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Identification of structure–activity relationships for adverse effects of pharmaceuticals in humans. Part A: Use of FDA post-market reports to create a database of hepatobiliary and urinary tract toxicities

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ABSTRACT

The Informatics and Computational Safety Analysis Staff at the US FDA's Center for Drug Evaluation and Research has created a database of pharmaceutical adverse effects (AEs) linked to pharmaceutical chemical structures and estimated population exposures. The database is being used to develop quantitative structure–activity relationship (QSAR) models for the prediction of drug-induced liver and renal injury, as well as to identify relationships among AEs. The post-market observations contained in the database were obtained from FDA's Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS) accessed through Elsevier PharmaPendium™ software. The database contains approximately 3100 unique pharmaceutical compounds and 9685 AE endpoints. To account for variations in AE reports due to different patient populations and exposures for each drug, a proportional reporting ratio (PRR) was used. The PRR was applied to all AEs to identify chemicals that could be scored as positive in the training data sets of QSAR models. Additionally, toxicologically similar AEs were grouped into clusters based upon both biological effects and statistical correlation. This clustering created a weight of evidence paradigm for the identification of compounds most likely to cause human harm based upon findings in multiple related AE endpoints.

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1. Introduction

The US FDA's Center for Drug Evaluation and Research (CDER), Informatics and Computational Safety Analysis Staff (ICSAS) is an applied regulatory research group that develops databases of toxicological and adverse human clinical information for use in data mining and quantitative structure–activity relationship (QSAR)¹ modeling (Benz, 2007). We have created a human health effects database containing human adverse effect (AE) reporting data that are being used for both of these purposes. Previous attempts to compile and construct QSAR models using FDA's Spontaneous Reporting

System (SRS) post-market AE data have shown some success (Matthews et al., 2004), but have also suggested that a larger database of observations would produce models with greater predictive performance. In the current investigation, data were collected from FDA's SRS and Adverse Event Reporting System (AERS) databases, as well as the published literature. A weight of evidence (WOE) methodology was applied to these data in order to identify compounds active at clusters of multiple related AE endpoints. Additionally, disproportionality analyses were performed to distinguish between active and inactive compounds. The study reported here focused on the hepatobiliary and renal tract organ system AEs which have attracted considerable attention in recent years due both to post-market AEs as well as evidence of mechanistic explanations of these effects (Fung et al., 2001).

FDA/CDER has primarily employed the SRS and AERS systems for collecting reports of pharmaceutical AEs from manufacturers, physicians and patients (<http://www.fda.gov/medwatch>). The SRS database was used from 1969 to October 1997 and then was replaced by the more comprehensive AERS database in November

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¹ Abbreviations used: AE, (pharmaceutical) adverse effect; AERS, FDA's Adverse Event Reporting System; HLT, MedDRA High Level Term; HLT, MedDRA High Level Term; PRR, proportional reporting ratio (disproportional analysis of pharmaceutical AEs); PT, MedDRA Preferred Term; QSAR, quantitative structure–activity relationship; SOC, MedDRA System Organ Class (term); SRS, FDA's Spontaneous Reporting System; WOE, weight of evidence.

1997. Both databases are publicly available through the US Department of Commerce, Technology Administration, National Technical Information Service (<http://www.ntis.gov>). One of the important functions of these databases is to facilitate monitoring of AEs that went undetected during pre-clinical animal testing and clinical trials. In general, clinical trials are more efficient at detecting beneficial pharmacological effects and dose-related organ toxicities than idiosyncratic occurrences (Navarro and Senior, 2006). Liver and renal AEs are often idiosyncratic, making them difficult to predict before a drug is marketed. Because the databases serve as repositories for reports of over 6 million human AEs, they are also well suited to providing information for use in building QSAR models. Such models can be used both in lead chemical selection by the pharmaceutical industry, as well as for decision support information within regulatory agencies.

Despite the potential utility of such models, little work has been done in this area due to difficulties involved with using AE reporting data. These problems include non-uniform reporting across toxicological endpoints, patients often taking more than one medication at a time, and a higher AE reporting frequency during the initial drug marketing period. Furthermore, merging of the SRS and AERS data is not straightforward due to substantial differences in the way data have been recorded in each system. AEs from the AERS data sets are described using the Medical Dictionary for Regulatory Activities (MedDRA) terms, and approximately 14,000 terms are arranged hierarchically to reflect both organ systems and categories of toxic effects. However, the SRS database uses the Coding Symbols for Thesaurus of Adverse Reaction (COSTAR) terms vocabulary (COSTART, 1995) which has fewer than 1200 terms. In order to combine the two databases, the COSTAR terms were mapped into MedDRA categories, and the MedDRA terms were then used as the basis for the work reported here.

A weight of evidence (WOE) methodology was applied to these data in order to identify compounds active at clusters of multiple related AE endpoints. This approach was inspired by the observations of Hyman Zimmerman (1999) that certain drugs causing drug-induced liver injury manifested by the presence of both increases in alanine or aspartate aminotransferases, as well as jaundice, in the same patient are most likely to cause serious human effects such as liver failure in that patient. Our operating WOE hypothesis is analogous, but not identical, to Hy's law and asserts that drugs causing a significant increase in more than one type of hepatobiliary AE in all patients are more dangerous than those causing only one serious AE. Additionally, disproportionality analyses were performed to distinguish between active and inactive compounds at these endpoints.

In this investigation we focused on liver and renal tract AE reports. The liver was chosen as an important organ system for analysis of AEs because drugs are the single most common cause of acute liver failure (Lee, 2005) and hepatotoxicity is the most common reason for the FDA to take regulatory action against a drug (Temple, 2007). A study of all safety withdrawals of prescription drugs from worldwide markets from 1960 to 1999 (Fung et al., 2001) showed that internationally the liver is the most common organ to be affected by toxicities leading to drug withdrawal, with 26.2% of all withdrawals being attributed to it. In recent years the FDA has partnered with members of academia and the pharmaceutical industry to form a workgroup focused solely on better understanding the causes and warning signs of drug-induced liver toxicity (<http://www.fda.gov/cder/livertox>).

The urinary tract was also chosen for analysis because our laboratory's previous QSAR modeling experience with the organ system (Matthews et al., 2004) suggested that a mechanism related to chemical structure was involved in renal toxicity, a theory also supported by the literature (Fielden et al., 2005). Additionally, many common classes of drugs have been linked to renal toxicity,

including NSAIDs, ACE inhibitors and antibiotics (Perazaella, 2003). NSAIDs specifically are thought to cause as many as 2.5 million adverse renal effects in the US each year (Sandhu and Heyneman, 2004). These AEs, such as the tubular dysfunction associated with tenofovir, occur despite clean renal profiles in clinical trials performed prior to drug marketing (Röling et al., 2006).

2. Materials and methods

2.1. Data compilation

The AE data used in this study came from three sources: AERS, SRS, and the published literature accessed through MicroMedex Integrated Index. FDA's AERS data were downloaded one endpoint at a time from MDL-Elsevier's PharmaPendium™ database using the information available May to August, 2006. PharmaPendium™ is a web-based relational database that contains FDA approval packages and related documents, as well as AERS reports for currently marketed drugs. Data for a total of 9685 endpoints were downloaded. The SRS data were gathered from publicly available CDs which contain text files summarizing the AEs encountered, the age and gender of the patient, the pharmaceutical taken, and whether or not the pharmaceutical in question was considered to be responsible for the AE. All of this information was linked together by a control number unique to each report. Each drug found in either AERS or SRS was then searched upon in MicroMedex DRUGDEX® and Martindale, The Complete Drug Reference databases for AE literature citations, and results were saved for later analysis. MicroMedex contains a review of pertinent literature citations concerning drugs that have been marketed in the US and other countries. Both Microsoft Excel and Access 2003 were used to organize these data.

In order to combine data from the AERS and SRS databases, the COSTAR vocabulary describing AEs in the SRS database was mapped into the MedDRA vocabulary describing AEs in the AERS database. The MedDRA vocabulary was chosen as the control vocabulary for this study because of its hierarchical organization and the diversity of terms it contains, as well as its status as the current standard vocabulary for the AERS database and PharmaPendium™. Within PharmaPendium™, all endpoints are organized hierarchically in the top four MedDRA levels: system organ classes (SOC), high level group terms (HLGT), high level terms (HLT), and preferred term (PT); the lowest level of the terminology (LLT) is not used. SOC refers to the broadest category and PT is the most specific endpoint description. PTs that were found in multiple SOC locations were moved to the single most appropriate position in the hierarchy. For example, jaundice AEs appeared in both 'Hepatobiliary disorders' and 'Skin and subcutaneous tissue disorders' and these AEs were merged under 'Hepatobiliary disorders.'

The hepatobiliary portion of this dataset contained 35 COSTAR terms, 28 of which had greater than 100 SRS reports. Endpoints with fewer than 100 reports could not be compared to similar endpoints due to the small number of active compounds, and thus were not used individually in this analysis. However, all 35 terms were mapped into the 229 MedDRA hepatobiliary terms. Of these 229 terms, 63 AEs had greater than 100 reports. The urinary tract dataset included 63 COSTAR terms, 49 of which had greater than 100 SRS reports. All 63 terms were mapped into 426 MedDRA terms, 82 of which had more than 100 AERS reports.

Pharmaceutical chemical names and structures were also standardized across the two databases. SRS data were historically recorded by proprietary drug name, but in many cases multiple trade names corresponded to a single active pharmaceutical ingredient. For the purposes of QSAR modeling, data for the same compound listed under multiple trade names needed to be pooled

under a standardized generic name. In the SRS database, 8638 trade names were mapped to 2919 generic pharmaceutical names. Additionally, the same active molecule was often present separately in the SRS database as different salts and esters. When appropriate, these records were combined to create a single record for all instances of the active compound. Inorganic chemicals, high molecular weight polymers (>5000 Da), complex mixtures, gases and salts could not be modeled by the QSAR software used in this investigation and were excluded from the analysis. In the SRS database, this left 1395 unique, modelable compounds. These compounds were linked to molecular structures using the ICSAS Chemical Dictionary and online chemical resources (ChemIDplus, 2006; USP, 2003). Of the 2699 generic pharmaceuticals in PharmaPendium™, 1734 were unique, modelable compounds, and 1019 of these had at least 1 AERS report and were therefore used in this study. Chemical structures were also linked to these compounds. All structures from the SRS and AERS databases were saved as “.mol” files and were also converted to simplified molecular input line entry system (SMILES) codes using MC4PC (MultiCASE, Inc.).

2.2. Estimation of patient exposure

In this investigation, counts of AEs for each drug at each endpoint of study were used to calculate drug activities. In order to detect true signals above the background of reporting noise, disproportionality analyses were performed. The particular analysis used was the proportional reporting ratio (PRR), which was chosen because it accounts for patient exposure to a drug based upon the frequency of reporting for that drug in the entire database (Evans et al., 2001). The PRR has been widely used in the detection of signals in AE reporting databases at regulatory agencies and pharmaceutical companies in many countries, including the UK Medicines and Healthcare Products Regulatory Agency (Moore et al., 2005). This calculation is based upon the assumption that in the absence of a toxicological mechanism causing an AE, AEs for drugs and endpoints occur independently. The number of reports that would occur with this independence is referred to as the expected value. Mathematically this translates into the fraction of total reports made up by each drug being constant across all endpoints throughout the database. The ample number of reports in both the SRS and AERS databases facilitated the calculation of separate expected values for each drug at each endpoint. The actual number of reports (observed) divided by this expected value denominator was then defined as the PRR (Fig. 1), which was used to detect drug–AE signals. This was used in conjunction with minimum report and χ^2 requirements.

To calculate the expected value, the total numbers of reports in the entire database of 9685 endpoints were summed for each drug. The total numbers of reports per endpoint were also summed. The fraction of total reports per drug multiplied by the total reports for

each endpoint was then calculated to be the expected value for each drug at each specific endpoint. To calculate the observed value, all reports for each drug at each endpoint were pooled. The χ^2 statistic was calculated as the observed minus the expected value, squared, divided by the expected value ($\chi^2 = (\text{observed} - \text{expected})^2 / \text{expected}$). When the observed value was significantly greater than the expected value, resulting in large PRR and χ^2 values, a drug was considered active at that endpoint. These calculations were performed separately for the SRS and AERS databases.

The significance of these values was determined by setting a threshold (cut-off) to distinguish active from inactive PRR values. The threshold was set at a PRR value of ≥ 2 , accompanied by a χ^2 of ≥ 4 and a minimum of 2 observed reports for the drug–AE combination. Several other paradigms were tested, including the use of the Yates correction, varying the minimum observed reports required to be classified as active from 1 to 10, and setting a PRR threshold value based upon fitting each AE to have 20% of the reported compounds be active, but none of these other paradigms produced predictions with as great an accuracy (Matthews et al., 2009a).

2.3. Clustering of related AEs

The 9685 MedDRA PTs downloaded from PharmaPendium™ were grouped into 23 SOC categories, including an Investigations group containing investigatory endpoints for each cluster. Two of these SOC categories, hepatobiliary disorders and renal and urinary disorders, along with their corresponding Investigations endpoints, were selected for further analysis in this study. Within each organ system, related AEs were clustered to fulfill several goals of this study. First, the clustering created a WOE paradigm in which the pool of positive drugs would represent drugs having exhibited AEs at multiple related AE endpoints. This was performed in concordance with the aforementioned hypothesis that having more than one type of serious AE represents a higher risk. Another reason for clustering toxicologically related AEs is that it creates a larger pool of active compounds than would often be found for a single endpoint, which is an important consideration when the data are to be used for QSAR modeling (Matthews et al., 2009a).

Clustering of related AEs was performed exclusively with the AERS endpoints. Once the toxicologically related endpoints were clustered, the SRS AEs were grouped into equivalent clusters based upon the mapping of the SRS terms to their AERS counterparts. This was done so that clusters from each database could be compared and/or combined during later analyses. The SRS endpoints were clustered regardless of whether the endpoints met the statistical requirements used to cluster AERS AEs described below; however, most of the liver and renal SRS endpoints clustered similarly to the AERS equivalent terms.

Three parameters were used for clustering of the hepatobiliary and urinary tract AE endpoints: the MedDRA hierarchy, toxicological mechanism, and predictive statistics. As previously noted, most of the AE endpoints were maintained within the hierarchical system used in PharmaPendium™, which is based upon the MedDRA hierarchy. MedDRA HGLTs in this hierarchy were used as the starting point for clustering of related AEs. In a few cases, AEs from different HGLT categories within a SOC were moved to more appropriate clusters based upon the expert opinions and prior experience of the authors. In other cases, certain AEs within a HGLT were moved to a more appropriate SOC category based upon similar toxicological mechanisms such as inducing neoplasms, congenital defects, or infection. Both of these steps were performed for all hepatobiliary and urinary tract AEs regardless of the number of reports for the endpoint. After these HGLT endpoints had been relocated, the AEs with fewer than 100 reports

$$\text{PRR} = [a(b+d)] / [b(a+c)]$$

- a = Number of reports at the endpoint of interest for the drug of interest
- b = Number of reports at the endpoint of interest for all other drugs in the database
- c = Number of reports at all other endpoints for the drug of interest
- d = Number of reports at all other endpoints for all other drugs in the database

Example: Haemolytic anaemia adverse effects for abacavir sulfate

a = 15

b = 1523

c = 3031

d = 241,386

$\text{PRR} = [15(1523+241386)] / [1523(15+3031)]$

$\text{PRR} = (15 \times 242909) / (1523 \times 3046)$

$\text{PRR} = 0.785$

Abacavir sulfate is evaluated as not active because $\text{PRR} < 2$.

Fig. 1. Calculation of the proportional reporting ratio (PRR).

within each cluster were pooled and treated as a single endpoint for performing correlative statistics and the remainder of the study. The idea for combining these reports came from the AE warnings in MedWatch which often pools AEs for a given organ system (e.g., AE warning for the renal and urinary tract). Furthermore, the AE endpoints were biologically related through their MedDRA HGLT classification. This pooling was done because the low number of positive compounds in small endpoints prohibited them from being statistically correlated to the larger endpoints, regardless of whether the 2 endpoints shared active compounds.

Once the AEs had been clustered based upon their MedDRA term hierarchy and toxicological activity, the individual PT endpoints within the clusters were examined for their statistical concordance with one another. The intention was to identify the PT endpoints that shared the largest number of active and inactive drugs, and to merge the AE data for the endpoints with the highest degree of concordance. This analysis was accomplished using a three-step procedure. (1) A statistical analysis of the AEs was done within each cluster, using the AE endpoint with the largest number of reports initially as the control to which all other AEs in the cluster were statistically compared. Cooper statistics (Cooper et al., 1979) were calculated to assess the ability of this control endpoint to predict the positive and negative compounds in each other PT endpoint in the cluster. (2) Each of the other PT endpoints within the cluster was then substituted and tested as the control. The AE that generated the best statistics for the greatest number of AEs in the cluster was chosen to represent the cluster as well as serve as the principal PT control endpoint. Permanent inclusion of other AEs in the cluster was based upon criteria of at least 90% specificity and approximately 15% sensitivity or more for endpoints with fewer than 1000 reports, or at least 20% sensitivity for endpoints with more than 1000 reports. (3) A pool of smaller endpoints in the cluster having fewer than 100 reports was treated as a single composite endpoint, and this endpoint was included or excluded from the cluster based upon the same statistical criteria.

2.4. Assignment of activity unit scores

2.4.1. Conversion of a drug PRR to an AU score for a single endpoint

In order to perform QSAR modeling the continuous distribution of PRR values over a 6-log range of values for individual pharmaceuticals at each hepatobiliary and urinary tract AE endpoint of study was converted to an activity unit (AU) score ranging from 10–80 AU. The use of an AU score is explained in Matthews and Contrera (1998) and Matthews et al. (2000, 2004). Briefly, active chemicals with a $PRR \geq 2$, a $\chi^2 \geq 4$, and ≥ 2 observed reports were assigned 30–80 AU; conversely, inactive and marginally active chemicals with lesser PRR, χ^2 and observed report values were assigned 10–29.9 AU. Chemicals were scored so that the AU values assigned within either the active or inactive ranges were proportional to the PRR value for each drug–AE combination. Because many drugs in the AERS and SRS databases had only 1–2 reports per AE endpoint, the PRR values of individual drugs with 2 reports were scaled separately from drugs having ≥ 3 reports. However, the final evaluation of drug AE activity was dependent upon results of QSAR optimization experiments (Matthews et al., 2008, 2009a,b). The following describes the AU scaling methods used for the active and inactive drugs:

(1) *Active drugs*: For compounds with a $PRR \geq 2$, $\chi^2 \geq 4$, and ≥ 3 observed reports, the score of the compound from this group with the highest PRR value for the endpoint was set at 80 AU and the drug(s) having exactly the cut-off PRR value of 2 were assigned 30 AU. The rest of the drugs in this group were then scored as the fraction of the highest PRR multiplied by 50 (the range of positive scores) plus 30. This additional 30 was added to each score to

account for the active AU range starting at 30. Active compounds with a $PRR \geq 2$ and a $\chi^2 \geq 4$, but only 2 observed reports were then scored as their own group by this same method.

(2) *Inactive and marginally active drugs*: Compounds were also split into two groups for scoring: compounds with a single observed report with PRR values at ≥ 2 , and compounds with PRR values < 2 . Both groups of compounds were assigned scores proportionally in the range of 10–29.9 AU; compounds with 10–19.9 AU were evaluated as inactive and compounds with 20–29.9 AU were considered marginally active. Compounds were scored by multiplying the fraction of the cut-off PRR value by 20, the range of inactive scores, and adding 10. An additional 10 was added to account for the inactive scores starting at 10 instead of 0.

2.4.2. Scoring of clusters

After an AU score had been calculated for each drug at each individual PT endpoint within a cluster, each of the drugs was assigned a composite AU score based upon the AU scores for that drug for all of the toxicologically related endpoints. Rather than taking an average AU score value of the individual endpoints per drug, this scoring was done using a WOE scheme so that the endpoints within each cluster that contained a greater number of reports contributed more heavily to the total cluster score. This WOE scheme was utilized to prevent a drug with a high AU in an endpoint with a relatively small number of AE reports from skewing the overall drug AU value for the cluster. To achieve this, the percentage of the total reports for each endpoint in each cluster was calculated. The AU score for each drug was then multiplied by this percentage and these values were summed across all of the endpoints in the cluster. This resulting set of values was proportionally converted to the 10–80 AU range by setting the highest value at an 80 AU and scoring the remaining compounds by multiplying the fraction of the highest value by 70 (the total range of scores) and then adding 10. The scores resulting from this conversion were demonstrated to be suitable for QSAR modeling (Matthews et al., 2009a).

2.4.3. Scoring of drugs based upon literature AE data

AEs for pharmaceuticals reported in the literature and in drug labeling were compiled for all of the modelable drugs identified in the AERS and SRS databases, and for additional drugs present in our own pharmaceutical chemical structure database. The findings from the literature, found by querying the MicroMedex Integrated Index, were qualitatively scored using the same activity scale used for the AERS and SRS AE data. We used these data to identify a subset of pharmaceuticals that were evaluated as active in the literature yet were inactive based upon PRR analyses of the AERS and SRS data. Each active drug in the literature was assigned an AU value of 31, 33, 35, 39, or 50 based upon the WOE of the related AEs. A pharmaceutical was considered to be active based upon either of two criteria: (1) the drug had been removed from the market due to organ specific liver or kidney toxicity, or (2) the drug had been shown to cause a specific AE in $>2\%$ of clinical trial patients. Since DRUGDEX[®] does not consistently state whether the study or clinical trial had a placebo control, there is a possibility that a small portion of these findings are not statistically significant. The highest score of 50 was given to a drug removed from the market because of the severity of AEs. The remaining scores were given in proportion to the number of PT endpoints with findings and the occurrence of findings in $>2\%$ of the patient population. These scores were kept separate from the AERS and SRS data sets for use in validating our scoring paradigm, as well as for later inclusion in QSAR modules (Matthews et al., 2009a).

2.5. Availability of experimental data

All of the AE data compiled for this investigation were obtained from publicly available sources. SRS and AERS databases are available through the US Department of Commerce National Technical Information Service (<http://www.ntis.gov>). The AERS and clinical trial AE data (1992 to present) are also available in Elsevier's PharmaPendium™ database. Additional AE data from the literature and drug labeling can be obtained using MicroMedex Integrated Index. All of these AE data were transformed to a format suitable for QSAR modeling. These data are protected under licensing agreements and will be available to the scientific community through our CRA-DA partners. The MedDRA vocabulary terms used in this investigation were obtained from PharmaPendium™ and are protected under licensing agreements with Northrop Grumman (<http://www.meddrasso.com>). Only a portion of these terms are presented to illustrate the methodology used in this investigation.

3. Results and discussion

3.1. Database size

One focus of this study was to compile the largest possible database of pharmaceutical molecules and their AEs. As a result, the completed AERS-based database contained 3,818,691 reports for 2699 unique generic compounds, and 3,523,985 reports for the 1019 compounds that could be modeled using QSAR software. The completed SRS-based database contained 2919 unique compounds, and 4,792,688 reports for the 1395 drugs that were modelable. Because the SRS and AERS patient reports often recorded more than one AE and medication, we estimate the total number of individual drug/AE combinations in our database was much larger and approximately 20,000,000 records. The total number of reports for all unique generic compounds could not be calculated due to file size limitations of the database software used. The combination of the AERS and SRS data sets produced a database containing approximately 3100 unique pharmaceutical compounds, 1660 of which could be modeled for liver and kidney toxicity. These compounds were reported to cause AEs at 9685 PT endpoints. All of these endpoints were hierarchically organized into 1310 HLT, 299 HLT, and 23 SOC categories. This database was considerably larger than that used for ICSAS' previous investigation, which contained about 1.5 million reports from the SRS database and 500 modelable chemicals (Matthews et al., 2004).

The large numbers of reports as well as modelable compounds in both the AERS and SRS databases allowed them to be analyzed separately, which was necessary for equitable treatment of all AEs. A major assumption underlying the use of a PRR is that confounding factors in reporting affect different endpoints and drugs equally. For example, if a drug has increased reporting rates in the first five years of marketing, reporting will be increased across all endpoints for this time period. However, this principle cannot be applied across databases. One reason for this is that the databases cover different time periods, so the combination of reports from both databases could result in PRRs that may not accurately reflect patient exposure levels at the time of reporting. Also, the SRS system had a limit of 4 AEs and 5 drugs per report, while AERS has no such limit (Szarfman et al., 2002). Combining the databases into a single database could have ignored additional AEs and drugs that might have been reported in SRS had it been allowed.

3.2. Estimation of patient exposure

The use of a PRR was suitable for this study for a number of reasons, one of the most significant of which was that it allows for a

correction for the background level of reporting across all drugs and endpoints when identifying significant signals. For example, if total reporting for a drug is increased during the first five years of marketing, the denominator of the PRR will also be increased across all endpoints, facilitating the identification of only the specific drug–AE combinations with large PRR values (Evans et al., 2001). Other issues this particular approach takes into consideration are the increased reporting for drugs that are taken by a large number of patients, without necessitating the gathering of data for actual drug sales. Although drug sales could hypothetically be estimated using records of the number of prescriptions written or information on the number of manufacturer shipping units delivered (IMS Health, 1996), accurate information on the volume of every single drug sold and used in the United States from 1969 to 2006 has not been compiled and these data were therefore not available for this investigation. The use of the PRR values permitted us to use all of the AEs reported over this 38 year period for all of the drugs marketed in the United States. Additionally, we have reported that QSAR modeling of SRS AEs data using relatively small training data sets and drug usage based upon shipping units had inadequate predictive performance (Matthews et al., 2004).

Additionally, the PRR also accounts for variation in the number of reports for different endpoints. Common endpoints such as headache will naturally have a larger number of reports than more specific endpoints such as blood bilirubin increased, and all drugs will have greater expected values at the more common endpoint. Furthermore, although nearly all of the drugs in our AE database have some sort of an AE, most of the drugs have low levels of AEs for most of the AE endpoints. The PRR facilitates the identification of a large subset of compounds that are considered as 'inactive,' and these inactive compounds are vital to the QSAR programs being able to identify actives. Basically, our use of PRR values allows for compounds to be ranked along a range or spectrum of activities.

Traditionally, the PRR is used by pharmacovigilance groups in conjunction with a requirement of a Yates correction ((observed – expected – 0.5)²/expected) value of at least 4 and at least 3 observed reports. However, for the purposes of this QSAR study, optimal identification of active drugs was achieved with the use of the less stringent criteria of PRR ≥ 2, a $\chi^2 \geq 4$, and ≥ 2 observed reports. This strategy resulted in an increased sensitivity for AE QSAR models, while sacrificing some specificity (Matthews et al., 2009a).

This difference in choice of methods is based upon the different goal of this study compared to that of a pharmacovigilance group. A pharmacovigilance group starts with a drug and attempts to identify AEs that might be related to or caused by the drug. With the pharmacovigilance aim, one wants to identify the strongest relationships to be further studied on a case-by-case basis in order to avoid a great deal of false alarms. In contrast, the goal of this study was to identify global structure–activity relationships (SAR) for drugs having toxicologically related AE findings (Matthews et al., 2009a). In addition, for the purposes of QSAR modeling, the highest possible percentage of active drugs needed to be identified in order to link chemical structure with AE properties. With a relatively high percentage of actives, QSAR software can search among all of the compounds with varying degrees of activity and identify the structural features most linked to the toxicity of study. If the more stringent approach had been employed and only the most active compounds were included in the QSAR models, the QSAR programs would have had too few examples of active drug molecules and would be unable to identify enough structural features related to AEs to make an active/inactive call. All of the global QSAR software programs evaluated in this laboratory have been demonstrated to require training datasets that contain roughly equal numbers of active and inactive chemicals to make

accurate predictions, and have optimal performance with 30–40% actives (Matthews et al., 2008).

QSAR models using these less stringent criteria were found to be optimal by comparing them to those constructed using the alternate scoring paradigm. QSAR models were generated from sets of compounds that were scored based on the Yates correction paradigm and those using the χ^2 criteria described above. Across different clusters of endpoints, the data that were scored based upon the χ^2 criteria consistently gave better predictive statistics. The sensitivities of the χ^2 data sets were greatly increased, with only small decreases in specificity, when compared to results using the Yates correction value (Matthews et al., 2009a).

Additionally, data were scored using a separate paradigm that used only a PRR value criterion and no minimum observed reports or χ^2 requirements. In this experiment, the cut-off between active and inactive compounds was set so that each AE contained 20% actives. As shown in Tables 1–11, the χ^2 scoring system often resulted in endpoints with close to 20% actives as well. QSAR models built using both of these paradigms created models with fairly similar predictive statistics, with the χ^2 models being superior in most cases. A further description of the use of QSAR modeling to determine the optimal scoring paradigm can be found in Matthews et al. (2009a).

3.3. Possible limitations in the investigation

A major limitation of PRR methods in the identification of significant drug-related AEs is that very strong signals for a particular drug–AE combination can dwarf other signals for that drug or AE (Evans et al., 2001). This occurs because a large number of reports for a specific drug or AE will inflate the denominator of the PRR, resulting in a larger observed value being required to give the same PRR for other drug–AE combinations. One such example is the increased denominator for all drugs having reports for urolithiasis due to the large amount of sulfonyleurea reports for this endpoint.

Another example can be seen in the inflated denominator for amphotericin B at all endpoints due to the large numbers of renal impairment reports for this drug. An additional weakness in this method is seen with well tolerated drugs that generally have few AEs. Because these drugs will have small expected values, the AEs at which they are reported may be more likely to result in a signal than would the same number of reports for a drug that is poorly tolerated and causes many AEs (Moore et al., 2005).

A second limitation of the PRR method used in this study is that it did not account for demographic differences in the AE database. No attempt was made to stratify the data according to the gender and age of the patient, and both parameters are known to affect the frequency of reporting of drug AEs (Almenoff et al., 2006). Stratification of our database for these parameters would have reduced the numbers of drugs available for individual QSAR models and resulted in lesser predictive performance of the models. We also did not attempt to look for and eliminate duplicate reporting of the same patient AEs. The assumption of our model was that these factors were made trivial by the large size of the AE database and did not significantly impact signal detection in drug-related hepatobiliary and urinary tract toxicity.

A third limitation of the modified PRR method used in this study is that the criteria for calling compounds active are not as stringent as those used by pharmacovigilance groups and those currently being used by the FDA for regulatory decisions. Therefore, it is possible that these models could result in erroneous positive predictions, and these predictions could only be disproved by large and costly clinical trials. While false positives are expected, they are estimated to be only $\leq 15\%$ for single endpoint models based upon the strict criteria used to construct the QSAR model which limits specificity to $\geq 85\%$. Furthermore, our recommendation for using a WoE evaluation of the *in silico* data would limit concerns to drugs having two or more significant findings for a given organ system. The less stringent PRR criteria were utilized to enhance the predictive performance of the QSAR models and cast the tightest possible

Table 1
Liver enzyme disorders cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	8970	Aspartate aminotransferase increase	Control	Control	Control	Control	Control	Control	Control	451	14
AERS	9262	Alanine aminotransferase increase	98	81	19	99	1	81	99	440	14
AERS	3766	Gamma-glutamyltransferase increase	95	56	44	97	3	56	97	356	17
AERS	1976	Transaminases increase	93	35	65	97	3	42	96	304	17
AERS	12909	Liver function test abnormal	92	47	53	95	5	40	97	526	14
AERS	1712	Liver enzyme disorders composite	93	31	69	97	3	40	96	261	18
SRS	17927	Aspartate aminotransferase increase	Control	Control	Control	Control	Control	Control	Control	721	15
SRS	14364	Alanine aminotransferase increase	95	68	32	98	2	72	97	676	15
SRS	5847	Gamma-glutamyl transpeptidase increase	92	29	71	97	3	43	94	510	14
SRS	6725	Lactic dehydrogenase increase	93	39	61	97	3	55	95	583	13
SRS	43974	Liver function test abnormal	91	49	51	95	5	43	96	642	19

Table 2
Cytotoxic injury cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	1244	Hepatic necrosis	Control	Control	Control	Control	Control	Control	Control	230	25
AERS	365	Autoimmune hepatitis	94	17	83	99	1	50	95	110	18
AERS	1616	Hepatic cirrhosis	94	34	66	98	2	50	96	231	17
AERS	4844	Hepatic failure	94	62	38	96	4	48	98	382	20
AERS	524	Hepatic fibrosis	95	33	67	99	1	59	96	156	21
AERS	5970	Hepatitis	92	53	47	94	6	36	97	443	19
AERS	2128	Hepatic steatosis	94	33	67	98	2	44	96	286	15
AERS	473	Hepatitis fulminant	94	29	71	98	2	45	96	156	24
AERS	5294	Hepatocellular damage	94	22	78	98	2	39	95	339	10
AERS	1320	Hepatotoxicity	94	45	55	97	3	46	97	261	22
AERS	2020	Hepatomegaly	94	43	57	97	3	50	97	294	17
AERS	1216	Cytotoxic injury composite	94	34	66	97	3	43	96	241	20
SRS	3225	Hepatic necrosis	Control	Control	Control	Control	Control	Control	Control	458	15
SRS	1742	Fatty liver	92	43	57	94	6	29	97	525	20
SRS	1939	Hepatic cirrhosis	93	24	76	97	3	29	96	379	16
SRS	5263	Hepatic failure	92	43	57	94	6	29	97	525	20
SRS	16377	Hepatitis	92	57	43	94	6	32	98	731	17
SRS	4761	Hepatocellular damage	93	53	47	95	5	35	97	551	19
SRS	2398	Hepatomegaly	92	39	61	95	5	30	97	423	21

Table 3
Cholestasis and jaundice cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	7105	Jaundice	Control	Control	Control	Control	Control	Control	Control	455	18
AERS	1706	Cholestasis	90	33	67	95	5	39	94	312	23
AERS	996	Hepatitis cholestatic	88	21	79	94	6	24	93	244	31
AERS	718	Jaundice cholestatic	91	18	82	98	2	41	93	209	18
AERS	1032	Hyperbilirubinaemia	91	25	75	97	3	43	94	216	23
SRS	11343	Jaundice	Control	Control	Control	Control	Control	Control	Control	688	19
SRS	8332	Jaundice cholestatic	89	39	61	94	6	41	94	607	20
SRS	14124	Bilirubinemia	91	48	52	95	5	50	95	701	17

Table 4
Bile duct disorders cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	338	Biliary tract disorder	Control	Control	Control	Control	Control	Control	Control	137	15
AERS	178	Bile duct stone	97	14	86	99	1	21	98	90	16
AERS	344	Cholangitis	97	33	67	98	2	30	99	126	18
AERS	286	Bile duct obstruction	97	33	67	98	2	32	99	106	21

net. High sensitivity was considered to be a highly desirable feature of QSAR model for safety applications within the Agency, as well as in prioritization of lead chemicals by industry. Furthermore, it is our recommendation within the Agency that these *in silico* data be used decision support information in conjunction with available experimental data. Thus, the positive AE predictions would represent precautions to be considered during clinical trials

and observations to be investigated through post-market surveillance.

Despite these three limitations, the advantage of our relatively conservative use of the post-market AE databases and PRR values is that it permits successful early identification of potentially harmful drugs and lead compounds with potential AE liabilities.

Table 5
Gall bladder disorders cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	5868	Blood bilirubin increase	Control	Control	Control	Control	Control	Control	Control	427	19
AERS	303	Bilirubin conjugated increase	93	14	86	99	1	61	93	128	14
AERS	2625	Cholelithiasis	91	20	80	97	3	34	93	307	15
AERS	2402	Gall bladder disorders composite	92	24	76	98	2	48	94	297	13

Table 6
Urolithiasis cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	349	Calculus urinary	Control	Control	Control	Control	Control	Control	Control	56	25
AERS	1478	Nephrolithiasis	96	57	43	96	4	17	99	228	20
AERS	111	Calculus ureteric	98	43	57	99	1	43	99	47	30
AERS	107	Urolithiasis composite	97	14	86	99	1	13	99	57	28
SRS	2327	Renal calculus	Control	Control	Control	Control	Control	Control	Control	353	14
SRS	284	Urolithiasis	96.77	20.83	79.17	99.48	0.52	58.82	97.24	88	19

Table 7
Blood in urine cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	381	White blood cells urine positive	Control	Control	Control	Control	Control	Control	Control	147	21
AERS	3937	Haematuria	93	16	84	95	5	9	97	392	14
SRS	10062	Haematuria	Control	Control	Control	Control	Control	Control	Control	642	12
SRS	3856	Albuminuria	94	40	60	97	3	43	97	459	15

3.4. Clustering of related adverse effects

A decision was made early in this investigation to attempt to bundle the PT AEs into a relatively small number of clusters of toxicologically related endpoints. This strategy was employed for four reasons:

(1) *Underreporting of AEs*: There is significant underreporting of the AEs of drugs, which clustering of endpoints helps to overcome. An AE for a specific drug may not be reported either because it was looked for and not found, or simply not looked for at all. This is particularly relevant for diagnostic tests where the results of one test might lead a physician not to order additional tests, although these tests may have been positive if they had been performed. For example, if a given drug has significant PRR values for a single liver enzyme release AE endpoint, and all liver enzyme release endpoints from a cluster have highly concordant and correlated AEs, we can assume that the given drug has a high probability of being active at the majority of the other liver enzyme release endpoints, even if they were not reported.

(2) *Active drugs for QSARs*: A paucity of active compounds is an obstacle in the QSAR modeling of AE data because marketed drugs are specifically designed to avoid causing AEs. AE clustering in-

creases the total percent of actives without also greatly increasing the false positive rate of the final QSAR models.

(3) *WOE risk assessment*: The identification of five independent clusters of hepatobiliary AEs facilitates the prioritization of drugs most likely to cause serious drug-induced liver injury (Zimmerman, 1999) by allowing for the identification of compounds active in two or more of these clusters.

(4) *Multiple AE endpoints*: Clustering AE endpoints reduces the number of QSARs that need to be constructed to predict drug-related AEs. There are 229 MedDRA terms for hepatobiliary and 426 for urinary tract findings. Although it would be technically feasible to construct 655 different QSAR models for these endpoints, it would be a time-consuming and costly task.

The clustering of hepatobiliary AEs resulted in five well-defined clusters in the AERS database, three of which had equivalent clusters in the SRS data set. These three clusters were: liver enzyme disorders, cytotoxic injury, and cholestasis and jaundice (Tables 1–3). The clusters bile duct disorders and gall bladder disorders (Tables 4 and 5) were only present in AERS, as SRS did not contain enough endpoints in either of these categories to form an equivalent cluster. A minimum of two related endpoints was required to be considered a cluster. When clustered based upon their equiva-

Table 8
Bladder disorders cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	572	Nocturia	Control	Control	Control	Control	Control	Control	Control	128	16
AERS	2696	Dysuria	95	50	50	96	4	21	99	342	14
AERS	2673	Urinary incontinence	94	35	65	95	5	13	99	346	16
AERS	2081	Urinary retention	93	40	60	94	6	12	99	327	20
AERS	1061	Polyuria	94	25	75	95	5	10	98	242	21
AERS	669	Micturition urgency	96	35	65	98	2	23	99	178	17
AERS	606	Bladder disorder	96	20	80	98	2	16	98	167	15
AERS	2864	Pollakiuria	96	60	40	96	4	24	99	321	15
AERS	311	Incontinence	97	30	70	98	2	22	99	116	23
AERS	216	Micturition disorder	97	25	75	99	1	26	99	82	23
AERS	146	Urine flow decrease	97	20	80	99	1	27	98	68	22
AERS	2019	Bladder composite	95	30	70	96	4	14	99	323	13
SRS	5782	Micturition frequency	Control	Control	Control	Control	Control	Control	Control	475	11
SRS	5995	Urinary retention	92	19	81	94	6	12	97	552	15
SRS	6970	Urinary incontinence	94	19	81	97	3	18	97	560	10
SRS	3898	Dysuria	95	41	59	98	2	41	98	475	11
SRS	2031	Polyuria	94	22	78	97	3	24	97	402	13
SRS	1382	Nocturia	96	22	78	99	1	40	97	256	12
SRS	1001	Micturition urgency	97	41	59	99	1	58	98	278	14

Table 9
Nephropathies cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	350	Nephritis	Control	Control	Control	Control	Control	Control	Control	141	26
AERS	819	Nephrotic syndrome	93	30	70	95	5	19	97	202	29
AERS	1158	Nephritis interstitial	93	49	51	94	6	24	98	215	34
AERS	281	Glomerulonephritis	95	27	73	98	2	34	97	113	26
AERS	261	Nephropathy	96	30	70	98	2	38	97	112	26
AERS	198	Renal tubular acidosis	95	16	84	98	2	21	97	68	41
AERS	973	Nephropathies composite	94	38	62	96	4	29	98	209	23
SRS	977	Glomerulonephritis	Control	Control	Control	Control	Control	Control	Control	279	14
SRS	1856	Nephrosis	97	63	37	97	3	41	99	364	16
SRS	4453	Nephritis	94	47	53	96	4	24	98	446	17
SRS	750	Renal tubular disorder	95	26	74	97	3	22	98	272	17
SRS	211	Nephrosclerosis	97	24	76	99	1	50	98	113	16

lent AERS AEs, all of the liver SRS AEs formed clusters that met the statistical requirements used in the AERS clustering.

The urinary tract AEs clustered into six groups in both the AERS and SRS databases. These clusters were: urolithiasis, blood in urine, bladder disorders, nephropathies, acute renal disorders, and kidney function tests (Tables 6–11). Two endpoints were maintained within clusters despite being slightly below the statistical requirements; they were haematuria and the urolithiasis in the blood in urine composite endpoint. This was done both because the statistics were close to the acceptable values, as well as because the endpoints were toxicologically related. As with the hepatobiliary

clusters, agreement between the AERS and SRS clusters was very good and only two SRS endpoints did not meet the statistical requirements used in clustering of AERS AEs. Both of these endpoints had greater than 1000 reports, but sensitivities between 15% and 20%.

The clustering of endpoints resulted in the unexpected observation that the criteria used to identify toxicologically correlated AE endpoints resulted in clusters of endpoints that were relatively stable and not influenced by the use of different minimal report cut-offs (Table 12). We observed that requiring anywhere from 1 to 5 observed reports for a compound to be considered active identified

Table 10
Acute renal disorders cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	1400	Renal tubular necrosis	Control	Control	Control	Control	Control	Control	Control	166	14
AERS	7031	Renal failure acute	91	83	17	91	9	18	100	461	23
AERS	5938	Renal impairment	94	30	70	95	5	12	98	407	14
AERS	1435	Oliguria	92	22	78	93	7	7	98	291	24
AERS	10526	Renal insufficiency	94	39	61	95	5	16	99	483	11
AERS	960	Anuria	94	43	57	95	5	16	99	258	24
AERS	689	Renal failure chronic	95	26	74	97	3	15	98	201	19
AERS	2375	Renal disorder composite	94	30	70	95	5	13	98	315	17
SRS	3202	Oliguria	Control	Control	Control	Control	Control	Control	Control	479	19
SRS	13640	Renal failure	92	62	38	95	5	44	97	674	19
SRS	18558	Renal failure acute	91	66	34	92	8	37	97	715	22
SRS	2324	Anuria	93	47	53	96	4	46	96	437	21
SRS	1935	Renal tubular necrosis	94	42	58	97	3	50	96	395	19
SRS	2711	Uremia	91	27	73	95	5	29	95	434	19

Table 11
Kidney function tests cluster statistics.

Database	Total reports	Adverse event	Concordance (%)	Sensitivity (%)	False negativity (%)	Specificity (%)	False positivity (%)	Positive predictivity (%)	Negative predictivity (%)	Number of drugs	Percent positive (%)
AERS	651	Blood creatine increase	Control	Control	Control	Control	Control	Control	Control	224	20
AERS	3826	Blood urea increase	93	68	32	94	6	34	98	397	22
AERS	7265	Blood creatinine increase	92	68	32	93	7	32	98	469	20
AERS	202	Blood creatinine decrease	96	23	77	99	1	56	97	111	16
AERS	151	Blood creatinine	95	16	84	98	2	30	96	72	32
SRS	25952	Creatinine urine increase	Control	Control	Control	Control	Control	Control	Control	700	17
SRS	9366	Renal function test abnormal	93	52	48	96	4	57	96	612	18
SRS	885	Creatinine renal clearance decrease	93	28	72	99	1	77	94	252	17
SRS	15389	Blood urea nitrogen-creatinine ratio increase	94	56	44	98	2	71	96	628	15

Table 12
Effect of minimal report cut-off on sensitivity and specificity.

Cytotoxic Injury Cluster AE	Observed reports cut-off											
	1		2		3		4		5		10	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Autoimmune hepatitis	20	97	22	98	17	99	15	99	15	99	5	100
Hepatic cirrhosis	31	96	33	97	34	98	33	98	38	98	50	99
Hepatic failure	58	95	58	96	62	96	60	96	67	96	73	97
Hepatic fibrosis	36	97	37	98	33	99	35	99	41	99	36	100
Hepatic steatosis	28	96	30	97	33	98	35	98	36	98	50	98
Hepatitis	53	94	55	94	53	94	54	95	56	95	50	96
Hepatitis fulminant	42	96	36	97	29	98	29	99	31	99	14	100
Hepatocellular damage	23	97	21	97	22	98	23	98	28	99	32	99
Hepatomegaly	36	96	39	97	43	97	48	98	51	98	50	98
Hepatotoxicity	46	95	42	96	45	97	48	97	54	98	64	99
Cytotoxic injury composite	35	95	36	96	34	97	35	98	44	98	45	99

exactly the same PT endpoints in all of our clusters. The correlations among the endpoints were only diminished when a cut-off of 10 observed reports was used. This observation is important because it suggests that the endpoints within a cluster are truly related in terms of the toxicological mechanism(s) by which the AEs are caused. Furthermore, these data suggest that the AE clusters are relatively stable and would not be expected to be dramatically influenced by the incremental addition of new AE data.

3.5. Scoring of compounds

This study used a novel scoring procedure involving the separation of compounds into four categories based upon the PRR value, χ^2 statistic, and observed reports. This was done to account for the extremely large PRR values present for some drug–AE combinations that had very low expected values. We observed that when all drugs were placed in a single data set and scored based upon a fraction of the highest PRR value, scores were skewed by a few very large PRR values which suppressed the scores of the remaining drugs in the set. Separately dealing with compounds having a $\text{PRR} \geq 2$, but either 1 observed report or a $\chi^2 < 4$ removed this suppression from the inactive compounds. This was achieved within the set of active compounds by scoring the drugs with only 2 observed reports separately. The compounds with exactly 2 observed reports had disproportionately high PRR values, which caused suppression of the PRR values of other drugs when lumped into a single category.

This scoring paradigm was validated by comparing literature reports from DRUGDEX[®] accessed through MicroMedex for each drug to the scores assigned to them for each of the major clusters. The clusters included in this analysis were liver enzyme disorders, cytotoxic injury and jaundice and cholestasis for the liver AEs, and acute renal disorders, nephropathies, kidney function tests and bladder disorders for the urinary tract AEs. The smaller clusters of AEs were not used for this validation because reports for the more obscure endpoints they contained could not be reliably identified in the literature. Additionally, this method of validation was only useful in the AERS database, as many of the drugs in the SRS database were significantly older and are not reported in detail in the current MicroMedex and DRUGDEX[®] databases as drugs marketed in the last decade are.

Tables 13 and 14 show the 10 highest scored drugs, the activity unit scores of the clusters in which they fall, and corresponding statements from DRUGDEX[®] for each of the clusters mentioned. In both the hepatobiliary and urinary tract sets, the cluster corresponding to acute organ failure was most aligned with the literature reports, with each of the top 10 scored drugs having literature findings. This corresponds to the cytotoxic injury and renal disorders clusters for the hepatobiliary and renal tract organ systems, respectively.

The only cluster with scores widely discordant from the literature findings was bladder disorders, with only three of the top 10 scored compounds having findings in DRUGDEX[®]. However, of these 10 compounds five are indicated for treatment of benign prostatic hyperplasia, of which the primary symptoms are urinary hesitancy, frequent urination and urinary retention. Three additional compounds of these 10 are indicated for the treatment of overactive bladder, incontinence and urinary frequency. These symptoms may have not been reported in the literature as AEs of these drugs because they are also the clinical indications. Thus, it is also possible that the high numbers of post-market reports for these drugs at the bladder disorder AEs were due largely to the conditions that the drugs were meant to treat, instead of any unintended adverse actions of the drugs.

The remaining four clusters were remarkably concordant with the DRUGDEX[®] findings. 60–90% of the top 10 scored drugs in each

cluster had findings in the literature in agreement with those in that specific cluster. Excluding the bladder disorders cluster, an average of 82% of the top 10 scored drugs had pertinent literature findings.

3.6. QSAR Model AEs

After the AE data were clustered and scored into five hepatobiliary and six urinary tract data sets, and the AERS, SRS, and literature data were combined, the data were used to prepare QSAR structure data files for five hepatobiliary and six urinary tract data models. The final list of AE endpoints included in the 11 QSAR models is presented in Table 15. The data are presented in a format to allow comparison of the name of the QSAR database with the MedDRA SOC, HGLT, HLT, and PT AE vocabulary terms. For example, the liver enzyme disorders QSAR model uses data from the investigations SOC, hepatobiliary investigations HGLT, liver function analyses and hepatic enzyme and function abnormalities HLTs, and 12 different PT terms (e.g., alanine aminotransferase). In addition, the table shows the relative contribution of the AEs of each PT to the entire AERS hepatobiliary database and to the QSAR model endpoint, respectively. For example, the alanine aminotransferase PT had 170 AE reports which represent 0.13% of the AERS hepatobiliary data set, and 0.36% of the liver enzyme disorders QSAR model endpoint. It should be noted, however, that the report counts in Table 15 include records for drug structures unsuitable for QSAR modeling (organometallics, mixtures, etc.), leading to higher totals than those presented in Tables 1–5. Furthermore, the SRS data were not presented in this format because of the vocabulary term limitations discussed earlier.

3.7. Alternative approaches

3.7.1. Adverse effects noted in clinical trials

Other approaches for building an AE database suitable for QSAR modeling were considered during the course of this investigation. For example, we considered developing a database of all AEs identified in Pharma clinical trials. Unfortunately, PharmaPendium[™] clinical trial records were limited to the most recent drug approval packages (1992 to present) at the time this investigation was conducted, and no alternative database containing these data was identified. Efforts to increase the number of earlier drug approval packages are now underway and future versions of PharmaPendium[™] will have earlier clinical trial data. However, the number of serious AEs noted in clinical trials was markedly lower than those seen in post-market records. The lower frequency was in part due to smaller number of patients exposed to the drug, and the adverse impact serious AEs would have had on drug approval for marketing. The lower frequencies of AEs in clinical trial data would have reduced the number of actives and hampered QSAR modeling.

3.7.2. Adverse effects noted in the public domain literature

Our efforts to harvest AE data from the literature and public domain using DRUGDEX[®] were extremely labor intensive and inefficient and could theoretically be improved upon. Although a daunting task, text-mining and automated linguistics could theoretically be used to build the AE database itself, and a PRR-related method could be applied to identify active drugs. This approach would require substantial resources that were not available to this project.

3.7.3. Addressing polypharmacology issues in post-market AE databases

Many investigators are reluctant to use AE data contained in FDA/CDER's post-market surveillance SRS and AERS databases,

Table 13
Top 10 drugs for each AERS liver cluster.

Drug name	Cluster score	Literature statement
<i>Liver enzyme disorders cluster</i>		
Bosentan	80	Elevations in aminotransferases by more than 3 times the upper limit of normal occurred in 11% of bosentan-treated patients compared to 2% of placebo-treated patients
Pemoline	72	Hepatotoxicity, including elevated liver enzymes, hepatitis, and jaundice, has been reported in patients receiving pemoline. Reports indicate a 1% to 2% incidence of hepatotoxicity
Troglitazone	61	1.9% Incidence of hepatotoxicity derived from 2 placebo-controlled clinical trials; more than 100 cases of liver damage have been reported to the United States Food and Drug Administration
Zileuton	57	Meaningful elevations (greater than 3 times the upper limit of normal) in alanine aminotransferase (ALT) occurred in 1.9% of zileuton-treated patients compared to 0.2% of controls
Tolcapone	53	Increases of more than 3 times the upper limit of normal in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred in 1% and 3% of patients receiving tolcapone 100 mg three times daily (TID) and 200 mg TID
Isoniazid	52	Asymptomatic elevations in liver function tests develop in 10–20% of all patients taking isoniazid
Estazolam	50	None
Thiabendazole	49	Transient, mild elevations of SGOT and bilirubin have been reported
Fluvastatin sodium	47	During clinical trials, 1.1% of patients developed persistent elevations in liver enzymes (ie, greater than 3 times the upper limit of normal)
Oxacillin sodium	46	Laboratory abnormalities may include a mild elevation of alanine aminotransferase, alkaline phosphatase, and eosinophilia
<i>Cytotoxic injury cluster</i>		
Halothane	80	Hepatotoxicity including hepatitis, and hepatic necrosis are described with the administration of halothane; Type I hepatotoxicity may occur in up to 25 to 30% of patients
Troglitazone	75	1.9% Incidence of hepatotoxicity derived from 2 placebo-controlled clinical trials; more than 100 cases of liver damage have been reported to the United States Food and Drug Administration
Pyrazinamide	73	Pyrazinamide is hepatotoxic and there is evidence that the risk of drug-induced hepatitis is dependent upon dosage
Acarbose	65	Transaminase elevations, hepatotoxicity, hepatic necrosis, right upper quadrant pain, dark urine, jaundice, hepatomegaly, and light-colored stools are reported
Nefazodone hydrochloride	63	Liver failure (life-threatening liver failure, 1 case per 250,000 to 300,000 patient years of treatment), hepatitis and increased liver function tests has been reported with nefazodone therapy
Bromfenac	61	Bromfenac was voluntarily withdrawn from the market June 22, 1998 due to post-marketing reports of severe hepatic failure including 4 deaths and 8 liver transplants
Trovafoxacin mesylate	60	According to information from the Food and Drug Administration (FDA), trovafloxacin has been associated with over 100 cases of liver toxicity. Fourteen cases involved acute liver failure
Pemoline	58	Hepatotoxicity, including elevated liver enzymes, hepatitis, and jaundice, has been reported in patients receiving pemoline. Reports indicate a 1% to 2% incidence of hepatotoxicity
Isoniazid	58	Clinical hepatitis with nausea, vomiting, fatigue, fever, abdominal pain, malaise, pruritus, and elevated liver function tests occurs in 0.3–1.3% of patients in most studies
Danazol	57	Danazol may produce increases in hepatic function tests, especially patients receiving doses of 400 mg daily or more, and hepatic dysfunction and jaundice have been reported
<i>Jaundice and cholestasis cluster</i>		
Chlorzoxazone	80	Administration of chlorzoxazone has been associated with hepatitis, hepatic necrosis, cholestasis, and hepatocellular injury.
Lomustine	78	None
Atazanavir sulfate	75	Unconjugated hyperbilirubinemia (asymptomatic) is seen frequently during atazanavir administration (up to 60% of patients; jaundice appeared in 17% of patients in the atazanavir groups)
Troglitazone	67	In the majority of patients, the liver injury was hepatocellular but a few patients had a mixed hepatocellular-cholestatic injury
Enflurane	67	Elevated liver enzymes, cholestatic reaction, hepatitis, fatal hepatic necrosis, hepatic coma, encephalopathy, and hepatic failure have been reported with enflurane anesthesia
Cephadrine	65	None
Halothane	63	It is often associated with massive liver cell necrosis and can lead to fulminant hepatic failure
Isoniazid	62	Jaundice may be noted and is thought to occur in about 0.6% of patients taking therapeutic doses
Disulfiram	62	Signs and symptoms include fatigue, headache, fever, pruritus, rash, myalgia, malaise, anorexia, nausea, vomiting, abdominal pain, ascites, jaundice, light stools, dark urine, and hepatomegaly
Isoflurane	59	Three weeks following exposure to isoflurane inhalational anesthesia, a 70-year-old, formerly healthy, woman developed cholestatic hepatitis. Two weeks after her surgery she experienced nausea, vomiting, and increasing weakness that was followed several days later with pruritus and progressive jaundice

and the MedWatch program because the AE data often are derived from patients receiving more than one medication (polypharmacology). There is potential uncertainty as to which drug caused an AE and many AEs could be interpreted as being drug–drug interactions. However, the SRS and the AERS databases indicate which drug the treating medical professional believes to have been primarily responsible for the adverse effect. Furthermore, MedWatch program drug warnings provide information on specific therapeutics and drug–drug interactions.

There is another approach to the polypharmacology issue that could be realized through an enhancement of the way post-market AEs are reported. Since all of the AERS AE reports are included in PharmaPendium™, and a future version of the software will contain the SRS AEs as well, it would be technically possible to have a PRR

value automatically calculated and presented for each drug and each post-market AE endpoint, each time PharmaPendium™ was updated. This PRR value would have a specified stringency, such as using the criteria we used in this investigation. The PRR value would enable the investigator to distinguish between drug-related AEs that are, or are not statistically significant for a given drug. Furthermore, the investigator would have useful information to interpret AE findings in patients that had received more than one medication. PharmaPendium™ would have two independent means of interpreting polypharmacology AEs in patients, one derived from the healthcare professional and the other derived from a pharmacovigilance perspective of the entire database of AEs. A side-by-side comparison of these values could lessen the uncertainty of interpreting polypharmacology in patients.

Table 14

Top 10 drugs for each AERS renal cluster.

Drug name	Cluster score	Literature statement
<i>Renal disorder cluster</i>		
Cerivastatin sodium	80	Cases of rhabdomyolysis with acute renal failure have been reported during treatment with cerivastatin
Cidofovir	73	Renal toxicity (manifested by greater than or equal to 2+ proteinuria, serum creatinine elevations of greater than or equal to 0.4 milligrams/deciliter (mg/dL), or decreased creatinine clearance less than or equal to 55 milliliters/minute (mL/min)) occurred in 79 of 135 (59%) of patients during a clinical trial with cidofovir
Dicloxacillin sodium	63	In one study, dicloxacillin in high doses was associated with renal impairment in 35 of 278 patients
Foscarnet sodium	59	Nephrotoxicity including increases in serum creatinine and acute renal failure are the most commonly observed adverse effects associated with foscarnet therapy, occurring to some degree in most patients
Furosemide	58	Intravenous furosemide has produced transient proteinuria. It is possible that furosemide increases the permeability of glomerular capillary walls for macromolecules
Indomethacin sodium	57	Acute renal failure has been reported after therapeutic administration of indomethacin
Cefepime hydrochloride	57	Renal failure has been reported in association with cefepime therapy during post-marketing surveillance
Tenofovir disoproxil fumarate	54	Renal insufficiency, acute renal failure, Fanconi syndrome, proteinuria, increased serum creatinine, acute tubular necrosis, and proximal tubulopathy have been reported in association with tenofovir therapy
Streptozocin	54	Renal toxicity has been reported in 28–73% of patients
Tobramycin sulfate	53	30 patients (14%) developed nephrotoxicity during the course of the study; the incidence of aminoglycoside-induced nephrotoxicity (AIN) ranges from 0% to 50% with 10% to 25% being the most commonly reported incidence of AIN in clinical trials
<i>Nephropathies cluster</i>		
Tenofovir disoproxil fumarate	80	Renal insufficiency, acute renal failure, Fanconi syndrome, proteinuria, increased serum creatinine, acute tubular necrosis, and proximal tubulopathy have been reported in association with tenofovir therapy
Propylthiouracil	79	Interstitial nephritis, nephritis and nephrotoxicity are described with the administration of propylthiouracil
Zoledronic acid	75	In clinical trials, intravenous doses of 8 milligrams (mg) significantly increased the risk of renal toxicity
Penicillamine	73	Numerous cases of penicillamine-induced nephrotic syndrome (PINS) and nephrosis have been reported
Nafcillin sodium	72	Although interstitial nephritis is not a common complication of nafcillin therapy, several isolated cases have been reported
Mycophenolic acid	70	Kidney tubular necrosis was reported in 6% to 10% of patients.
Phendimetrazine tartrate	69	None
Tacrolimus	69	Nephrotoxicity was reported in 36% to 40% and 52% of liver and kidney transplant patients receiving tacrolimus
Sulfamethoxazole	64	Toxic nephrosis with oliguria and anuria, in the absence of crystalluria, has occurred during sulfonamide therapy; however, no specific case reports have been attributable to sulfamethoxazole given alone. In these cases, lesions found at autopsy were consistent with tubular necrosis or necrotizing angitis
Etoposide	64	None
<i>Kidney function tests cluster</i>		
Sorbitol (Mannitol) TOTAL	80	None
Demeclocycline hydrochloride	70	None
Foscarnet sodium	66	In 1 series of patients treated with continuous infusions of foscarnet, increases in serum creatinine of at least 25% from baseline (acute renal failure) were reported in 37 of 56 courses of treatment (66%)
Probuco	64	None
Cidofovir	61	Nephrotoxicity, characterized by: increased serum creatinine, proteinuria, glycosuria and reductions in serum phosphate, uric acid and bicarbonate, have been reported with cidofovir therapy.
Milrinone lactate	58	Mild elevations in serum creatinine and renal failure have been reported in patients receiving milrinone
Zoledronic acid	54	In clinical trials, 9–15% of patients who received 4 milligrams of zoledronic acid over a 15-min interval experienced renal deterioration as defined by elevations in serum creatinine level
Nafcillin sodium	52	None
Lomefloxacin hydrochloride	50	None
Amiloride hydrochloride	49	Long-term therapy with amiloride has been reported to increase serum creatinine concentrations
<i>Bladder disorder cluster</i>		
Tolterodine tartrate	80	None
Arginine hydrochloride	77	None
Solifenacin succinate	62	Urinary retention was reported in up to 5% of patients receiving solifenacin in one study; it was only observed at the higher doses (10–20 mg/day)
Doxazosin mesylate	57	Hematuria, micturition disorder, micturition frequency, and nocturia have been reported in post-marketing experience
Terazosin hydrochloride	54	None
(dex)Brompheniramine maleate	54	None
Oxybutynin chloride	53	Urinary hesitancy and/or retention have occurred
Dutasteride	52	None
tamsulosin hydrochloride	50	None
Alfuzosin hydrochloride	49	None

4. Conclusions

The two primary goals of this investigation were: (1) to ascertain whether or not AE reporting frequencies are related to the toxic effects of drugs in humans, and (2) to use these data to create training sets for QSAR models to predict the AEs of pharmaceuticals. The identification of compounds most likely to cause AEs in

either the hepatobiliary or urinary tract, as predicted by a high AU score, and the subsequent validation of these predictions by findings from the literature, clearly satisfied our first goal. The remainder of this study was focused on transforming the raw data from the AERS and SRS databases into data suitable for QSAR modeling. The use of a PRR system, in which the expected value was based on reporting frequencies throughout the database, allowed

Table 15
Summary of the AE endpoints included in FDA hepatobiliary and urinary tract AE QSAR models.

FDA QSAR model		Post market pharmaceutical adverse effect					AE statistics		
Organ system	Model endpoint	System organ class (SOC, LEVEL 1)	High level group term (HGLT, LEVEL 2)	High level term (HLT, LEVEL 3)	Preferred term (PT, LEVEL 4)	Database	# Reports	Database (%)	Model endpoint ^a (%)
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Alanine aminotransferase	AERS	170	0.130	0.36
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Alanine aminotransferase abnormal	AERS	114	0.087	0.24
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Alanine aminotransferase increase	AERS	11354	8.690	23.90
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Aspartate aminotransferase	AERS	164	0.126	0.35
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Aspartate aminotransferase Abnormal	AERS	102	0.078	0.21
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Aspartate aminotransferase increase	AERS	11095	8.492	23.35
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Gamma-glutamyltransferase	AERS	74	0.057	0.16
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Gamma-glutamyltransferase abnormal	AERS	78	0.060	0.16
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Gamma-glutamyltransferase increased	AERS	4539	3.474	9.55
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Hepatic enzyme increased	AERS	1765	1.351	3.72
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Liver function test abnormal	AERS	15640	11.970	32.92
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Transaminases increased	AERS	2412	1.846	5.08
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Gamma glutamyl transpeptidase increase	SRS	N/A	N/A	N/A
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Lactic dehydrogenase increased	SRS	N/A	N/A	N/A
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Hepatic enzyme and function abnormalities	Liver function test abnormal	SRS	N/A	N/A	N/A
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	SGOT increased	SRS	N/A	N/A	N/A
Hepatobiliary	Liver enzyme disorders	Investigations	Hepatobiliary investigations	Liver function analyses	SGPT increased	SRS	N/A	N/A	N/A
					SUBTOTAL		47507	36.36	100.00
Hepatobiliary	Cytotoxic injury	Hepatobiliary disorders	Hepatic failure and associated disorders	Hepatocellular damage and hepatitis	Alcoholic liver disease	AERS	33	0.025	0.10
Hepatobiliary	Cytotoxic injury	Hepatobiliary disorders	Hepatic failure and associated disorders	Hepatocellular damage and hepatitis	Autoimmune hepatitis	AERS	523	0.400	1.59
Hepatobiliary	Cytotoxic injury	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic fibrosis and cirrhosis	Biliary cirrhosis	AERS	84	0.064	0.26
Hepatobiliary	Cytotoxic injury	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic fibrosis and cirrhosis	Biliary cirrhosis primary	AERS	100	0.077	0.30

Table 15 (continued)

FDA QSAR model		Post market pharmaceutical adverse effect					AE statistics		
Organ system	Model endpoint	System organ class (SOC, LEVEL 1)	High level group term (HGLT, LEVEL 2)	High level term (HLT, LEVEL 3)	Preferred term (PT, LEVEL 4)	Database	# Reports	Database (%)	Model endpoint ^a (%)
Hepatobiliary	Cholestasis and jaundice	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis and jaundice	Jaundice	AERS	8546	6.541	60.45
Hepatobiliary	Cholestasis and jaundice	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis and jaundice	Jaundice cholestatic	AERS	908	0.695	6.42
Hepatobiliary	Cholestasis and jaundice	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis and jaundice	Jaundice	SRS	N/A	N/A	N/A
Hepatobiliary	Cholestasis and jaundice	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis and jaundice	Jaundice cholestatic	SRS	N/A	N/A	N/A
					SUBTOTAL		14138	10.82	100.00
Hepatobiliary	Bile duct disorders	Hepatobiliary disorders	Bile duct disorders	Obstructive bile duct disorders (excl. neoplasms)	Bile duct obstruction	AERS	356	0.272	24.30
Hepatobiliary	Bile duct disorders	Hepatobiliary disorders	Bile duct disorders	Obstructive bile duct disorders (excl. neoplasms)	Bile duct stone	AERS	241	0.184	16.45
Hepatobiliary	Bile duct disorders	Hepatobiliary disorders	Bile duct disorders	Structural and other bile duct disorders	Biliary tract disorder	AERS	431	0.330	29.42
Hepatobiliary	Bile duct disorders	Hepatobiliary disorders	Bile duct disorders	Bile duct infections and inflammations	Cholangitis	AERS	437	0.334	29.83
					SUBTOTAL		1465	1.12	100.00
Hepatobiliary	Gall bladder disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Bilirubin conjugated increase	AERS	380	0.291	2.65
Hepatobiliary	Gall bladder disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Blood bilirubin increased	AERS	7297	5.585	50.81
Hepatobiliary	Gall bladder disorders	Investigations	Hepatobiliary investigations	Liver function analyses	Blood bilirubin unconjugated	AERS	2	0.002	0.01
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholecystitis	AERS	1185	0.907	8.25
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholecystitis acute	AERS	270	0.207	1.88
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholecystitis chronic	AERS	119	0.091	0.83
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholelithiasis	AERS	3488	2.670	24.29
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholelithiasis obstructive	AERS	13	0.010	0.09
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Gallbladder disorders NEC	Gall bladder disorder	AERS	1430	1.094	9.96
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Gallbladder disorders NEC	Gall bladder obstruction	AERS	18	0.014	0.13
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Gallbladder disorders NEC	Gall bladder oedema	AERS	42	0.032	0.29
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Gallbladder disorders NEC	Gall bladder pain	AERS	75	0.057	0.52
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Gallbladder disorders NEC	Gall bladder perforation	AERS	28	0.021	0.19
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Gallbladder disorders NEC	Hydrocholecystis	AERS	14	0.011	0.10

Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholecystitis	SRS	N/A	N/A	N/A
Hepatobiliary	Gall bladder disorders	Hepatobiliary disorders	Gallbladder disorders	Cholecystitis and cholelithiasis	Cholelithiasis	SRS	N/A	N/A	N/A
					SUBTOTAL		14361	10.99	100.00
Hepatobiliary	PT not modeled	Congenital, familial and genetic disorders	All congenital PTs	All congenital PTs	All congenital PTs	AERS	40	0.031	N/A
Hepatobiliary	PT not modeled	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	All neoplasm PTs	All neoplasm PTs	All neoplasm PTs	AERS	1668	1.277	N/A
Hepatobiliary	PT not modeled	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic enzyme and function abnormalities	Hepatic function abnormal	AERS	5843	4.472	N/A
Hepatobiliary	PT not modeled	Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic and hepatobiliary disorders NEC	Liver disorder	AERS	4186	3.204	N/A
Hepatobiliary	PT not modeled	Other	Other	Other	Other	AERS	8565	6.555	N/A
					SUBTOTAL (Not modeled)		20302	15.54	N/A
					Total AE for modeled hepatobiliary terms		110355	84.46	
					Total AE for unmodeled hepatobiliary terms		20302	15.54	
					Total Hepatobiliary AEs		130657	100.00	
Urinary tract	Urolithiasis	Renal and urinary disorders	Urolithiasis	Urinary tract lithiasis (excl. renal)	Calculus bladder	AERS	89	0.08	3.16
Urinary tract	Urolithiasis	Renal and urinary disorders	Urolithiasis	Urinary tract lithiasis (excl. renal)	Calculus ureteric	AERS	147	0.13	5.21
Urinary tract	Urolithiasis	Renal and urinary disorders	Urolithiasis	Urinary tract lithiasis (excl. renal)	Calculus urinary	AERS	374	0.33	13.27
Urinary tract	Urolithiasis	Investigations	Renal and urinary tract investigations and urinalysis	Urinalysis NEC	Crystal urine	AERS	11	0.01	0.39
Urinary tract	Urolithiasis	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Crystalluria	AERS	123	0.11	4.36
Urinary tract	Urolithiasis	Renal and urinary disorders	Urolithiasis	Renal lithiasis	Nephrolithiasis	AERS	2075	1.81	73.61
Urinary tract	Urolithiasis	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Crystalluria	SRS	N/A	N/A	N/A
Urinary tract	Urolithiasis	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Crystalluria calcium	SRS	N/A	N/A	N/A
Urinary tract	Urolithiasis	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Crystalluria sulfamide	SRS	N/A	N/A	N/A
Urinary tract	Urolithiasis	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Crystalluria urate	SRS	N/A	N/A	N/A
					SUBTOTAL		2819	2.46	100.00
Urinary tract	Blood in urine	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Haematuria	AERS	5236	4.57	86.85
Urinary tract	Blood in urine	Investigations	Renal and urinary tract investigations and urinalysis	Urinalysis NEC	Haemoglobin urine present	AERS	97	0.08	1.61
Urinary tract	Blood in urine	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Pyuria	AERS	196	0.17	3.25
Urinary tract	Blood in urine	Investigations	Renal and urinary tract investigations and urinalysis	Urinalysis NEC	White blood cells urine positive	AERS	500	0.44	8.29
Urinary tract	Blood in urine	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Hematuria	SRS	N/A	N/A	N/A

(continued on next page)

Table 15 (continued)

FDA QSAR model		Post market pharmaceutical adverse effect					AE statistics		
Organ system	Model endpoint	System organ class (SOC, LEVEL 1)	High level group term (HGLT, LEVEL 2)	High level term (HLT, LEVEL 3)	Preferred term (PT, LEVEL 4)	Database	# Reports	Database (%)	Model endpoint ^a (%)
Urinary tract	Blood in urine	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalites	Pyuria	SRS	N/A	N/A	N/A
					SUBTOTAL		6029	5.26	100.00
Urinary tract	Bladder disorders	Renal and urinary disorders	Bladder and bladder neck disorders (excl. calculi)	Bladder disorders NEC	Bladder disorder	AERS	846	0.74	4.29
Urinary tract	Bladder disorders	Renal and urinary disorders	Bladder and bladder neck disorders (excl. calculi)	Bladder disorders NEC	Bladder neck obstruction	AERS	26	0.02	0.13
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Bladder pain	AERS	284	0.25	1.44
Urinary tract	Bladder disorders	Renal and urinary disorders	Bladder and bladder neck disorders (excl. calculi)	Bladder infections and inflammations	Cystitis hemorrhagic	AERS	385	0.34	1.95
Urinary tract	Bladder disorders	Renal and urinary disorders	Bladder and bladder neck disorders (excl. calculi)	Bladder infections and inflammations	Cystitis interstitial	AERS	75	0.07	0.38
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Dysuria	AERS	3380	2.95	17.16
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Enuresis	AERS	294	0.26	1.49
Urinary tract	Bladder disorders	Renal and urinary disorders	Bladder and bladder neck disorders (excl. calculi)	Myoneurogenic bladder disorders	Hypertonic bladder	AERS	133	0.12	0.68
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Incontinence	AERS	455	0.40	2.31
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Micturition disorder	AERS	252	0.22	1.28
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Micturition urgency	AERS	842	0.73	4.27
Urinary tract	Bladder disorders	Renal and urinary disorders	Bladder and bladder neck disorders (excl. calculi)	Myoneurogenic bladder disorders	Neurogenic bladder	AERS	110	0.10	0.56
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	Nocturia	AERS	672	0.59	3.41
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Pollakiuria	AERS	3608	3.15	18.32
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	Polyuria	AERS	1350	1.18	6.85
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Stress incontinence	AERS	90	0.08	0.46
Urinary tract	Bladder disorders	Renal and urinary disorders	Bladder and bladder neck disorders (excl. calculi)	Bladder disorders NEC	Urinary bladder hemorrhage	AERS	102	0.09	0.52
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Urinary hesitation	AERS	255	0.22	1.29
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Urinary incontinence	AERS	3530	3.08	17.92
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Urinary retention	AERS	2568	2.24	13.04
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Urine flow decreased	AERS	164	0.14	0.83
Urinary tract	Bladder disorders	Investigations	Renal and urinary tract investigations and urinalysis	Urinary tract function analyses	Urine Output Decreased	AERS	277	0.24	1.41
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Dysuria	SRS	N/A	N/A	N/A

Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Incontinence urinary	SRS	N/A	N/A	N/A
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	Polyuria	SRS	N/A	N/A	N/A
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Urinary frequency	SRS	N/A	N/A	N/A
Urinary tract	Bladder disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Bladder and urethral symptoms	Urinary retention	SRS	N/A	N/A	N/A
					SUBTOTAL		19698	17.18	100.00
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Diabetic nephropathy	AERS	112	0.10	2.22
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Fanconi syndrome acquired	AERS	159	0.14	3.15
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Glomerulonephritis and nephrotic syndrome	Glomerulonephritis	AERS	379	0.33	7.52
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Glomerulonephritis and nephrotic syndrome	Glomerulonephritis focal	AERS	85	0.07	1.69
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Glomerulonephritis and nephrotic syndrome	Glomerulonephritis membranous	AERS	115	0.10	2.28
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Glomerulonephritis and nephrotic syndrome	Glomerulonephritis proliferative	AERS	198	0.17	3.93
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephritis NEC	Lupus nephritis	AERS	57	0.05	1.13
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephritis NEC	Nephritis	AERS	438	0.38	8.69
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephritis NEC	Nephritis interstitial	AERS	1472	1.28	29.19
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Nephropathy	AERS	326	0.28	6.47
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Nephrosclerosis	AERS	153	0.13	3.03
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Glomerulonephritis and nephrotic syndrome	Nephrotic syndrome	AERS	1158	1.01	22.97
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Renal tubular acidosis	AERS	249	0.22	4.94
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Renal tubular atrophy	AERS	76	0.07	1.51
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephritis NEC	Tubulointerstitial nephritis	AERS	65	0.06	1.29
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Fanconi syndrome (anemia)	SRS	N/A	N/A	N/A
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephritis NEC	Nephritis	SRS	N/A	N/A	N/A
Urinary tract	Nephropathies	Renal and urinary disorders	Nephropathies	Nephropathies and tubular disorders	Nephrosclerosis	SRS	N/A	N/A	N/A
					SUBTOTAL		5042	4.40	100.00
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Acute prerenal failure	AERS	206	0.18	0.48
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Anuria	AERS	1248	1.09	2.91
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal disorders NEC	Azotaemia	AERS	137	0.12	0.32
Urinary tract	Acute renal disorders	Investigations	Renal and urinary tract investigations and urinalysis	Urinary tract histopathology procedures	Biopsy kidney abnormal	AERS	129	0.11	0.30
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal obstructive disorders	Hydronephrosis	AERS	605	0.53	1.41
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal structural abnormalities and trauma	Kidney enlargement	AERS	68	0.06	0.16

(continued on next page)

Table 15 (continued)

FDA QSAR model		Post market pharmaceutical adverse effect					AE statistics		
Organ system	Model endpoint	System organ class (SOC, LEVEL 1)	High level group term (HGLT, LEVEL 2)	High level term (HLT, LEVEL 3)	Preferred term (PT, LEVEL 4)	Database	# Reports	Database (%)	Model endpoint ^a (%)
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal structural abnormalities and trauma	Kidney small	AERS	58	0.05	0.14
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal disorders NEC	Nephrogenic diabetes insipidus	AERS	96	0.08	0.22
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Oliguria	AERS	1906	1.66	4.44
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal vascular and ischaemic conditions	Renal artery stenosis	AERS	205	0.18	0.48
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal structural abnormalities and trauma	Renal atrophy	AERS	91	0.08	0.21
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal disorders NEC	Renal disorder	AERS	5522	4.82	12.87
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Renal failure acute	AERS	9015	7.86	21.01
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Renal failure chronic	AERS	867	0.76	2.02
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal disorders NEC	Renal hemorrhage	AERS	119	0.10	0.28
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Renal impairment	AERS	7289	6.36	16.98
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal vascular and ischaemic conditions	Renal infarct	AERS	130	0.11	0.30
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Renal insufficiency	AERS	12975	11.32	30.23
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal disorders NEC	Renal interstitial fibrosis	AERS	154	0.13	0.36
Urinary tract	Acute renal disorders	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	Renal pain	AERS	430	0.38	1.00
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal vascular and ischaemic conditions	Renal tubular necrosis	AERS	1598	1.39	3.72
Urinary tract	Acute renal disorders	Investigations	Renal and urinary tract investigations and urinalysis	Urinary tract imaging procedures	Ultrasound kidney abnormal	AERS	68	0.06	0.16
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Anuria	SRS	N/A	N/A	N/A
Urinary tract	Acute renal disorders	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal failure and impairment	Oliguria	SRS	N/A	N/A	N/A
							42916	37.44	100.00
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Blood creatine increased	AERS	826	0.72	5.06
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Blood creatinine	AERS	206	0.18	1.26
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Blood creatinine decreased	AERS	259	0.23	1.59

Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Blood creatinine increased	AERS	9290	8.10	56.94
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Blood urea	AERS	164	0.14	1.01
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Blood urea abnormal	AERS	144	0.13	0.88
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Blood urea increased	AERS	4825	4.21	29.58
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Creatinine renal clearance decreased	AERS	507	0.44	3.11
Urinary tract	Kidney function test	Investigations	Renal and urinary tract investigations and urinalysis	Renal function analyses	Renal function test abnormal	AERS	93	0.08	0.57
					SUBTOTAL		16314	14.23	100.00
Urinary tract	PT not modeled	Congenital, familial and genetic disorders	All congenital PTs	All congenital PTs	All congenital PTs	AERS	676	0.59	N/A
Urinary tract	PT not modeled	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	All neoplasm PTs	All neoplasm PTs	All neoplasm PTs	AERS	1803	1.57	N/A
Urinary tract	PT not modeled	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	Chromaturia	AERS	3127	2.73	N/A
Urinary tract	PT not modeled	Renal and urinary disorders	Renal disorders (excl. nephropathies)	Renal obstructive disorders	Obstructive uropathy	AERS	1179	1.03	N/A
Urinary tract	PT not modeled	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	Proteinuria	AERS	2058	1.80	N/A
Urinary tract	PT not modeled	Investigations	Renal and urinary tract investigations and urinalysis	Urinalysis NEC	Urine analysis abnormal	AERS	1431	1.25	N/A
Urinary tract	PT not modeled	Other	Other	Other	Other	AERS	11549	10.07	N/A
					SUBTOTAL (Not modeled)		21823	19.04	N/A
					Total AE for modeled urinary tract terms		92818	80.96	
					Total AE for unmodeled urinary tract terms		21823	19.04	
					Total urinary tract AEs		114641	100.00	

^a Totals include compounds that are unsuitable for QSAR modeling.

for the comparison of AE endpoints and the drugs active at these different endpoints. The WOE paradigm created by clustering toxicologically related endpoints facilitated the identification of the compounds most likely to cause human harm based upon activities at multiple related AEs. These results were in concordance with Zimmerman's (1999) generally accepted principles on drug-induced liver injury. The successful modeling of this transformed data is described in Matthews et al. (2009a).

The majority of the obstacles encountered during this investigation were related to inconsistencies within the AERS and SRS source data. Because confounding factors, such as increased reporting during the first five years of marketing, duplicate reports and reporting for patients taking multiple drugs, could not be eliminated, it was assumed that all such factors affected each drug and AE equally. The assumption used in the calculation of expected values, that drugs and AEs are reported independently in the absence of toxicological activity, could also be biased by unequal effects of inconsistent reporting. Future improvements to our databases could include incorporation of a scheme to eliminate duplicate reports, as well as the use of some of the more sophisticated disproportionality analyses such as the Bayesian methods. Moreover, the AERS database is thought to grow by approximately 1000 new reports each day (Szarfman et al., 2004), and the addition of these data could be used to enhance the current study.

There may be concerns about all of the assumptions that were made in this investigation and the methods used to identify drugs with significant findings. These concerns should be ameliorated by the demonstrated proof of principle that the QSAR database and models were able to accurately predict the activities of drugs not considered in the investigation. The second report in this study contains the results of an external validation study (Matthews et al., 2009a) which shows that the QSAR models were able to predict hepatobiliary effects of drugs not included in the database or models. In addition, it is the intent of this laboratory to conduct prospective studies of the performance of the QSAR models using drug warning and labeling information that was recently reported in FDA/CDER's MedWatch Program (June 2006 to present), which were not considered in the current investigation. The results of this prospective study will be reported in a subsequent publication from this laboratory.

In the future, our group will apply the methodology developed in this study to the development of models for drug-induced toxicity at other targets, such as the cardiovascular and endocrine systems. Our hope is to use available QSAR technology to predict potential AEs and ultimately reduce or eliminate their impact on patients. Another relevant expansion of this research is to correlate significant AEs with specific drug pharmacological and toxicological mechanisms. Because most drugs have multiple pharmacological effects and diverse mechanisms of action in addition to the intended pharmacological effect, it is possible that these additional mechanisms are related to AEs. These may be detected by using QSARs to predict novel (off-target) drug targets that link the AEs studied here to specific drug mechanisms (Matthews et al., 2009b).

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