metrics is suitable for the role of assessing the evidential weight provided by any toxicity test. In the case of animal models, the sensitivity addresses only the ability of such models to detect toxicity that will subsequently manifest itself in humans. This is a necessary, but not sufficient, measure of evidential weight. Suppose, for example, that the animal model always indicates toxicity found in humans; it would then have a sensitivity of 100%. However, if, in addition, the model always indicates toxicity, even in humans, its evidential value is no better than simply dismissing *every* compound as toxic from the outset. Thus, a useful toxicity test must also be able to give insight into when toxicity seen in the animal model is not observed in humans, which requires knowledge of the *specificity* of the test.

There is, of course, an obvious reason for the focus on sensitivity in animal model evaluation: if a compound is found to be positive in an animal model, it is unlikely to go into human evaluation. Nevertheless, the fact remains that sensitivity alone cannot be an adequate guide to the value of animal models.

The case of the PPV is more subtle. This metric is a measure of the probability that human toxicity will be correctly identified, given that the animal model detected toxicity. As such, PPVs are conditional probabilities, the condition being the pre-existence of a positive animal test result. This makes PPVs dependent on the prevalence of toxicity in compounds, and thus an inappropriate measure of the reliability of the test with any specific compound (e.g. 10, 13).

Thus, any appropriate metric of the evidential value of animal models requires knowledge of *both* the sensitivity *and* the specificity of the model. This, in turn, implies that the appropriate metrics for the evidential weight provided by an animal model are LRs (e.g. 13). In general, these are ratios of functions of the sensitivity and specificity, which can be extracted from the 2 × 2 matrix given above. In the specific case of animal models in general, two LRs are relevant. The first is the so-called PLR, which is given by:

$$\text{PLR} = \text{sensitivity}/(1 - \text{specificity}) = (a / a + c)/(b/ b + d)$$

This LR captures the ability of an animal model to add evidential weight to the belief that a specific compound is toxic. Any animal model that gives a PLR that is statistically significantly higher than 1.0, can be regarded as contributing evidential weight to the probability that the compound under test will be toxic in humans.

The other relevant LR is the so-called iNLR, given by:

$$\text{iNLR} = \text{specificity}/(1 - \text{sensitivity}) = (d / b + d)/(c / a + c)$$

This LR captures the ability of an animal model to add evidential weight to the belief that a specific compound is not toxic: any animal model that gives an iNLR that is statistically significantly higher than 1.0, can be regarded as contributing evidential weight to the probability that the compound under test will not be toxic in humans.

It is worth noting at this point that the above definitions imply that a good animal model for detecting human toxicity is not necessarily also good for detecting an absence of toxicity. That is, a high PLR does not guarantee a high iNLR; this will emerge as a key issue in this study.

The above definitions also underscore the need for data on the human toxicity of compounds that

fail initial animal tests. Again, a key feature of the current study is that this issue has been overcome via data mining methods. Data were obtained from a leading pharmaceutical safety consultancy, Instem Scientific Limited (Harston, Cambridge, UK; http://www.instem-lss.com 'Safety Intelligence Programme'), with funding provided by FRAME. All the information stemmed from publicly accessible sources, including: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), the FDA Adverse Event Reporting System (FAERS), DrugBank (http://www.drugbank.ca), and the National Toxicology Program (http://ntp.niehs.nih.gov). Data were available for more than 2,300 drug compounds in humans and preclinical species.

Inference of the good quality of the data used in this evaluation is outlined in the *Discussion*. Compounds were selected that feature in the FAERS, FDA New Drug Applications (FDA NDAs) and DrugBank. Thus, the drugs selected for this analysis are in clinical use, and have undergone preclinical testing: human and animal data are therefore available for them. A non-redundant list of parent moieties was created, for example, by normalising therapeutic products to their generic names (e.g. Lipitor to Atorvastatin). This yielded 2,366 compounds.

A signature of the effects of each compound was created, focusing on tissue-level effects (e.g. bradycardia and arrhythmic disorder would both be considered to be effects on heart tissues), as well as the individual observations, which were mapped to their MedDRA (Medical Dictionary for Regulatory Activities; http://www.meddramsso.com) counterparts. MedDRA observations are classified into four levels, Level 1 being the most specific and Level 4 providing a more generic 'System Organ Class'. These classifications help to eliminate false positives that may arise from species-specific observations, and help the identification of concordant observations that might otherwise have been missed, by their 'rolling up' into more-generic terms.

LRs were derived for broad tissue-level effects ($n$ = 52), and more-specific biomedical observations (BMOs; $n$ = 384), mapped to MedDRA classifications (Levels 1 [most specific] to Level 4 [more generic 'organ class']). Fourteen BMO classifications not involving dogs were eliminated from the study. A total of 3,275 comparisons were made between the human and the dog, for 2,366 compounds, involving 436 (52 + 384) classifications of effects. The Instem Scientific data on which our analysis was based are shown in the Appendix, and the full set of data, including 95% Confidence Intervals, are available on the FRAME website (www.frame.org.uk).

With regard to potential bias: FNs are more common than FPs, since there is a bias resulting from a 'precautionary principle' not to progress positives to human administration. This has been mitigated by limiting the dataset to compounds reported in the FAERS database. Therefore, all the compounds are certain to have proceeded to market, and animal preclinical data are available for these compounds. Specific details of how the FPs that were identified arose were not sought, because they were not pertinent to this analysis, and this was not feasible, given the nature of the dataset. It must be assumed that the dog data were correlated with the human data retrospectively, and/or the human data arose from post-marketing studies, and/or clinical trials were applied for and approved, since the adverse effect(s) in dogs were minor and/or mitigated by other data.

## Results

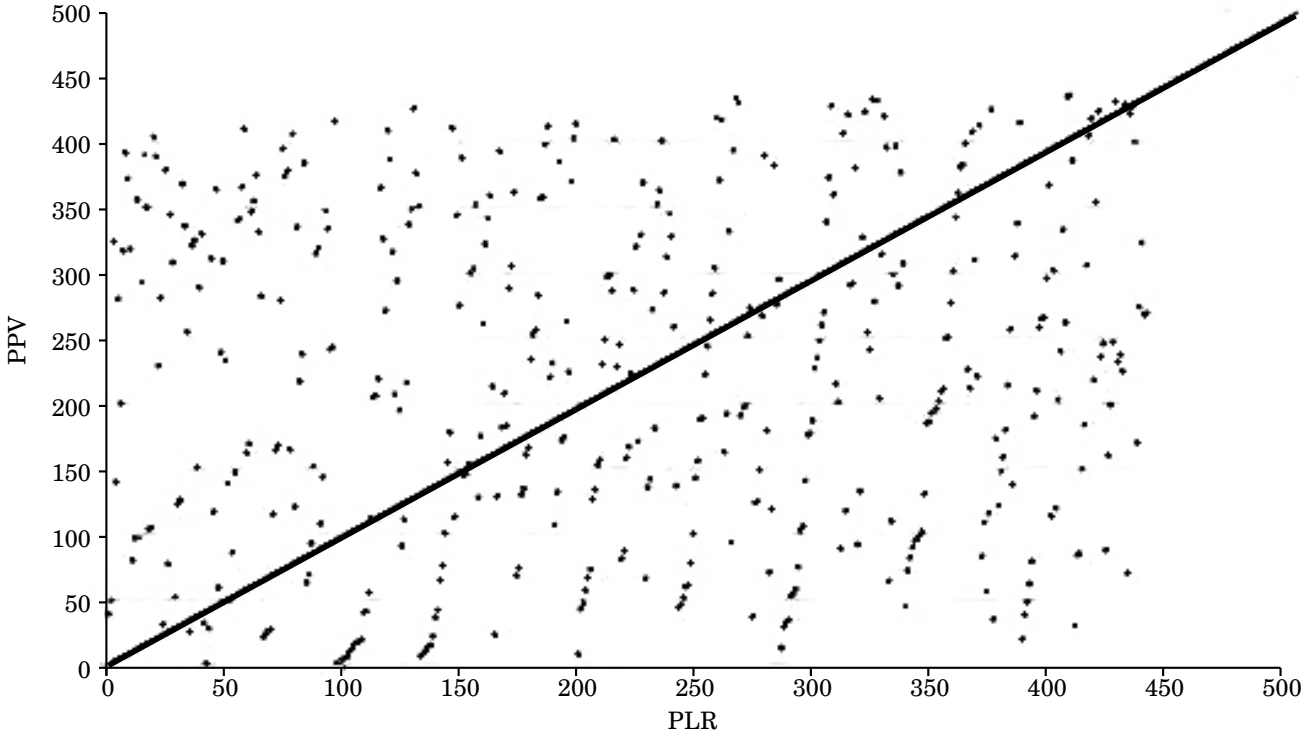
The inappropriate nature of PPVs is demonstrated in Figure 2, which shows a scatter plot of 'ranked' PPVs against equivalent ranked PLRs. Each PPV and PLR was ranked according to its value for each of the 436 classifications of effects, and these ranks were plotted against each other. The disparity is evidenced by the scatter of points, few of which lie close to the $y = x$ line that shows an ideal correlation. The misclassifications and misplaced assumptions of the accuracy of canine data for the prediction of human adverse drug reactions (ADRs) are clear. For example, MedDRA 'Level 4, Vascular Disorder' was ranked 20/436 with regard to the most favourable classifications for human predictivity based on PPV, but its cognate PLR ranked 404/436 — one of the least predictive. Conversely, MedDRA classification 'Level 2, Ventricular Conduction' ranked 30/436 by PLR, but 406/436 by PPV.

Dog PLRs were generally high (median ~28), implying that compounds that are toxic in dogs are likely also to be toxic in humans. However, because the PLRs vary considerably (range 4.7–548.7), with no obvious pattern regarding the form of toxicity, the reliability of this aspect of canine models cannot be generalised or regarded with confidence.

In contrast, the calculated inverse negative LRs (iNLRs) are substantially more consistent, but their median value of 1.11 (range 1.01–1.92) supports the view that dogs provide essentially no evidential weight to this aspect of toxicity testing. Specifically, the fact that a compound shows no toxic effects in dogs provides essentially no insight into whether the compound will also show no toxic effects in humans.

This lack of evidential weight has important implications for the role of dogs in toxicity testing, especially for the pharmaceutical industry. The critical observation for deciding whether a candidate drug can proceed to testing in humans is the absence of toxicity in tests on animals. However,

**Figure 2: Scatter plot illustrating the lack of correlation of PPVs and PLRs of biomedical observations (BMOs) and tissue effects in humans and dogs**




*PPVs and PLRs for all 436 results were ordered according to their value, with the highest ranking first and the lowest last. For each BMO and tissue effect, the corresponding PPV and PLR rank were plotted against each other. If a perfect correlation exists, all points should lie on the line, where, for example, the 10th, 50th, and 100th highest PPV value would also be the 10th, 50th, and 100th highest PLR values. However, the significant scatter of the data points demonstrates that little correlation exists between PPV and PLR. For example: the 20th highest PPV ranks only 404/436 for PLR, whereas the 30th highest PLR ranks only 406/436 for PPV.*

our findings show that the predictive value of the animal test in this regard is barely greater than that that would be obtained by chance (see below).

## Discussion

The analysis presented here is urgently required, to support informed debate about the worth of animal models in preclinical testing. It is acknowledged among some stakeholders (if not universally among all stakeholders) that assessment of the scientific value of animal data in drug development is necessary, has been scarce, and has been thwarted for decades by the unavailability of relevant data for analysis (e.g. 14). Nevertheless, primarily due to concerns over privacy and commercial interests, data sharing and making data available continue to be resisted, in spite of assurances to the contrary from industry (14).

Those few analyses that have been done, tend to reflect unfavourably on animal models, including the dog. In 2012, a study that expressly set out to minimise bias, showed that 63% of serious ADRs had no counterparts in animals, and less than 20% of serious ADRs had a true positive corollary in animal studies (15). Other similar examples exist for testing generally (e.g. 16–18) and more-specifically, for example, in teratology (e.g. 19, 20) and drug-induced liver injury (e.g. 5, 21). One notable study claimed a good concordance for dog and human toxicology (10), though neither the predictive nature of the animal data for humans, nor the evidential weight provided by those data, were addressed (22).

We have, for the first time, addressed the salient question of *contribution of evidential weight for or against the toxicity of a given compound in humans* by data from dog tests, by using the appropriate metrics of LRs. Furthermore, we have applied the apposite LRs to a dataset of unprecedented scale, to critically question the value of the use of the dog as a preclinical species in the testing of new pharmaceuticals.

Substantiation of data quality is evidenced by: the methods used to source the data and the assured quality of the databases supplying them (listed above); the ways in which the data had been used recently as a basis for scientific publications and presentations (e.g. 23–26); and the international corporate and academic clients that have used the consultancy and its data (e.g. AstraZeneca; see 23–26). In addition, the impact of 'missing data' (i.e. unpublished data held by pharmaceutical companies) was mitigated by strictly limiting the dataset to drugs "with the greatest chance of having been evaluated in all the species included in the study" (here, dogs and humans). In other words, "…lack of evidence for an association between a compound and a specific BMO demonstrates a real absence of effect, and is not due to missing data" (Instem Scientific Ltd. Analysis Report, unpublished).

Naturally, there must be caveats. Our analysis was limited to data that are published and publicly available. It is widely acknowledged that many animal experimental results/preclinical data remain unpublished and/or proprietary, for a variety of reasons (e.g. 15, 27–30). Such publication bias is a major problem (e.g. 31–34), and, compounded by other factors such as size and quality of the animal studies, variability in the requirements for reporting animal studies, 'optimism bias', and lack of randomisation and blinding (28, 35), it means that gauging the true contribution of animal data to human toxicology is impossible — at least for third parties without access to pharmaceutical company files. All datasets are imperfect to varying degrees. However, it is only possible to use data which are available, and to ensure that, as far as feasible, those data are of good quality and as free from biases as possible, and that their analysis and derived conclusions are as objective as possible.

It must be made abundantly clear that we, the authors of this report, did not make decisions regarding the toxicity/non-toxicity of drugs, or decide upon or apply any criteria to such decisions. The mining of the data, and the decisions on toxicity of the drugs, were independent of the authors of this paper, and were made by one or both of the authors of the drug/toxicity papers and/or database submissions used, and the data-mining consultancy/curators of the Safety Intelligence Programme, Instem Scientific Limited. Therefore, if any pharmaceutical industry stakeholders have issues or concerns with our conclusions, we would encourage them to conduct further analyses by using their own proprietary data, and/or to facilitate such investigations by making available anonymised data, in accordance with the promotion of transparency encouraged by EU *Directive 2010/63/EU* (36), as well as to engage fully in constructive discussion and debate with us and our colleagues in animal protection organisations.

Our findings have practical implications for the use of animal models for toxicity testing, especially in the pharmaceutical industry. Reliance on flawed models of toxicity testing leads to two types of failure. If the models have poor PLRs, then there is a risk that many potentially useful compounds will be wrongly discarded, because of 'false positives' produced by the toxicity model. On the other hand, if the models have poor iNLRs, then many toxic compounds will wrongly find their way into human tests, and will fail in clinical trials. The relatively high PLRs found in this study show that animal models may not be leading to the loss of many potentially valuable candidate drugs through false positives. However, our results do imply that many toxic drugs are not being detected by animal models, leading to the risk of unnecessary harm to humans.

In this regard, our findings are entirely consistent with the acknowledged failure of animal models in general to provide guidance on likely toxicity ahead of the entry of compounds into human trials. Drug attrition has increased significantly over the past two decades (e.g. 3, 4, 37–42): 92–94% of all drugs that pass preclinical tests fail in clinical trials, mostly due to unforeseen toxicities (43–45), and half of those that succeed may be subsequently withdrawn or re-labelled due to ADRs not detected in animal tests (46). ADRs are a major cause of premature death in developed countries (47). A major contributing factor is the inadequacy of preclinical animal tests: one recent study showed that 63% of ADRs had no counterpart in animals, and less than 20% had a positive corollary in animal studies (15).

With specific regard to the dog, the most extensive study prior to the report we present here, concluded that 92% of dog toxicity studies did not provide relevant information in addition to that provided by the rat, and that the other 8% did not result in the immediate withdrawal of drugs from development, indicating that dog studies are not required for the prediction of safe doses for humans (17). There is a scientific basis for this: among several notable species differences which confound the extrapolation of data from dogs to humans, significant differences between humans and dogs in their cytochrome P450 enzymes (CYPs) — the major enzymes involved in drug metabolism — have been acknowledged for some time, compelling the conclusion that, "…it is readily seen that the dog is frequently not a good metabolic model for man and is poorly comparable to the rat and mouse" (for references, see 46). The lack of knowledge of canine CYPs has been highlighted, which is surprising, considering the extent of the use of dogs in preclinical testing. This problem is likely to be amplified by intra-species differences, as well as by inter-species differences (49). It may therefore be argued that, if many differ-

ences exist between different breeds or strains of the same species, then extrapolating pharmacokinetic data from that highly variable species to humans must not only be difficult, but must also be patently unreliable.

## Conclusions

This analysis of the most comprehensive quantitative database of publicly-available animal toxicity studies yet compiled, suggests that dogs are highly inconsistent predictors of toxic responses in humans, and that the predictions they can provide are little better than those that could be obtained by chance — or tossing a coin — when considering whether or not a compound should proceed to testing in humans. In other words: "…for any putative source of evidential weight to be deemed useful, its specificity and sensitivity must be such that LR+ [PLR] >1. Tossing a coin contributes no evidential weight to a given hypothesis, as the sensitivity and specificity are the same — 50% — and thus the LR+ [PLR] is equal to 1" (22).

Dog PLRs were generally high, showing that a drug which is toxic in the dog is likely to be toxic in humans. However, they were extremely variable and with no obvious pattern, suggesting this aspect of dog tests cannot be considered particularly reliable or helpful. Further, though not within the scope of this analysis, it is of great interest whether the dog revealed any significant toxicities, that were also present in humans, that other species such as the rat did not. In other words, did the dog 'catch' any true human toxicities not caught by the rat? It has been previously argued that such toxicities are relatively low in number (e.g. the development of just 11% of new compounds was terminated due to effects uniquely seen in dogs, though the human significance of these could not be determined), which would further diminish any value the canine model may have in this respect (50).

More importantly, while iNLRs were much more consistent, they revealed that dogs provide essentially no evidential weight to this aspect of toxicity testing. Specifically, if a compound shows no toxic effects in dogs, this provides essentially no insight into whether the compound will also show no toxic effects in humans. This is crucial: the critical observation for deciding whether a candidate drug can proceed to testing in humans is the absence of toxicity in tests on animals, and our findings show that the predictive value of the dog test in this regard is barely greater than by chance.

A quantitative example illustrates this. Suppose researchers wish to investigate a candidate compound belonging to a family which prior experience indicates has a 70% probability of freedom from ADRs in humans. Before conducting tests in humans, the drug is tested in dogs. By using the median iNLR figure found by our study, if the compound shows no sign of toxicity in the dog, the probability that the compound will also show no toxic effects in humans will have been increased by the animal testing from 70% to 72%. The testing thus contributes essentially no additional confidence in the outcome, but at considerable extra cost, both in monetary terms and in terms of animal welfare. This also has obvious practical relevance to the issue of high attrition rates in clinical trials on new drug candidates.

It is argued that a comprehensive suite of more reliable alternative methods is now available (14, 51, 52). Combined with considerable public concern over the use of dogs in science (53), the high ethical costs of doing so, given the sensitive nature of dogs (e.g. 15, 54), and the expressed desire for the use of dogs as a second species in drug testing to have a scientific, rather than a habitual, basis (14), we conclude that the preclinical testing of pharmaceuticals in dogs cannot currently be justified on scientific or ethical grounds.

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# Appendix

## Table A1: Raw data from Instem Scientific's 'Safety Intelligence Programme', showing the number of drugs associated with ADRs in humans and dogs

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | **Adverse effect: tissue-level or BMO (MedDRA Level 1–4)** | **Human/Dog a (TP)** | **Dog b (FP)** | **Human c (FN)** | **Neither d (TN)** | **Dog total** | **Human total** |
| 1 | Level 1 — qrs prolongation | 10 | 0 | 22 | 2334 | 10 | 32 |
| 2 | Level 2 — glomerulonephritis and nephrotic syndrome | 13 | 0 | 104 | 2249 | 13 | 117 |
| 3 | Level 2 — kidney neoplastic disorder | 8 | 0 | 57 | 2301 | 8 | 65 |
| 4 | Level 1 — ocular hypertension | 6 | 0 | 17 | 2343 | 6 | 23 |
| 5 | Level 3 — glaucoma and ocular hypertension | 6 | 0 | 19 | 2341 | 6 | 25 |
| 6 | Level 2 — glaucomas (excluding congenital) | 6 | 0 | 19 | 2341 | 6 | 25 |
| 7 | Level 1 — nephrotic syndrome | 8 | 0 | 68 | 2290 | 8 | 76 |
| 8 | Level 2 — renal neoplasms (malignant) | 7 | 0 | 49 | 2310 | 7 | 56 |
| 9 | Level 3 — renal and urinary tract neoplasms (malignant and unspecified) | 7 | 0 | 50 | 2309 | 7 | 57 |
| 10 | Level 2 — urinary tract neoplasms (unspecified malignancy not elsewhere classified; nec) | 6 | 0 | 27 | 2333 | 6 | 33 |
| 11 | Level 1 — kidney neoplastic disorder | 6 | 0 | 27 | 2333 | 6 | 33 |
| 12 | Level 1 — orthostatic hypotension | 10 | 0 | 170 | 2186 | 10 | 180 |
| 13 | Level 2 — hepatic peroxisome proliferation | 5 | 0 | 16 | 2345 | 5 | 21 |
| 14 | Level 1 — cholestatic jaundice | 7 | 0 | 131 | 2228 | 7 | 138 |
| 15 | Brain | 78 | 1 | 854 | 1433 | 79 | 932 |
| 16 | Level 2 — renal failure and impairment | 62 | 2 | 510 | 1792 | 64 | 572 |
| 17 | Bodily fluid | 474 | 18 | 980 | 894 | 492 | 1454 |
| 18 | Skin | 154 | 7 | 1066 | 1139 | 161 | 1220 |
| 19 | Large intestine | 44 | 2 | 810 | 1510 | 46 | 854 |
| 20 | Kidney | 214 | 11 | 696 | 1445 | 225 | 910 |
| 21 | Heart | 509 | 27 | 727 | 1103 | 536 | 1236 |
| 22 | Liver | 515 | 31 | 853 | 967 | 546 | 1368 |
| 23 | Vasculature | 465 | 28 | 842 | 1031 | 493 | 1307 |
| 24 | Nervous tissue | 165 | 10 | 1001 | 1190 | 175 | 1166 |
| 25 | Level 2 — cholestasis and jaundice | 47 | 3 | 418 | 1898 | 50 | 465 |
| 26 | Nerve | 43 | 3 | 459 | 1861 | 46 | 502 |
| 27 | Level 4 — cardiac disorder | 480 | 34 | 698 | 1154 | 514 | 1178 |
| 28 | Muscle | 168 | 12 | 829 | 1357 | 180 | 997 |
| 29 | Level 4 — blood and lymphatic system disorders | 28 | 2 | 465 | 1871 | 30 | 493 |
| 30 | Level 4 — hepatobiliary disorder | 472 | 34 | 787 | 1073 | 506 | 1259 |
| 31 | Level 3 — hepatic and hepatobiliary disorders | 338 | 26 | 764 | 1238 | 364 | 1102 |
| 32 | Level 3 — renal disorder | 75 | 6 | 394 | 1891 | 81 | 469 |
| 33 | Ear | 12 | 1 | 444 | 1909 | 13 | 456 |
| 34 | Level 4 — vascular disorder | 415 | 35 | 835 | 1081 | 450 | 1250 |
| 35 | Bodily fluid liver | 304 | 26 | 848 | 1188 | 330 | 1152 |
| 36 | Level 3 — renal disorders (excluding nephropathies) | 113 | 10 | 591 | 1652 | 123 | 704 |
| 37 | Level 4 — skin and subcutaneous tissue disease | 195 | 18 | 619 | 1534 | 213 | 814 |
| 38 | Level 2 — hepatic lipid peroxidation | 32 | 3 | 129 | 2202 | 35 | 161 |
| 39 | Level 4 — investigation | 339 | 32 | 723 | 1272 | 371 | 1062 |
| 40 | Level 1 — kidney failure | 21 | 2 | 292 | 2051 | 23 | 313 |

*All entries are numbered for identification only (column 1). The second column (**parameters**) indicates the specific biomedical observation (BMO) in question (e.g. 'bradycardia' or 'arrhythmic disorder'), or tissue-level effects (e.g. 'heart', which would encompass these two BMOs). The BMOs were mapped to their MedDRA (Medical Dictionary for Regulatory Activities) counterpart, which are classified into four levels, level 1 being the most specific and level 4 providing a more generic 'System Organ Class'. The number of drugs for which ADRs were observed in each species is shown in columns 3–8. **Human/Dog** represents drugs for which an ADR was reported in both humans and dogs: these are True Positives (TPs), and correspond to cell 'a' in the 2 × 2 matrix (see* Methods, Figure 1*). **Dog** represents drugs for which an ADR was reported in dogs, but not in humans: these are False Positives (FPs), and correspond to cell 'b' in the 2 × 2 matrix. **Human** represents drugs for which an ADR was reported in humans, but not in dogs: these are False Negatives (FNs), and correspond to cell 'c' in the 2 × 2 matrix. **Neither** represents drugs for which an absence of ADRs was evident in both humans and dogs: these are True Negatives (TNs), and correspond to cell 'd' in the 2 × 2 matrix. Notably, lack of an association between a compound and a specific BMO was assumed (by the data provider) to demonstrate a real absence of effect, and not be due to missing data. To minimise the impact of missing data, the group of compounds in the dataset were chosen with the greatest chance of having been evaluated in all the species included in the study (see* Methods*). The total number of drugs exhibiting ADRs in each species, regardless of the presence or absence of ADRs in the other species, is given in the final two columns: **Dog** = a + b (TP + FP); **Human** = a + c (TP + FN).*

*nec = not elsewhere classified.*

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | **Adverse effect: tissue-level or BMO (MedDRA Level 1–4)** | **Human/Dog a (TP)** | **Dog b (FP)** | **Human c (FN)** | **Neither d (TN)** | **Dog total** | **Human total** |
| 41 | Level 4 — injury, poisoning and procedural complications | 276 | 27 | 670 | 1393 | 303 | 946 |
| 42 | Level 4 — renal and urinary disorders | 222 | 22 | 630 | 1492 | 244 | 852 |
| 43 | Breast | 20 | 2 | 434 | 1910 | 22 | 454 |
| 44 | Adrenal gland | 10 | 1 | 224 | 2131 | 11 | 234 |
| 45 | Pancreas | 19 | 2 | 421 | 1924 | 21 | 440 |
| 46 | Level 3 — cardiac and vascular investigations (excluding enzyme tests) | 320 | 34 | 647 | 1365 | 354 | 967 |
| 47 | Level 3 — arrhythmic disorder | 294 | 32 | 577 | 1463 | 326 | 871 |
| 48 | Level 3 — skin vascular abnormalities | 182 | 20 | 482 | 1682 | 202 | 664 |
| 49 | Level 2 — trophic disorders | 9 | 1 | 110 | 2246 | 10 | 119 |
| 50 | Level 4 — musculoskeletal disorder | 105 | 12 | 706 | 1543 | 117 | 811 |
| 51 | Neuromuscular tissue | 104 | 12 | 712 | 1538 | 116 | 816 |
| 52 | Level 4 — neurological disorder | 85 | 10 | 627 | 1644 | 95 | 712 |
| 53 | Haemolymphoid tissue | 68 | 8 | 748 | 1542 | 76 | 816 |
| 54 | Joint | 17 | 2 | 420 | 1927 | 19 | 437 |
| 55 | Level 1 — cardiac hypertrophy | 25 | 3 | 106 | 2232 | 28 | 131 |
| 56 | Level 2 — hepatic microsomal lipid peroxidation | 8 | 1 | 26 | 2331 | 9 | 34 |
| 57 | Level 1 — interstitial nephritis | 8 | 1 | 108 | 2249 | 9 | 116 |
| 58 | Respiratory tissue | 70 | 9 | 653 | 1634 | 79 | 723 |
| 59 | Level 2 — haemolysis | 15 | 2 | 330 | 2019 | 17 | 345 |
| 60 | Level 4 — respiratory, thoracic and mediastinal disorders | 112 | 15 | 717 | 1522 | 127 | 829 |
| 61 | Level 1 — muscle twitching | 29 | 4 | 162 | 2171 | 33 | 191 |
| 62 | Level 2 — non-site specific vascular disorders nec | 137 | 19 | 382 | 1828 | 156 | 519 |
| 63 | Level 3 — vascular disorder | 150 | 21 | 525 | 1670 | 171 | 675 |
| 64 | Level 2 — skin vasomotor conditions | 171 | 24 | 331 | 1840 | 195 | 502 |
| 65 | Level 1 — vasodilation | 113 | 16 | 246 | 1991 | 129 | 359 |
| 66 | Level 2 — nephropathies and tubular disorders nec | 56 | 8 | 313 | 1989 | 64 | 369 |
| 67 | Level 1 — congestive heart failure | 7 | 1 | 158 | 2200 | 8 | 165 |
| 68 | Prostate gland | 7 | 1 | 234 | 2124 | 8 | 241 |
| 69 | Level 3 — chemical injury and poisoning | 168 | 25 | 544 | 1629 | 193 | 712 |
| 70 | Level 2 — poisoning and toxicity | 168 | 25 | 544 | 1629 | 193 | 712 |
| 71 | Level 2 — vascular test | 193 | 29 | 580 | 1564 | 222 | 773 |
| 72 | Stomach | 86 | 13 | 863 | 1404 | 99 | 949 |
| 73 | Level 2 — electrocardiogram observation | 59 | 9 | 306 | 1992 | 68 | 365 |
| 74 | Level 2 — rate and rhythm disorders nec | 208 | 32 | 530 | 1596 | 240 | 738 |
| 75 | Level 3 — muscular disorder | 78 | 12 | 632 | 1644 | 90 | 710 |
| 76 | Level 3 — epidermal and dermal conditions | 13 | 2 | 354 | 1997 | 15 | 367 |
| 77 | Urogenital tissue | 70 | 11 | 695 | 1590 | 81 | 765 |
| 78 | Level 3 — decreased and non-specific blood pressure disorders and shock | 153 | 25 | 498 | 1690 | 178 | 651 |
| 79 | Bodily fluid kidney | 61 | 10 | 479 | 1816 | 71 | 540 |
| 80 | Level 3 — general system disorders nec | 30 | 5 | 502 | 1829 | 35 | 532 |
| 81 | Level 3 — central nervous system vascular disorders | 18 | 3 | 266 | 2079 | 21 | 284 |
| 82 | Level 1 — jaundice | 12 | 2 | 327 | 2025 | 14 | 339 |
| 83 | Level 2 — dermal and epidermal conditions nec | 12 | 2 | 329 | 2023 | 14 | 341 |
| 84 | Level 1 — hypertrophy | 6 | 1 | 68 | 2291 | 7 | 74 |
| 85 | Level 3 — respiratory and mediastinal neoplasms (malignant and unspecified) | 6 | 1 | 72 | 2287 | 7 | 78 |
| 86 | Level 2 — lower respiratory tract neoplasms | 6 | 1 | 79 | 2280 | 7 | 85 |
| 87 | Level 3 — respiratory tract neoplastic disorder | 6 | 1 | 79 | 2280 | 7 | 85 |
| 88 | Level 2 — hepatocellular damage and hepatitis nec | 215 | 36 | 582 | 1533 | 251 | 797 |
| 89 | Level 2 — heart rate and pulse investigations | 203 | 34 | 529 | 1600 | 237 | 732 |
| 90 | Level 3 — arteriosclerosis, stenosis, vascular insufficiency and necrosis | 171 | 29 | 564 | 1602 | 200 | 735 |
| 91 | Level 1 — acute kidney failure | 34 | 6 | 289 | 2037 | 40 | 323 |
| 92 | Lung | 96 | 17 | 733 | 1520 | 113 | 829 |
| 93 | Level 2 — myocardial disorder | 73 | 13 | 198 | 2082 | 86 | 271 |
| 94 | Level 2 — vascular hypotensive disorders | 145 | 26 | 470 | 1725 | 171 | 615 |
| 95 | Level 3 — myocardial disorder | 100 | 18 | 321 | 1927 | 118 | 421 |
| 96 | Level 2 — muscle observation | 50 | 9 | 336 | 1971 | 59 | 386 |
| 97 | Bodily fluid cardiovascular | 105 | 19 | 608 | 1634 | 124 | 713 |
| 98 | Level 4 — immunological disorder | 44 | 8 | 527 | 1787 | 52 | 571 |
| 99 | Level 2 — cerebrovascular and spinal necrosis and vascular insufficiency | 11 | 2 | 138 | 2215 | 13 | 149 |
| 100 | Level 2 — inflammatory kidney disease | 11 | 2 | 155 | 2198 | 13 | 166 |

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | **Adverse effect: tissue-level or BMO (MedDRA Level 1–4)** | **Human/Dog a (TP)** | **Dog b (FP)** | **Human c (FN)** | **Neither d (TN)** | **Dog total** | **Human total** |
| 101 | Uterus | 11 | 2 | 201 | 2152 | 13 | 212 |
| 102 | Bladder | 11 | 2 | 293 | 2060 | 13 | 304 |
| 103 | Level 3 — cardiac disorder signs and symptoms | 65 | 12 | 509 | 1780 | 77 | 574 |
| 104 | Level 3 — hypertension | 96 | 18 | 520 | 1732 | 114 | 616 |
| 105 | Pituitary gland | 16 | 3 | 221 | 2126 | 19 | 237 |
| 106 | Level 2 — hepatic failure and associated disorders | 16 | 3 | 274 | 2073 | 19 | 290 |
| 107 | Level 1 — hypotension | 140 | 27 | 442 | 1757 | 167 | 582 |
| 108 | Level 2 — bronchospasm and obstruction | 31 | 6 | 376 | 1953 | 37 | 407 |
| 109 | Level 3 — bronchial disorders (excluding neoplasms) | 31 | 6 | 376 | 1953 | 37 | 407 |
| 110 | Eye | 77 | 15 | 762 | 1512 | 92 | 839 |
| 111 | Level 3 — injury | 120 | 24 | 511 | 1711 | 144 | 631 |
| 112 | Level 1 — hepatic apoptosis | 15 | 3 | 111 | 2237 | 18 | 126 |
| 113 | Level 2 — central nervous system vascular disorders | 10 | 2 | 90 | 2264 | 12 | 100 |
| 114 | Level 3 — haemolyses and related conditions | 15 | 3 | 339 | 2009 | 18 | 354 |
| 115 | Level 2 — hepatic collagen synthesis | 5 | 1 | 23 | 2337 | 6 | 28 |
| 116 | Level 1 — atrial flutter | 5 | 1 | 26 | 2334 | 6 | 31 |
| 117 | Level 1 — glutathione depletion | 5 | 1 | 29 | 2331 | 6 | 34 |
| 118 | Level 2 — haematological analyses nec | 5 | 1 | 29 | 2331 | 6 | 34 |
| 119 | Level 1 — liver failure | 10 | 2 | 221 | 2133 | 12 | 231 |
| 120 | Level 1 — cardiomyocyte apoptosis | 5 | 1 | 32 | 2328 | 6 | 37 |
| 121 | Level 2 — cardioprotection | 5 | 1 | 35 | 2325 | 6 | 40 |
| 122 | Level 3 — haematology investigations (including blood groups) | 5 | 1 | 40 | 2320 | 6 | 45 |
| 123 | Level 1 — lung neoplastic disorder | 5 | 1 | 49 | 2311 | 6 | 54 |
| 124 | Level 2 — encephalopathies (toxic and metabolic) | 5 | 1 | 49 | 2311 | 6 | 54 |
| 125 | Level 2 — respiratory tract and pleural neoplasms (malignancy unspecified nec) | 5 | 1 | 50 | 2310 | 6 | 55 |
| 126 | Level 2 — diabetic complications (renal) | 5 | 1 | 52 | 2308 | 6 | 57 |
| 127 | Level 1 — abnormal liver function | 10 | 2 | 323 | 2031 | 12 | 333 |
| 128 | Level 2 — hepatic enzymes and function abnormalities | 10 | 2 | 323 | 2031 | 12 | 333 |
| 129 | Level 1 — toxic hepatitis | 5 | 1 | 94 | 2266 | 6 | 99 |
| 130 | Level 3 — cardiac physiological observation | 229 | 46 | 322 | 1769 | 275 | 551 |
| 131 | Level 2 — cardiac disorder | 64 | 13 | 378 | 1911 | 77 | 442 |
| 132 | Digestive tissue | 49 | 10 | 731 | 1576 | 59 | 780 |
| 133 | Level 4 — general disorders and administration site conditions | 58 | 12 | 599 | 1697 | 70 | 657 |
| 134 | Level 2 — ventricular arrhythmias and cardiac arrest | 118 | 25 | 390 | 1833 | 143 | 508 |
| 135 | Level 2 — peripheral vasoconstriction, necrosis and vascular insufficiency | 101 | 22 | 209 | 2034 | 123 | 310 |
| 136 | Salivary gland | 9 | 2 | 440 | 1915 | 11 | 449 |
| 137 | Level 1 — vasoconstriction | 100 | 23 | 185 | 2058 | 123 | 285 |
| 138 | Level 1 — cardiotoxicity | 26 | 6 | 142 | 2192 | 32 | 168 |
| 139 | Level 1 — thrombosis | 13 | 3 | 186 | 2164 | 16 | 199 |
| 140 | Mouth | 13 | 3 | 297 | 2053 | 16 | 310 |
| 141 | Level 2 — ischaemic coronary artery disease | 89 | 21 | 413 | 1843 | 110 | 502 |
| 142 | Level 1 — tachycardia | 112 | 27 | 402 | 1825 | 139 | 514 |
| 143 | Level 3 — hepatic physiological phenomenon | 267 | 65 | 519 | 1515 | 332 | 786 |
| 144 | Level 2 — hypertension | 73 | 18 | 480 | 1795 | 91 | 553 |
| 145 | Level 3 — coronary arterial disease | 93 | 23 | 413 | 1837 | 116 | 506 |
| 146 | Level 1 — nephrotoxicity | 36 | 9 | 212 | 2109 | 45 | 248 |
| 147 | Level 1 — injury | 20 | 5 | 150 | 2191 | 25 | 170 |
| 148 | Level 1 — left ventricular hypertrophy | 8 | 2 | 62 | 2294 | 10 | 70 |
| 149 | Level 1 — asthma | 12 | 3 | 218 | 2133 | 15 | 230 |
| 150 | Level 1 — kidney papillary necrosis | 4 | 1 | 27 | 2334 | 5 | 31 |
| 151 | Level 2 — atrial natriuretic factor secretion | 4 | 1 | 28 | 2333 | 5 | 32 |
| 152 | Level 2 — renal disorders (congenital) | 4 | 1 | 32 | 2329 | 5 | 36 |
| 153 | Level 3 — renal and urinary tract disorders (congenital) | 4 | 1 | 37 | 2324 | 5 | 41 |
| 154 | Level 1 — acute lung injury | 4 | 1 | 39 | 2322 | 5 | 43 |
| 155 | Level 1 — pulmonary toxicity | 4 | 1 | 46 | 2315 | 5 | 50 |
| 156 | Level 2 — herg current | 4 | 1 | 77 | 2284 | 5 | 81 |
| 157 | Level 2 — inflammation | 4 | 1 | 109 | 2252 | 5 | 113 |
| 158 | Level 2 — non-site specific gastrointestinal haemorrhages | 4 | 1 | 125 | 2236 | 5 | 129 |
| 159 | Level 2 — hepatic and hepatobiliary disorders | 138 | 36 | 524 | 1668 | 174 | 662 |
| 160 | Level 1 — torsade de pointes | 19 | 5 | 163 | 2179 | 24 | 182 |

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | **Adverse effect: tissue-level or BMO (MedDRA Level 1–4)** | **Human/Dog a (TP)** | **Dog b (FP)** | **Human c (FN)** | **Neither d (TN)** | **Dog total** | **Human total** |
| 161 | Level 1 — arrhythmic disorder | 79 | 21 | 383 | 1883 | 100 | 462 |
| 162 | Level 2 — heart failure | 30 | 8 | 326 | 2002 | 38 | 356 |
| 163 | Level 1 — hypertension | 71 | 19 | 477 | 1799 | 90 | 548 |
| 164 | Level 2 — renal and urinary tract injuries nec | 26 | 7 | 185 | 2148 | 33 | 211 |
| 165 | Level 1 — renal injury | 26 | 7 | 185 | 2148 | 33 | 211 |
| 166 | Level 2 — renal structural abnormalities and trauma | 26 | 7 | 189 | 2144 | 33 | 215 |
| 167 | Level 2 — allergic conditions | 26 | 7 | 374 | 1959 | 33 | 400 |
| 168 | Level 3 — allergic conditions | 26 | 7 | 377 | 1956 | 33 | 403 |
| 169 | Level 2 — coronary necrosis and vascular insufficiency | 62 | 17 | 409 | 1878 | 79 | 471 |
| 170 | Level 2 — left ventricular failure | 21 | 6 | 165 | 2174 | 27 | 186 |
| 171 | Level 4 — congenital, familial and genetic disorders | 21 | 6 | 294 | 2045 | 27 | 315 |
| 172 | Level 2 — central nervous system haemorrhages and cerebrovascular accidents | 7 | 2 | 209 | 2148 | 9 | 216 |
| 173 | Level 3 — lower respiratory tract disorders (excluding obstruction and infection) | 38 | 11 | 368 | 1949 | 49 | 406 |
| 174 | Bone | 31 | 9 | 398 | 1928 | 40 | 429 |
| 175 | Level 2 — signs and symptoms | 24 | 7 | 439 | 1896 | 31 | 463 |
| 176 | Level 2 — non-site specific embolism and thrombosis | 17 | 5 | 230 | 2114 | 22 | 247 |
| 177 | Level 2 — non-site specific injuries nec | 20 | 6 | 158 | 2182 | 26 | 178 |
| 178 | Level 1 — ventricular tachyarrhythmia | 10 | 3 | 32 | 2321 | 13 | 42 |
| 179 | Cardiovascular tissue | 73 | 22 | 445 | 1826 | 95 | 518 |
| 180 | Level 1 — long qt interval | 23 | 7 | 186 | 2150 | 30 | 209 |
| 181 | Level 1 — cardiac arrest | 23 | 7 | 211 | 2125 | 30 | 234 |
| 182 | Level 2 — renal disorder | 19 | 6 | 185 | 2156 | 25 | 204 |
| 183 | Level 2 — cardiac conduction abnormality | 44 | 14 | 278 | 2030 | 58 | 322 |
| 184 | Level 1 — bradycardia | 78 | 25 | 271 | 1992 | 103 | 349 |
| 185 | Level 4 — metabolism and nutrition disorders | 62 | 20 | 368 | 1916 | 82 | 430 |
| 186 | Level 3 — tissue disease | 24 | 8 | 218 | 2116 | 32 | 242 |
| 187 | Level 1 — pulmonary oedema | 18 | 6 | 145 | 2197 | 24 | 163 |
| 188 | Level 4 — eye disorder | 9 | 3 | 88 | 2266 | 12 | 97 |
| 189 | Level 2 — muscular disorder | 15 | 5 | 286 | 2060 | 20 | 301 |
| 190 | Level 3 — immunological disorder | 12 | 4 | 258 | 2092 | 16 | 270 |
| 191 | Level 3 — cardiac and vascular disorders congenital | 9 | 3 | 173 | 2181 | 12 | 182 |
| 192 | Level 2 — renal observation | 6 | 2 | 85 | 2273 | 8 | 91 |
| 193 | Oesophagus | 9 | 3 | 258 | 2096 | 12 | 267 |
| 194 | Level 3 — gastrointestinal haemorrhage | 6 | 2 | 159 | 2199 | 8 | 165 |
| 195 | Level 2 — gastrointestinal haemorrhage | 6 | 2 | 177 | 2181 | 8 | 183 |
| 196 | Level 1 — hepatic injury | 61 | 21 | 341 | 1943 | 82 | 402 |
| 197 | Level 2 — abdominal injury | 61 | 21 | 343 | 1941 | 82 | 404 |
| 198 | Level 1 — hepatotoxicity | 92 | 32 | 386 | 1856 | 124 | 478 |
| 199 | Musculoskeletal tissue | 23 | 8 | 525 | 1810 | 31 | 548 |
| 200 | Level 2 — pulmonary oedema | 20 | 7 | 197 | 2142 | 27 | 217 |
| 201 | Level 1 — liver disorder | 17 | 6 | 211 | 2132 | 23 | 228 |
| 202 | Level 1 — muscular disorder | 8 | 3 | 113 | 2242 | 11 | 121 |
| 203 | Level 1 — liver cirrhosis | 8 | 3 | 139 | 2216 | 11 | 147 |
| 204 | Nose | 8 | 3 | 401 | 1954 | 11 | 409 |
| 205 | Level 1 — hypoxia | 13 | 5 | 150 | 2198 | 18 | 163 |
| 206 | Level 2 — conditions associated with abnormal gas exchange | 13 | 5 | 151 | 2197 | 18 | 164 |
| 207 | Level 2 — muscle tone abnormalities | 13 | 5 | 232 | 2116 | 18 | 245 |
| 208 | Level 1 — ventricular arrhythmia | 41 | 16 | 159 | 2150 | 57 | 200 |
| 209 | Level 3 — neuromuscular disorder | 23 | 9 | 351 | 1983 | 32 | 374 |
| 210 | Level 3 — heart failure | 53 | 21 | 388 | 1904 | 74 | 441 |
| 211 | Bodily fluid cardiac | 53 | 21 | 443 | 1849 | 74 | 496 |
| 212 | Level 4 — endocrine disorder | 10 | 4 | 125 | 2227 | 14 | 135 |
| 213 | Level 2 — hepatic monooxygenase system | 5 | 2 | 15 | 2344 | 7 | 20 |
| 214 | Level 1 — sudden cardiac death | 5 | 2 | 48 | 2311 | 7 | 53 |
| 215 | Level 3 — encephalopathy | 5 | 2 | 52 | 2307 | 7 | 57 |
| 216 | Thyroid gland | 10 | 4 | 266 | 2086 | 14 | 276 |
| 217 | Level 3 — diabetes-related disorder | 5 | 2 | 63 | 2296 | 7 | 68 |
| 218 | Level 2 — vascular smooth muscle cell proliferation | 5 | 2 | 69 | 2290 | 7 | 74 |
| 219 | Level 1 — acute liver failure | 5 | 2 | 76 | 2283 | 7 | 81 |
| 220 | Level 1 — muscle rigidity | 5 | 2 | 134 | 2225 | 7 | 139 |

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | Adverse effect: tissue-level or BMO (MedDRA Level 1–4) | Human/Dog a (TP) | Dog b (FP) | Human c (FN) | Neither d (TN) | Dog total | Human total |
| 221 | Level 1 — vascular disorder | 5 | 2 | 144 | 2215 | 7 | 149 |
| 222 | Level 2 — vascular anomalies congenital nec | 5 | 2 | 147 | 2212 | 7 | 152 |
| 223 | Level 2 — purpuras (excluding thrombocytopenic) | 5 | 2 | 198 | 2161 | 7 | 203 |
| 224 | Level 3 — coagulopathies and bleeding diatheses (excluding thrombocytopenic) | 5 | 2 | 220 | 2139 | 7 | 225 |
| 225 | Level 3 — infections (pathogen unspecified) | 5 | 2 | 270 | 2089 | 7 | 275 |
| 226 | Level 2 — cardiomyopathy | 32 | 13 | 227 | 2094 | 45 | 259 |
| 227 | Level 4 — neoplasms benign, malignant and unspecified (including cysts and polyps) | 66 | 27 | 359 | 1914 | 93 | 425 |
| 228 | Level 2 — parenchymal lung disease | 12 | 5 | 182 | 2167 | 17 | 194 |
| 229 | Level 2 — myocardial contraction | 81 | 34 | 130 | 2121 | 115 | 211 |
| 230 | Level 2 — pulmonary vascular resistance | 28 | 12 | 61 | 2265 | 40 | 89 |
| 231 | Level 2 — musculoskeletal and connective tissue signs and symptoms nec | 28 | 12 | 115 | 2211 | 40 | 143 |
| 232 | Level 3 — musculoskeletal disorder | 28 | 12 | 117 | 2209 | 40 | 145 |
| 233 | Level 1 — endothelial dysfunction | 7 | 3 | 77 | 2279 | 10 | 84 |
| 234 | Level 2 — vascular malformations and acquired anomalies | 7 | 3 | 175 | 2181 | 10 | 182 |
| 235 | Level 1 — cardiac disorder | 7 | 3 | 240 | 2116 | 10 | 247 |
| 236 | Level 4 — gastrointestinal disorder | 7 | 3 | 280 | 2076 | 10 | 287 |
| 237 | Level 3 — heart valve disorder | 16 | 7 | 128 | 2215 | 23 | 144 |
| 238 | Level 3 — vascular physiological observation | 91 | 40 | 201 | 2034 | 131 | 292 |
| 239 | Level 2 — non-site specific necrosis and vascular insufficiency nec | 52 | 23 | 285 | 2006 | 75 | 337 |
| 240 | Level 1 — cardiac lesion | 9 | 4 | 56 | 2297 | 13 | 65 |
| 241 | Level 2 — cell metabolism disorders nec | 9 | 4 | 117 | 2236 | 13 | 126 |
| 242 | Level 1 — pulmonary fibrosis | 9 | 4 | 121 | 2232 | 13 | 130 |
| 243 | Level 2 — neuromuscular disorder | 9 | 4 | 216 | 2137 | 13 | 225 |
| 244 | Bodily fluid vascular | 22 | 10 | 301 | 2033 | 32 | 323 |
| 245 | Level 1 — hepatitis | 22 | 10 | 367 | 1967 | 32 | 389 |
| 246 | Level 3 — metabolic disorder | 11 | 5 | 133 | 2217 | 16 | 144 |
| 247 | Level 3 — vasculitis | 11 | 5 | 298 | 2052 | 16 | 309 |
| 248 | Level 3 — pulmonary vascular disorder | 24 | 11 | 206 | 2125 | 35 | 230 |
| 249 | Level 1 — bronchial spasm | 13 | 6 | 246 | 2101 | 19 | 259 |
| 250 | Level 3 — respiration disorder | 15 | 7 | 277 | 2067 | 22 | 292 |
| 251 | Level 2 — supraventricular arrhythmia | 34 | 16 | 238 | 2078 | 50 | 272 |
| 252 | Level 1 — cholestasis | 19 | 9 | 181 | 2157 | 28 | 200 |
| 253 | Level 1 — contracture | 27 | 13 | 91 | 2235 | 40 | 118 |
| 254 | Level 1 — aortic valve insufficiency | 8 | 4 | 60 | 2294 | 12 | 68 |
| 255 | Level 2 — diseases of aortic valve | 8 | 4 | 79 | 2275 | 12 | 87 |
| 256 | Level 3 — fatal outcomes | 6 | 3 | 50 | 2307 | 9 | 56 |
| 257 | Level 2 — death and sudden death | 6 | 3 | 50 | 2307 | 9 | 56 |
| 258 | Gallbladder | 10 | 5 | 201 | 2150 | 15 | 211 |
| 259 | Level 3 — miscellaneous and site unspecified neoplasms (malignant and unspecified) | 8 | 4 | 171 | 2183 | 12 | 179 |
| 260 | Cartilage | 4 | 2 | 39 | 2321 | 6 | 43 |
| 261 | Level 2 — biliary excretion | 4 | 2 | 41 | 2319 | 6 | 45 |
| 262 | Level 1 — arterial thrombosis | 4 | 2 | 46 | 2314 | 6 | 50 |
| 263 | Level 1 — fibrosis | 6 | 3 | 132 | 2225 | 9 | 138 |
| 264 | Level 2 — fibrosis | 6 | 3 | 132 | 2225 | 9 | 138 |
| 265 | Level 2 — vasculitides | 8 | 4 | 228 | 2126 | 12 | 236 |
| 266 | Level 1 — acute hepatitis | 6 | 3 | 151 | 2206 | 9 | 157 |
| 267 | Level 2 — muscle weakness | 6 | 3 | 188 | 2169 | 9 | 194 |
| 268 | Level 1 — myoclonus | 4 | 2 | 113 | 2247 | 6 | 117 |
| 269 | Level 2 — neurological signs and symptoms nec | 4 | 2 | 119 | 2241 | 6 | 123 |
| 270 | Integumentary tissue | 6 | 3 | 428 | 1929 | 9 | 434 |
| 271 | Level 3 — renal physiological observation | 72 | 37 | 225 | 2032 | 109 | 297 |
| 272 | Level 3 — embolism and thrombosis | 23 | 12 | 392 | 1939 | 35 | 415 |
| 273 | Level 1 — cardiomyopathy | 9 | 5 | 104 | 2248 | 14 | 113 |
| 274 | Level 1 — hepatocyte damage | 9 | 5 | 117 | 2235 | 14 | 126 |
| 275 | Level 3 — biliary tract neoplasm | 48 | 27 | 188 | 2103 | 75 | 236 |
| 276 | Level 3 — haemorrhage | 28 | 16 | 502 | 1820 | 44 | 530 |
| 277 | Level 1 — vasospasm | 7 | 4 | 65 | 2290 | 11 | 72 |
| 278 | Endocrine tissue | 7 | 4 | 299 | 2056 | 11 | 306 |
| 279 | Bodily fluid muscle | 40 | 23 | 405 | 1898 | 63 | 445 |
| 280 | Level 1 — liver neoplastic disorder | 24 | 14 | 96 | 2232 | 38 | 120 |

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | **Adverse effect: tissue-level or BMO (MedDRA Level 1–4)** | **Human/Dog a (TP)** | **Dog b (FP)** | **Human c (FN)** | **Neither d (TN)** | **Dog total** | **Human total** |
| 281 | Level 2 — biliary tract neoplasm | 24 | 14 | 99 | 2229 | 38 | 123 |
| 282 | Level 2 — hepatobiliary neoplasms (malignancy unspecified) | 24 | 14 | 99 | 2229 | 38 | 123 |
| 283 | Level 1 — renal disorder | 12 | 7 | 148 | 2199 | 19 | 160 |
| 284 | Level 1 — ventricular tachycardia | 27 | 16 | 147 | 2176 | 43 | 174 |
| 285 | Level 2 — l-type calcium current | 10 | 6 | 90 | 2260 | 16 | 100 |
| 286 | Level 1 — haemorrhage | 15 | 9 | 269 | 2073 | 24 | 284 |
| 287 | Level 1 — cerebral vasospasm | 5 | 3 | 27 | 2331 | 8 | 32 |
| 288 | Level 3 — ancillary infectious topics | 5 | 3 | 86 | 2272 | 8 | 91 |
| 289 | Level 2 — inflammatory disorders following infection | 5 | 3 | 86 | 2272 | 8 | 91 |
| 290 | Level 2 — lower respiratory tract inflammatory and immunologic conditions | 5 | 3 | 163 | 2195 | 8 | 168 |
| 291 | Level 1 — muscle spasm | 8 | 5 | 98 | 2255 | 13 | 106 |
| 292 | Level 1 — myocardial disorder | 22 | 14 | 60 | 2270 | 36 | 82 |
| 293 | Level 2 — cardiac afterload | 11 | 7 | 40 | 2308 | 18 | 51 |
| 294 | Level 2 — liver cirrhosis | 14 | 9 | 239 | 2104 | 23 | 253 |
| 295 | Level 1 — ischaemic disease | 20 | 13 | 141 | 2192 | 33 | 161 |
| 296 | Level 1 — ischaemic cardiomyopathy | 20 | 13 | 156 | 2177 | 33 | 176 |
| 297 | Level 1 — ventricular fibrillation | 27 | 18 | 127 | 2194 | 45 | 154 |
| 298 | Level 3 — hepatobiliary neoplasms (malignant and unspecified) | 24 | 16 | 116 | 2210 | 40 | 140 |
| 299 | Level 1 — st-segment elevation | 9 | 6 | 30 | 2321 | 15 | 39 |
| 300 | Level 1 — necrosis | 9 | 6 | 59 | 2292 | 15 | 68 |
| 301 | Level 2 — necrosis | 9 | 6 | 60 | 2291 | 15 | 69 |
| 302 | Level 2 — hemorrhage | 18 | 12 | 372 | 1964 | 30 | 390 |
| 303 | Level 1 — apoptosis | 6 | 4 | 92 | 2264 | 10 | 98 |
| 304 | Level 2 — arterial and aortic injuries | 3 | 2 | 12 | 2349 | 5 | 15 |
| 305 | Level 1 — neoplastic disorder | 6 | 4 | 118 | 2238 | 10 | 124 |
| 306 | Level 2 — neoplasms unspecified (malignancy and site unspecified nec) | 6 | 4 | 122 | 2234 | 10 | 128 |
| 307 | Level 2 — hepatic lipid level | 3 | 2 | 20 | 2341 | 5 | 23 |
| 308 | Level 1 — renal fibrosis | 3 | 2 | 22 | 2339 | 5 | 25 |
| 309 | Level 1 — right ventricular hypertrophy | 3 | 2 | 22 | 2339 | 5 | 25 |
| 310 | Level 1 — hepatic mitochondrial swelling | 3 | 2 | 36 | 2325 | 5 | 39 |
| 311 | Level 1 — glomerular sclerosis | 3 | 2 | 39 | 2322 | 5 | 42 |
| 312 | Level 2 — pericardium disorder | 3 | 2 | 47 | 2314 | 5 | 50 |
| 313 | Small intestine | 6 | 4 | 233 | 2123 | 10 | 239 |
| 314 | Level 1 — hypersensitive vasculitis | 3 | 2 | 85 | 2276 | 5 | 88 |
| 315 | Level 1 — inflammation | 3 | 2 | 96 | 2265 | 5 | 99 |
| 316 | Level 2 — cutaneous vasculitis | 3 | 2 | 102 | 2259 | 5 | 105 |
| 317 | Level 2 — peripheral vascular disorder | 3 | 2 | 143 | 2218 | 5 | 146 |
| 318 | Connective tissue | 3 | 2 | 204 | 2157 | 5 | 207 |
| 319 | Level 2 — muscle tone abnormal | 10 | 7 | 208 | 2141 | 17 | 218 |
| 320 | Level 1 — pulmonary hypertension | 17 | 12 | 94 | 2243 | 29 | 111 |
| 321 | Level 2 — systemic vascular resistance | 24 | 17 | 79 | 2246 | 41 | 103 |
| 322 | Level 2 — hepatic cytochrome p450 level | 7 | 5 | 50 | 2304 | 12 | 57 |
| 323 | Level 1 — renal impairment | 7 | 5 | 276 | 2078 | 12 | 283 |
| 324 | Level 2 — hepatic protein biosynthesis | 11 | 8 | 61 | 2286 | 19 | 72 |
| 325 | Bone-marrow | 15 | 11 | 302 | 2038 | 26 | 317 |
| 326 | Level 3 — lipid metabolism disorder | 19 | 14 | 137 | 2196 | 33 | 156 |
| 327 | Level 2 — lipid metabolism and deposit disorders nec | 19 | 14 | 137 | 2196 | 33 | 156 |
| 328 | Level 1 — hepatic necrosis | 46 | 34 | 177 | 2109 | 80 | 223 |
| 329 | Level 1 — premature cardiac complex | 4 | 3 | 51 | 2308 | 7 | 55 |
| 330 | Level 3 — pericardium disorder | 4 | 3 | 72 | 2287 | 7 | 76 |
| 331 | Level 1 — muscle weakness | 4 | 3 | 174 | 2185 | 7 | 178 |
| 332 | Level 1 — myocardial infarction | 21 | 16 | 296 | 2033 | 37 | 317 |
| 333 | Level 2 — pulmonary hypertension | 17 | 13 | 108 | 2228 | 30 | 125 |
| 334 | Level 3 — electrolyte and fluid balance conditions | 9 | 7 | 107 | 2243 | 16 | 116 |
| 335 | Level 4 — infections and infestations | 9 | 7 | 381 | 1969 | 16 | 390 |
| 336 | Level 1 — hepatomegaly | 16 | 13 | 116 | 2221 | 29 | 132 |
| 337 | Ovary | 11 | 9 | 327 | 2019 | 20 | 338 |
| 338 | Level 1 — hepatic steatosis | 18 | 15 | 135 | 2198 | 33 | 153 |
| 339 | Level 1 — cardiogenic shock | 6 | 5 | 83 | 2272 | 11 | 89 |
| 340 | Testis | 19 | 16 | 260 | 2071 | 35 | 279 |

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | Adverse effect: tissue-level or BMO (MedDRA Level 1–4) | Human/Dog a (TP) | Dog b (FP) | Human c (FN) | Neither d (TN) | Dog total | Human total |
| 341 | Level 1 — heart failure | 13 | 11 | 208 | 2134 | 24 | 221 |
| 342 | Level 1 — centrilobular hepatic necrosis | 7 | 6 | 27 | 2326 | 13 | 34 |
| 343 | Level 3 — acid-base disorders | 7 | 6 | 50 | 2303 | 13 | 57 |
| 344 | Level 2 — action potential duration | 38 | 35 | 91 | 2202 | 73 | 129 |
| 345 | Level 3 — procedural related injuries and complications nec | 13 | 12 | 193 | 2148 | 25 | 206 |
| 346 | Level 2 — cardiovascular injuries | 15 | 14 | 107 | 2230 | 29 | 122 |
| 347 | Level 1 — atrial fibrillation | 16 | 15 | 162 | 2173 | 31 | 178 |
| 348 | Level 2 — action potential | 28 | 27 | 101 | 2210 | 55 | 129 |
| 349 | Level 1 — hyperaemia | 7 | 7 | 34 | 2318 | 14 | 41 |
| 350 | Level 2 — hepatic glutathione level | 7 | 7 | 37 | 2315 | 14 | 44 |
| 351 | Level 2 — cardiac function diagnostic procedures | 13 | 13 | 180 | 2160 | 26 | 193 |
| 352 | Level 2 — liver respiration | 5 | 5 | 32 | 2324 | 10 | 37 |
| 353 | Level 1 — coronary artery vasospasm | 5 | 5 | 38 | 2318 | 10 | 43 |
| 354 | Level 2 — hepatic RNA synthesis | 4 | 4 | 18 | 2340 | 8 | 22 |
| 355 | Level 2 — renal vascular and ischaemic conditions | 6 | 6 | 65 | 2289 | 12 | 71 |
| 356 | Level 1 — ECG abnormality | 9 | 9 | 161 | 2187 | 18 | 170 |
| 357 | Level 2 — circulatory collapse and shock | 8 | 8 | 135 | 2215 | 16 | 143 |
| 358 | Level 1 — complete atrioventricular block | 5 | 5 | 52 | 2304 | 10 | 57 |
| 359 | Level 2 — effective renal plasma flow | 4 | 4 | 29 | 2329 | 8 | 33 |
| 360 | Level 1 — hepatic fibrosis | 7 | 7 | 116 | 2236 | 14 | 123 |
| 361 | Level 1 — oedema | 5 | 5 | 64 | 2292 | 10 | 69 |
| 362 | Level 2 — total fluid volume increased | 5 | 5 | 72 | 2284 | 10 | 77 |
| 363 | Level 2 — metabolic acidoses (excluding diabetic acidoses) | 4 | 4 | 41 | 2317 | 8 | 45 |
| 364 | Level 2 — oedema | 5 | 5 | 73 | 2283 | 10 | 78 |
| 365 | Level 2 — bile acid biosynthesis | 3 | 3 | 40 | 2320 | 6 | 43 |
| 366 | Level 3 — increased intracranial pressure and hydrocephalus | 4 | 4 | 92 | 2266 | 8 | 96 |
| 367 | Level 2 — increased intracranial pressure disorders | 4 | 4 | 92 | 2266 | 8 | 96 |
| 368 | Level 3 — neurological disorder | 5 | 5 | 153 | 2203 | 10 | 158 |
| 369 | Thymus gland | 5 | 5 | 164 | 2192 | 10 | 169 |
| 370 | Level 2 — cerebrospinal fluid tests (excluding microbiology) | 3 | 3 | 69 | 2291 | 6 | 72 |
| 371 | Level 1 — intracranial hypertension | 3 | 3 | 69 | 2291 | 6 | 72 |
| 372 | Level 3 — neurological, special senses and psychiatric investigations | 3 | 3 | 70 | 2290 | 6 | 73 |
| 373 | Level 2 — vascular tissue neoplasm | 3 | 3 | 71 | 2289 | 6 | 74 |
| 374 | Level 2 — nervous system haemorrhagic disorders | 3 | 3 | 105 | 2255 | 6 | 108 |
| 375 | Level 2 — coronary blood flow | 40 | 41 | 41 | 2244 | 81 | 81 |
| 376 | Level 2 — bile flow | 14 | 15 | 59 | 2278 | 29 | 73 |
| 377 | Level 2 — cardiac and vascular procedural complications | 11 | 12 | 183 | 2160 | 23 | 194 |
| 378 | Level 1 — infarct size | 20 | 22 | 95 | 2229 | 42 | 115 |
| 379 | Level 2 — coronary arterial disease | 7 | 8 | 64 | 2287 | 15 | 71 |
| 380 | Level 3 — bile duct disorder | 7 | 8 | 192 | 2159 | 15 | 199 |
| 381 | Level 2 — hepatic portal blood flow | 6 | 7 | 26 | 2327 | 13 | 32 |
| 382 | Level 2 — heart weight | 6 | 7 | 36 | 2317 | 13 | 42 |
| 383 | Level 2 — hepatic glycogen level | 5 | 6 | 18 | 2337 | 11 | 23 |
| 384 | Level 2 — hepatocyte proliferation | 5 | 6 | 39 | 2316 | 11 | 44 |
| 385 | Level 2 — liver weight | 53 | 66 | 156 | 2091 | 119 | 209 |
| 386 | Level 2 — hepatic glucose release | 4 | 5 | 10 | 2347 | 9 | 14 |
| 387 | Level 1 — left ventricular dysfunction | 4 | 5 | 49 | 2308 | 9 | 53 |
| 388 | Level 2 — atrioventricular conduction | 9 | 12 | 32 | 2313 | 21 | 41 |
| 389 | Level 1 — myocardial infarct size | 9 | 12 | 42 | 2303 | 21 | 51 |
| 390 | Level 2 — hepatic drug metabolism | 6 | 8 | 54 | 2298 | 14 | 60 |
| 391 | Level 1 — muscle hypotonia | 3 | 4 | 43 | 2316 | 7 | 46 |
| 392 | Level 2 — left ventricular mass | 3 | 4 | 45 | 2314 | 7 | 48 |
| 393 | Level 2 — hepatic blood flow | 8 | 11 | 64 | 2283 | 19 | 72 |
| 394 | Level 1 — myocardial fibrosis | 5 | 7 | 37 | 2317 | 12 | 42 |
| 395 | Level 2 — renal blood flow | 28 | 40 | 63 | 2235 | 68 | 91 |
| 396 | Level 1 — atrioventricular block | 7 | 10 | 94 | 2255 | 17 | 101 |
| 397 | Level 2 — hepatobiliary signs and symptoms | 17 | 25 | 142 | 2182 | 42 | 159 |
| 398 | Level 1 — coronary artery thrombosis | 4 | 6 | 9 | 2347 | 10 | 13 |
| 399 | Level 2 — site specific embolism and thrombosis nec | 4 | 6 | 12 | 2344 | 10 | 16 |
| 400 | Level 2 — renal function | 6 | 9 | 104 | 2247 | 15 | 110 |
| 401 | Level 2 — ventricular refractory period | 2 | 3 | 6 | 2355 | 5 | 8 |
| 402 | Level 2 — hepatic cytochrome p450 function | 4 | 6 | 76 | 2280 | 10 | 80 |
| 403 | Level 1 — high cardiac output | 2 | 3 | 17 | 2344 | 5 | 19 |
| 404 | Level 1 — chronic hepatitis | 2 | 3 | 22 | 2339 | 5 | 24 |
| 405 | Level 1 — myocarditis | 2 | 3 | 46 | 2315 | 5 | 48 |

| | Parameters | Number of drugs | | | | | |
|---|---|---|---|---|---|---|---|
| | **Adverse effect: tissue-level or BMO (MedDRA Level 1–4)** | **Human/Dog a (TP)** | **Dog b (FP)** | **Human c (FN)** | **Neither d (TN)** | **Dog total** | **Human total** |
| 406 | Level 2 — non-infectious myocarditis | 2 | 3 | 50 | 2311 | 5 | 52 |
| 407 | Level 4 — pregnancy, puerperium and perinatal conditions | 2 | 3 | 65 | 2296 | 5 | 67 |
| 408 | Level 1 — st-segment depression | 2 | 3 | 67 | 2294 | 5 | 69 |
| 409 | Level 1 — inflammatory kidney disease | 2 | 3 | 68 | 2293 | 5 | 70 |
| 410 | Level 2 — cardiac conduction | 5 | 8 | 28 | 2325 | 13 | 33 |
| 411 | Level 1 — infarction | 5 | 8 | 74 | 2279 | 13 | 79 |
| 412 | Level 1 — hepatocyte hypertrophy | 15 | 25 | 40 | 2286 | 40 | 55 |
| 413 | Level 2 — site-specific vascular disorders nec | 3 | 5 | 29 | 2329 | 8 | 32 |
| 414 | Level 2 — bile duct infections and inflammations | 3 | 5 | 42 | 2316 | 8 | 45 |
| 415 | Level 2 — liver vascular disorder | 4 | 7 | 78 | 2277 | 11 | 82 |
| 416 | Level 2 — renal vascular resistance | 9 | 16 | 48 | 2293 | 25 | 57 |
| 417 | Level 3 — hepatobiliary investigations | 6 | 11 | 241 | 2108 | 17 | 247 |
| 418 | Level 2 — hepatic function test | 6 | 11 | 241 | 2108 | 17 | 247 |
| 419 | Level 2 — cardiac function | 8 | 15 | 88 | 2255 | 23 | 96 |
| 420 | Level 1 — centrilobular hypertrophy | 9 | 18 | 22 | 2317 | 27 | 31 |
| 421 | Level 1 — ventricular premature complex | 8 | 16 | 117 | 2225 | 24 | 125 |
| 422 | Level 3 — vascular injury | 5 | 10 | 59 | 2292 | 15 | 64 |
| 423 | Level 2 — ventricular conduction | 2 | 4 | 6 | 2354 | 6 | 8 |
| 424 | Level 2 — mixed acid-base disorders | 2 | 4 | 17 | 2343 | 6 | 19 |
| 425 | Level 1 — acidosis | 2 | 4 | 17 | 2343 | 6 | 19 |
| 426 | Level 1 — tachyarrhythmia | 2 | 4 | 33 | 2327 | 6 | 35 |
| 427 | Level 1 — hepatic enzyme level | 3 | 6 | 104 | 2253 | 9 | 107 |
| 428 | Level 2 — coronary vascular resistance | 13 | 28 | 25 | 2300 | 41 | 38 |
| 429 | Level 3 — hepatic and biliary neoplasms (benign) | 15 | 33 | 106 | 2212 | 48 | 121 |
| 430 | Level 1 — ischaemia-reperfusion injury | 5 | 11 | 67 | 2283 | 16 | 72 |
| 431 | Level 2 — biliary secretion | 4 | 9 | 36 | 2317 | 13 | 40 |
| 432 | Level 2 — left ventricular pressure | 7 | 17 | 33 | 2309 | 24 | 40 |
| 433 | Level 1 — altered hepatic foci | 2 | 5 | 14 | 2345 | 7 | 16 |
| 434 | Level 1 — cholangitis | 2 | 5 | 24 | 2335 | 7 | 26 |
| 435 | Level 2 — hepatic enzyme function | 2 | 5 | 28 | 2331 | 7 | 30 |
| 436 | Level 1 — arteriosclerosis | 2 | 5 | 37 | 2322 | 7 | 39 |
| 437 | Level 2 — hepatobiliary neoplasms benign | 13 | 33 | 105 | 2215 | 46 | 118 |
| 438 | Level 2 — renal plasma flow | 3 | 8 | 30 | 2325 | 11 | 33 |
| 439 | Level 2 — left ventricular function | 3 | 8 | 31 | 2324 | 11 | 34 |
| 440 | Level 2 — myocardial blood flow | 7 | 19 | 24 | 2316 | 26 | 31 |
| 441 | Level 1 — hepatocellular adenoma | 12 | 33 | 97 | 2224 | 45 | 109 |
| 442 | Level 2 — hepatic vacuolation | 2 | 6 | 9 | 2349 | 8 | 11 |
| 443 | Level 2 — cerebral blood flow | 5 | 16 | 79 | 2266 | 21 | 84 |
| 444 | Level 3 — neurological physiological observation | 5 | 16 | 83 | 2262 | 21 | 88 |
| 445 | Level 2 — peripheral vascular resistance | 7 | 24 | 53 | 2282 | 31 | 60 |
| 446 | Level 2 — ventricular repolarisation | 2 | 7 | 17 | 2340 | 9 | 19 |
| 447 | Level 2 — left ventricular systolic blood pressure | 5 | 19 | 24 | 2318 | 24 | 29 |
| 448 | Level 2 — hepatocyte vacuolation | 5 | 26 | 22 | 2313 | 31 | 27 |
| 449 | Level 1 — hepatocyte degeneration | 2 | 12 | 16 | 2336 | 14 | 18 |
| 450 | Level 2 — left ventricular contraction | 2 | 12 | 16 | 2336 | 14 | 18 |