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# Identification of structure–activity relationships for adverse effects of pharmaceuticals in humans: Part C: Use of QSAR and an expert system for the estimation of the mechanism of action of drug-induced hepatobiliary and urinary tract toxicities

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ABSTRACT

This report describes an *in silico* methodology to predict off-target pharmacologic activities and plausible mechanisms of action (MOAs) associated with serious and unexpected hepatobiliary and urinary tract adverse effects in human patients. The investigation used a database of 8,316,673 adverse event (AE) reports observed after drugs had been marketed and AEs noted in the published literature that were linked to 2124 chemical structures and 1851 approved clinical indications. The Integrity™ database of drug patent and literature studies was used to find pharmacologic targets and proposed clinical indications. BioEpisteme™ QSAR software was used to predict possible molecular targets of drug molecules and Derek™ for Windows expert system software to predict chemical structural alerts and plausible MOAs for the AEs. AEs were clustered into five types of liver injury: liver enzyme disorders, cytotoxic injury, cholestasis and jaundice, bile duct disorders, and gall bladder disorders, and six types of urinary tract injury: acute renal disorders, nephropathies, bladder disorders, kidney function tests, blood in urine, and urolithiasis. Results showed that drug-related AEs were highly correlated with: (1) known drug class warnings, (2) predicted off-target activities of the drugs, and (3) a specific subset of clinical indications for which the drug may or may not have been prescribed.

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## 1. Introduction

This is the third part of an investigation conducted by the US FDA's Center for Drug Evaluation and Research (CDER), Informatics and Computational Safety Analysis Staff (ICSAS) to identify structure–activity relationships for adverse effects of pharmaceuticals observed in humans. In the first report we described the creation of a health effects database containing human adverse event reporting data derived from two pharmaceutical post-market surveillance databases maintained by the FDA, the Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS), as well as from the published literature (Ursem et al., 2009). In that first report, we described a disproportion statistical analysis method that was used to identify a subset of pharmaceuticals that had significant hepatobiliary and urinary tract adverse effects (AEs) in patients. In the second report we described the creation of quantitative structure–activity relationship (QSAR) models to predict hepatobiliary and urinary tract AEs of drugs using four different state of the art global QSAR software programs and the methods that were employed to optimize the predictive performance of these models (Matthews et al., 2009). The QSAR models permit the prediction of potential AEs of pharmaceutical molecules solely based upon the pharmaceutical molecular structure. For this part of the investigation we identified specific properties of drugs that correlate with the hepatobiliary and urinary tract AEs that

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**Nomenclature**

| | |
|---|---|
| Actives | a subset of drugs that caused AEs in patients |
| AE | (pharmaceutical) adverse effect |
| AERS | FDA's Adverse Event Reporting System |
| BP | optimal break point to distinguish active drugs (with significant AEs) from inactive drugs |
| DfW | Derek for Windows™ (structure–activity software) |
| Inactives | a subset of drugs that had no significant AEs |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOA | mechanism of action |
| PCIR | proportional clinical indication ratio (disproportion analyses) |
| PE | physiological effect |
| PPTR | proportional pharmacological target ratio (disproportion analyses) |
| PRR | proportional reporting ratio (disproportion analyses) |
| (Q)SAR | (quantitative) structure–activity relationship |
| SRS | FDA's Spontaneous Reporting System |
| WOE | weight of evidence |

can be used to identify plausible mechanisms of action (MOA) by which drugs might have caused the AEs.

### 1.1. Adverse reactions in US drug labeling

In the United States, the reporting of adverse reactions to prescription drugs and biologic products is required by Title 21 of the Code of Federal Regulations (21 CFR 201.57(c)(7)). There, an AE is described as an undesirable effect that is reasonably associated with use of the pharmaceutical that may be the result of the pharmacological action of the drug or be unpredictable in its occurrence. The detailed content and format of the adverse reaction section of drug labeling is defined in two FDA guidances: (1) Adverse reactions section of labeling for human prescription drug and biological products—content and format (http://www.fda.gov/cder/guidance/5537fnl.htm) and (2) Labeling for human prescription drug and biological products—implementing the new content and format requirements (http://www.fda.gov/cder/guidance/6005dft.htm). The major emphasis of the adverse reaction section of these two guidances is on the reporting of AEs observed in clinical trials carried out prior to drug approval. Five elements described in this section are: (1) description of AE data source, (2) statement of the significance of the AEs, (3) listing of the most common AEs, (4) listing of uncommon AEs, and (5) commentary on types of AEs. In contrast, the guidance places little emphasis on the reporting of "spontaneous" AEs, those that occur after a drug is marketed. The listing of AE reports from post-market surveillance in the US and foreign spontaneous reports is presented separately in US drug labeling and is qualified by the statement: "Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Adverse reactions vary in their clinical significance, ranging from minor to serious. The serious drug adverse reactions are reported separately in greater detail in special labeling sections entitled "warnings and precautions," "contraindications," and "boxed warning." The information is highlighted in order for healthcare practitioners to recognize and consider when making prescriptions for patients. The content and format of serious drug adverse reaction labeling is described in the FDA guidance: warnings and precautions, contraindications, and boxed warning sections of labeling for human prescription drug and biological products—content and format (http://www.fda.gov/cder/guidance/5538dft.htm).

Contraindications are restricted to clinical situations for which the AE risk from use of the drug clearly outweighs the therapeutic benefit, and they are restricted to known hazards that are listed. Contraindications cannot be based upon theoretical possibilities.

FDA/CDER originally employed the post-market SRS and currently uses the AERS to collect reports of "spontaneous" pharmaceutical AEs from manufacturers, physicians and patients (http://www.fda.gov/medwatch) and uses this information to monitor AEs that may not have been identified during pre-clinical animal testing and detected during pre-market clinical trials. Post-market AE data are also analyzed by pharmacovigilance groups to identify any significant drug-related AE signal that would then be the subject of further study and analysis. Traditionally, a proportional reporting ratio (PRR) is used by pharmacovigilance groups to account for variations in AE reports due to different patient populations and exposures for each drug (Evans et al., 2001; Moore et al., 2005). In addition, the AE data are sometimes used by the FDA to provide more general, chemical class-specific warnings for drugs having a common profile of AEs.

The pharmacological class of a pharmaceutical is reported in the "indications and usage" section of drug labeling as specified by 21CFR 201.57(a)(6). Background information on pharmacological class information reporting in drug labeling is described in the FDA guidance: Labeling for human prescription drugs—determining established pharmacologic class for use in the highlights of prescription information (http://www.fda.gov/cder/guidance/7472dft.htm). This guidance specifies that a drug (or specific chemical class) is indicated for a specific clinical indication(s). The pharmacologic class is defined in terms of one or more of three drug properties: (1) mechanism of action (MOA), a pharmacological action at the receptor, membrane, or tissue level; (2) physiological effect (PE), a pharmacological effect at the organ, system, or whole body level; and (3) chemical molecular structure.

The purpose of the pharmacological class information is to inform healthcare professionals that the pharmacological class has been determined to be scientifically valid and clinically meaningful by the FDA. This statement verifies that: (1) the pharmacological class of the drug is known and not theoretical, (2) the drug therapeutic effects are related to the clinical indication, and (3) certain undesirable AEs may occur that are related to the drug pharmacology. The drug class reporting rule specifically excludes the listing of any off-target (i.e., non-therapeutic) pharmacological MOAs and PEs of a drug, and any other information which is regarded as hypothetical. Thus, even though the majority of drugs are each known to possess several different off-target MOAs and/or PEs, these data are excluded from drug labeling. One of the consequences of this omission is that there is no simple way to connect off-target pharmaceutical MOAs and PEs with the unintended or unpredicted AEs of pharmaceuticals that are observed in clinical trials and in post-market surveillance.

### 1.2. Predicting adverse human drug effect MOA

There has been substantial progress in the application of *in silico* computational toxicology methods to provide predictions of test chemical toxicological activities and use these data to perform risk assessment of environmental chemicals, food additives and pharmaceuticals (Matthews and Contrera, 2007; Benz, 2007), However,