



# Feature

## Generation of a drug-induced renal injury list to facilitate the development of new approach methodologies for nephrotoxicity

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Drug-induced renal injury (DIRI) causes >1.5 million adverse events annually in the USA alone. Although standard biomarkers exist for DIRI, they lack the sensitivity or specificity to detect nephrotoxicity before the significant loss of renal function. In this study, we describe the creation of DIRIL – a list of drugs associated with DIRI and nephrotoxicity – from two literature datasets with DIRI annotation, confirmed using FDA drug labeling. DIRIL comprises 317 orally administered drugs covering all 14 anatomical, therapeutic and chemical (ATC) classification categories. Of the 317 drugs, 171 were DIRI-positive and 146 were DIRI-negative. DIRIL will be a relevant and invaluable resource for discovery of new approach methods (NAMs) to predict the occurrence and possible severity of DIRI earlier in drug development.

**Keywords:** Drug-induced renal injury; drug-induced kidney injury; nephrotoxicity; new approach methods; drug safety; organ toxicity

### Introduction

The kidney is one of the essential organs in the human body and functions to remove waste products, regulate the body's electrolytes and acid levels, and produce hormones that affect the function of other major organs. Consequently,

the kidney is more susceptible to drug-induced injury because it is exposed to higher concentrations of circulating drugs and/or metabolites than any other organ system.<sup>(p1),(p2)</sup> For example, the kidney is a highly vascular organ that receives ~25% of resting cardiac output and the

reabsorption of the glomerular filtrate gradually increases the concentration of intraluminal nephrotoxins.<sup>(p2)</sup>

Currently, kidney disease is ranked as the tenth leading cause of death in the USA, contributing to 52 547 deaths in 2020 alone.<sup>(p3)</sup> Although nephrotoxicity

has a broad definition as the rapid deterioration of kidney function or kidney injury due to the damaging and toxic effects of drugs, chemicals and toxins,<sup>(p4)</sup> in this article we will focus on drug-induced nephrotoxicity also known as drug-induced renal injury (DIRI). About 20% of reports of nephrotoxicity are drug-induced<sup>(p4)</sup> and comprise four major renal syndromes: acute renal failure, nephrotic syndrome, renal tubular dysfunction and chronic renal failure.<sup>(p2)</sup> DIRI can lead to the development of acute kidney injury, chronic kidney disease or end-stage renal disease, causing >1.5 million adverse events within the USA annually, with a documented frequency of ~26% in adult populations.<sup>(p5),(p6),(p7),(p8)</sup>

Although the kidney is highly susceptible to drug-induced injury, the standards for detecting and reporting DIRI before the significant loss of renal function are insufficient. The literature shows that 90% of clinical drug candidates fail during Phases I, II and III of clinical trials and drug approval.<sup>(p9)</sup> Further analyses have shown a lack of clinical efficacy and unmanageable toxicity are responsible for many clinical trial failures.<sup>(p9)</sup> The accumulation of drug candidates in vital organs is one of the major drivers of organ toxicity.<sup>(p9)</sup> Because kidney function is needed for removing waste products, it is vital to health and susceptible to drug-induced injury. In addition, establishing human relevancy of toxicity findings in animal studies remains a challenge<sup>(p10)</sup> because there is poor translation from animal models to humans. Despite this, the majority of mechanistic studies on kidney injury are conducted in rodent models.<sup>(p11)</sup> Similarly, there is a low success rate of only 3.6% of drugs that progress from Phase I to approval in clinical trials.<sup>(p12)</sup> Overall, these data illustrate a pressing need for the development of alternative methods to reliably predict drug-induced nephrotoxicity in early drug development.

There are several biomarkers used in the investigation of nephrotoxicity, although they have many limitations. For example, historically, serum creatinine (sCr) and blood urea nitrogen (BUN) are used to diagnose kidney injury in humans; but these methods only detect later-stage damage and are inaccurate because they can be influenced by other factors such as body mass or protein intake.<sup>(p1)</sup> Additionally,

there are several nephrotoxicity biomarkers such as kidney injury molecule-1 (KIM-1),  $\beta$ 2-microglobulin (B2M), cystatin C, clusterin and trefoil factor-3 (TFF-3) that have been accepted as highly sensitive and specific urinary biomarkers by the FDA and the EMA to monitor DIRI in preclinical studies and in some clinical trials.<sup>(p1),(p4),(p13)</sup> These biomarkers show great potential but the correlations of levels with the subsequent development of clinically significant nephrotoxicity and the long-term impact on kidney function remain unclear.<sup>1</sup> Therefore, new approaches methods (NAMs) have been actively investigated for DIRI studies.<sup>(p14),(p15),(p16)</sup>

Many investigators and regulatory agencies are exploring NAMs for improved drug safety, particularly in the early stage of drug development.<sup>(p10)</sup> NAMs offer benefits in terms of increased speed, reduced resource requirements and can provide more-informative results than current approaches.<sup>(p17)</sup> The FDA considers NAMs to include a broad range of methods such as *in vitro*, *in chemico* and *in silico* methods.<sup>(p10)</sup> NAMs present an opportunity to reduce the number of animals used in testing, refine current methods that still require animals and replace animal testing whenever possible.<sup>(p17)</sup> Currently, there are several new techniques and models, such as microphysiological systems (MPS),<sup>(p18),(p19),(p20)</sup> QSAR computer-based models and *in vitro* and *in silico* toxicity prediction tools.<sup>(p10)</sup> To demonstrate the utility of NAMs for DIRI, they need to be tested on a large number of drugs with known DIRI annotation. For that purpose, we developed the Drug-Induced Renal Injury List (DIRIL).

### The development of DIRIL

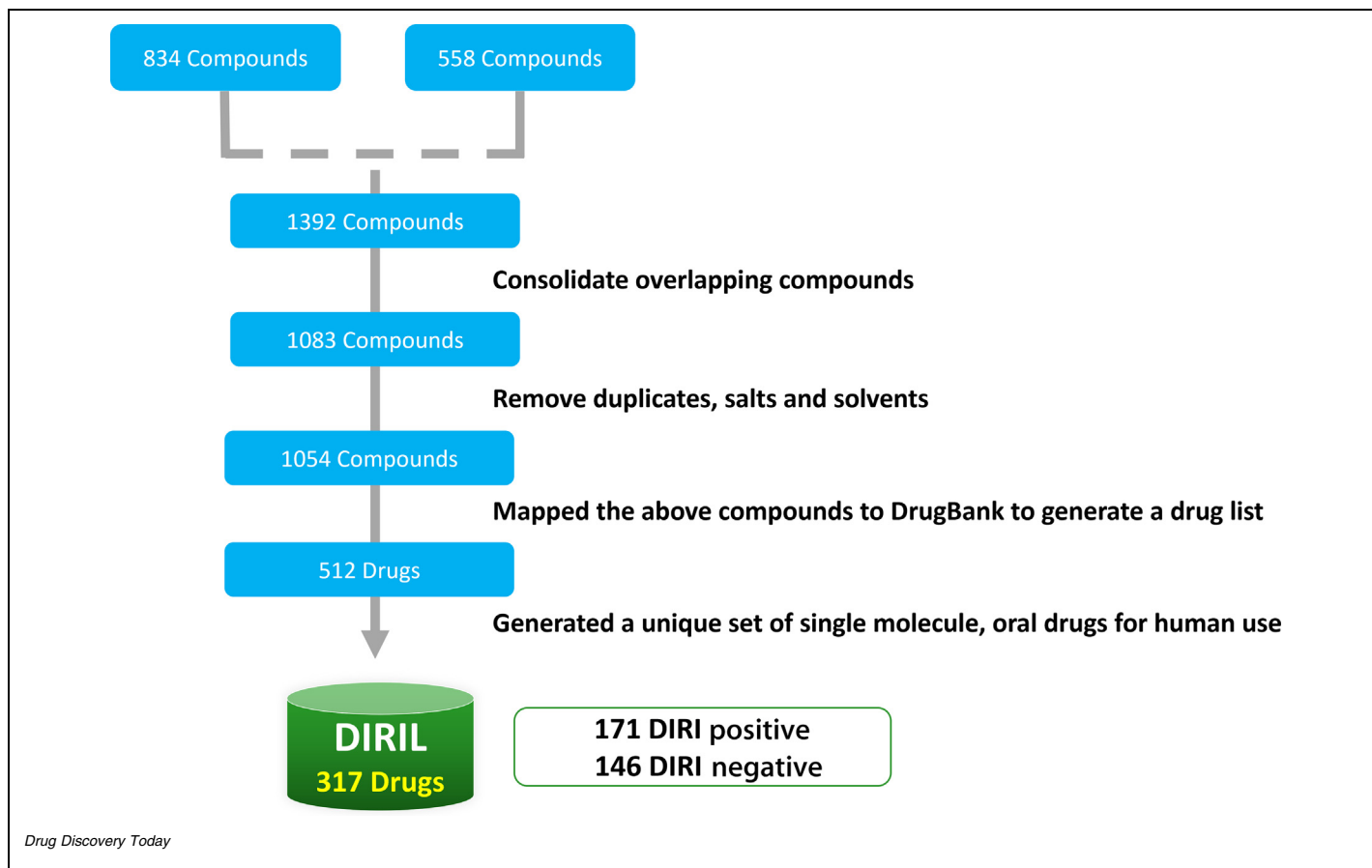
DIRIL was assembled from literature data with specific criteria: it had to be highly curated with a large number of drugs, using comparable methods to annotate DIRI with a binary classification system. A literature search yielded two viable datasets (Gong et al.<sup>(p21)</sup> and Shi et al.<sup>(p6)</sup>).

The Gong et al.<sup>(p21)</sup> dataset comprises 848 chemical and herbal compounds collated from four databases [Side Effect Resource (SIDER), DrugBank, ChEMBL and TCM] and two peer-reviewed articles. The authors checked the accuracy and validity of each data point using clinical or experimental reports. Nephrotoxic com-

pounds found to cause kidney injury or disease were classified as positive compounds, whereas compounds without related side effects or therapeutic and protective effects for the kidney were classified as negative. By removing duplicates and keeping only the compounds with an International Chemical Identifier (InCHI) key, a total of 834 compounds (363 nephrotoxic, 471 non-nephrotoxic) from the dataset were brought forward into DIRIL.

Shi et al.<sup>(p6)</sup> collected a total of 565 compounds from the SIDER database and the Zhang et al. article.<sup>(p22)</sup> Any drug within the SIDER database that had a nephrotoxicity-related adverse drug reaction (ADR) with a frequency of  $\geq 0.1\%$  was classified as positive. The non-nephrotoxic structures were extracted from Zhang et al.,<sup>(p22)</sup> who defined negative compounds as the drugs without nephrotoxic ADRs from the SIDER database. After removing drugs without a InCHI key or compound identifier (CID), 558 drugs (282 nephrotoxic, 276 non-nephrotoxic) from this dataset were brought forward into DIRIL.

As shown in [Figure 1](#), combining the two datasets from Gong et al.<sup>(p21)</sup> and from Shi et al.,<sup>(p6)</sup> after consolidating the overlapping compounds by CID, yielded a total of 1083 unique compounds (see [Supplementary material S1B online](#)). This list underwent a standardized chemical data processing strategy as proposed by Denis Fourches and colleagues.<sup>(p23)</sup> This processing approach involved removing compounds that cannot be appropriately handled by conventional cheminformatics techniques, such as inorganic and organometallic compounds, counterions, salts and mixtures. In addition, duplicate compounds resulting from this process were removed based on their canonical SMILES (simplified molecular-input line-entry system). These preprocessing steps were carried out using a semi-automated workflow developed by Domenico Gadaleta and colleagues.<sup>(p24)</sup> The resulting list of compounds was mapped to DrugBank by their PubChem CIDs to generate a list of 512 single-molecule drugs. This list of drugs was further verified with the Anatomical, Therapeutic and Chemical (ATC) Index<sup>(p25),(p26)</sup> to identify these drugs with 'oral' listed as the route of administration, which led to 317 single-

**FIGURE 1**

Visual flowchart of the development of drug-induced renal injury list (DIRIL; see [Supplementary material file S1 online](#) for further information on curation).

molecule, oral administered drugs for human use that conformed with our database definition.

Of the 317 drugs in DIRIL, some were presented in the Gong and Shi datasets with consistent DIRI annotation. For these drugs, their DIRI calls from the original authors were kept in DIRIL. For those drugs that had conflicting DIRI calls between Gong and Shi datasets, their DIRI annotation was determined by FDA labeling data retrieved from FDALabel<sup>(p27)</sup> through manual readings. In the end, of 317 drugs in DIRIL, 171 were nephrotoxic (DIRI positive) and 146 were non-nephrotoxic (DIRI negative) (see [Supplementary material S1A online](#)).

#### Consideration of the ATC classification

The DIRIL dataset contains all 14 anatomical drug categories, as classified by WHO's ATC Classification System.<sup>(p25),(p26)</sup> However, ~91% of the drugs are from seven of the 14 categories, with drugs related to the cardiovascular and nervous system cat-

egories being most predominant ([Figure 2a](#)). Antivirals for systemic use (J05), antineoplastic agents (L01) and psychoanaleptics (N06) were the most predominant among the therapeutic categories, with 19% of drugs combined ([Figure 2b,c](#)).

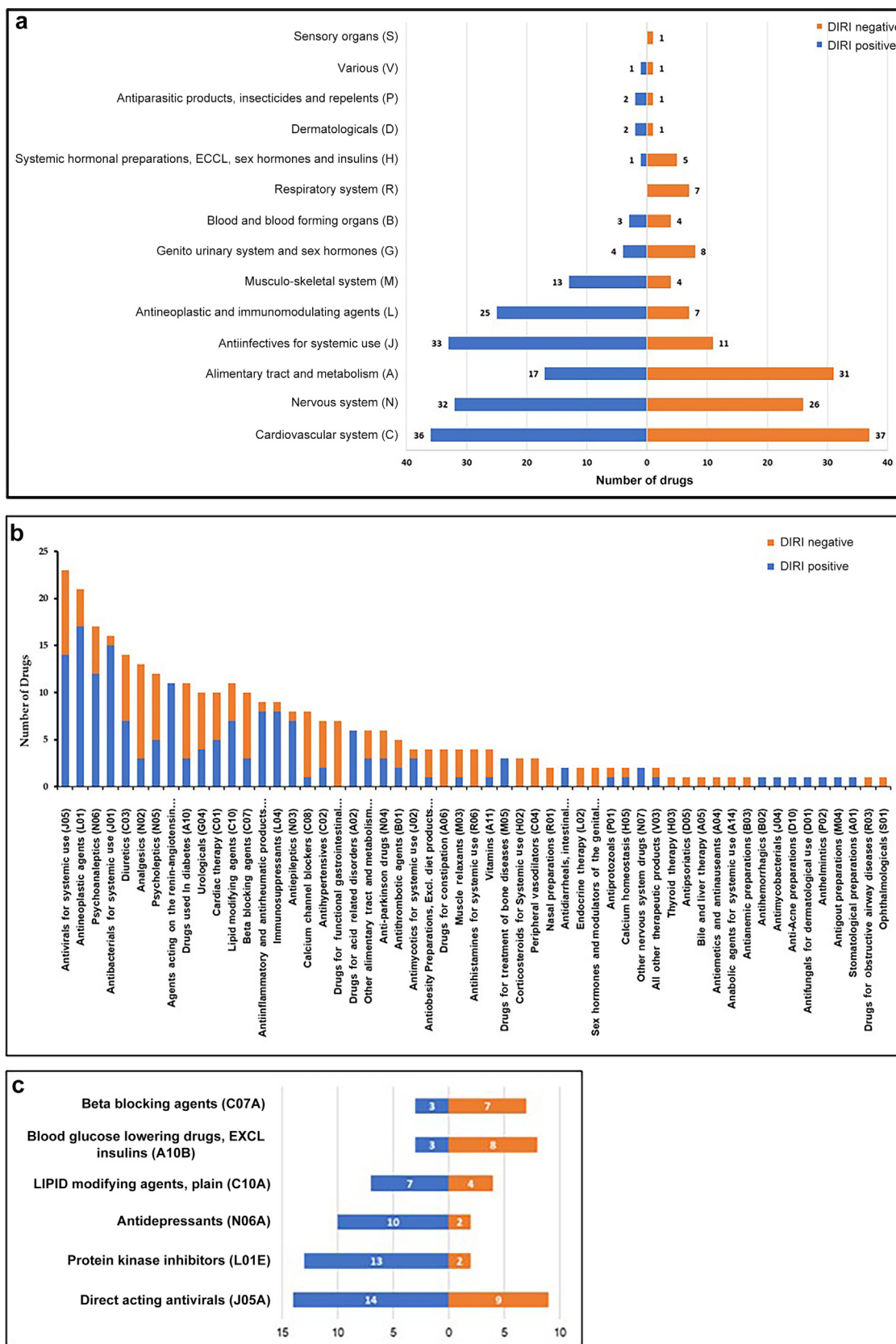
#### Consideration of daily dose, molecular weight and lipophilicity

Parameters like daily dose, molecular weight and lipophilicity are vital in the study and prediction of human toxicity risk. Daily dose is known to be frequently associated with a variety of drug-induced toxicities; this is particularly evident in drug-induced liver injury.<sup>(p28),(p29),(p30),(p31)</sup> We analyzed the relationship between daily dose, retrieved from WHO's ATC Index,<sup>(p25),(p26)</sup> and nephrotoxicity ([Figure 3a](#)). However, there was no clear separation between the nephrotoxic and non-nephrotoxic drugs by daily dose, meaning that, for the drugs within DIRIL, there was

no conclusive relationship between daily dose and nephrotoxicity.

Molecular weight is a key parameter in the vascular transportation of therapeutic drugs, influencing pharmacokinetic parameters like biodistribution and clearance rate,<sup>(p32)</sup> and clearance mechanisms.<sup>(p32),(p33)</sup> Smaller molecules have the ability to navigate complex vasculature, allowing them to interact with nearly all tissues and cell types within the body more easily.<sup>(p34)</sup> We analyzed the relationship between nephrotoxicity and molecular weight and found that the majority of the non-nephrotoxic drugs had a molecular weight <600 Da ([Figure 3b](#)), whereas an overwhelming majority of the drugs with a molecular weight >600 Da were nephrotoxic.

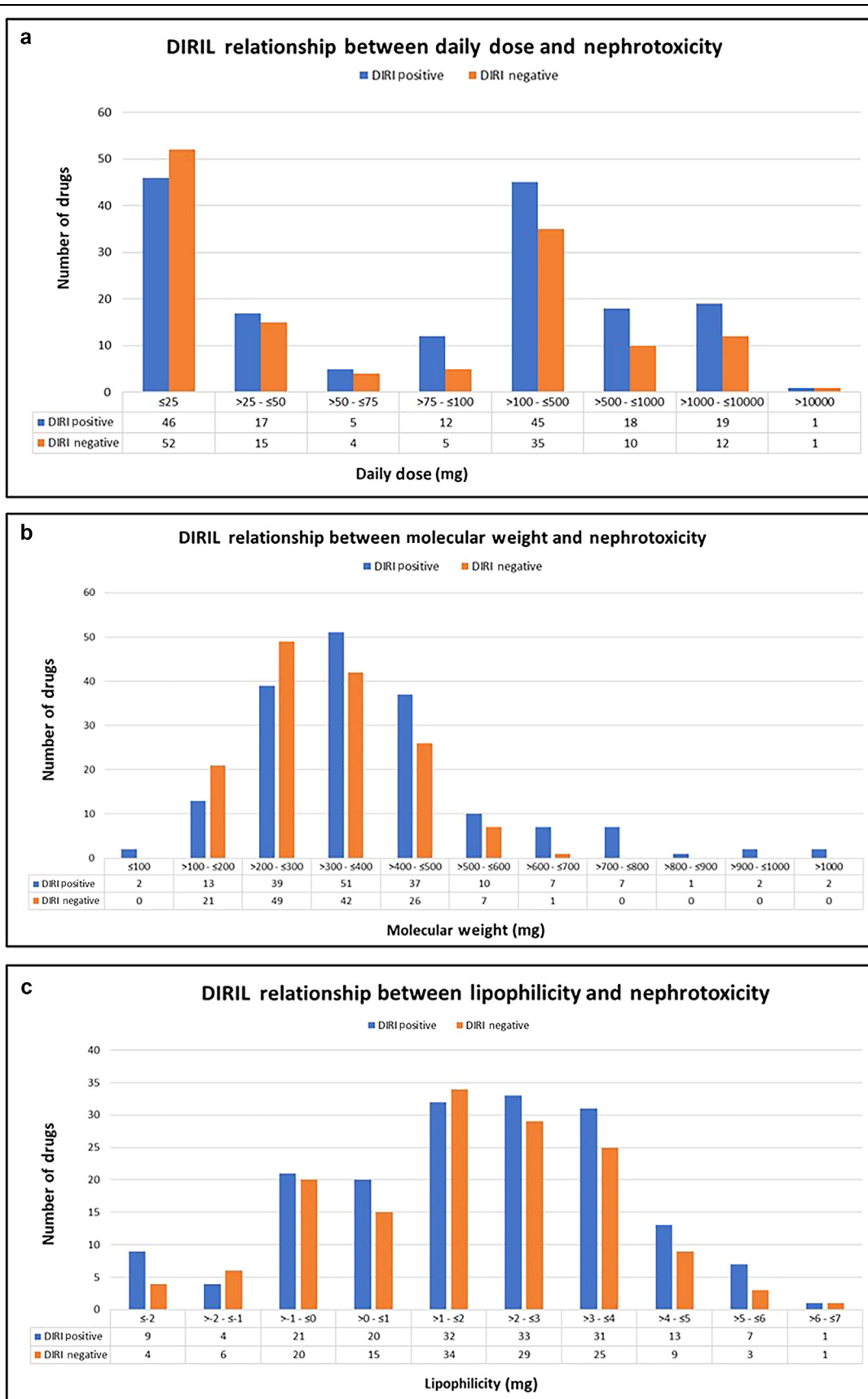
We also analyzed lipophilicity and hydrophilicity because these parameters influence the volume of distribution, including permeability across lipid membranes.<sup>(p35)</sup> Lipophilicity and hydrophilicity can be measured by the octanol: water



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FIGURE 2

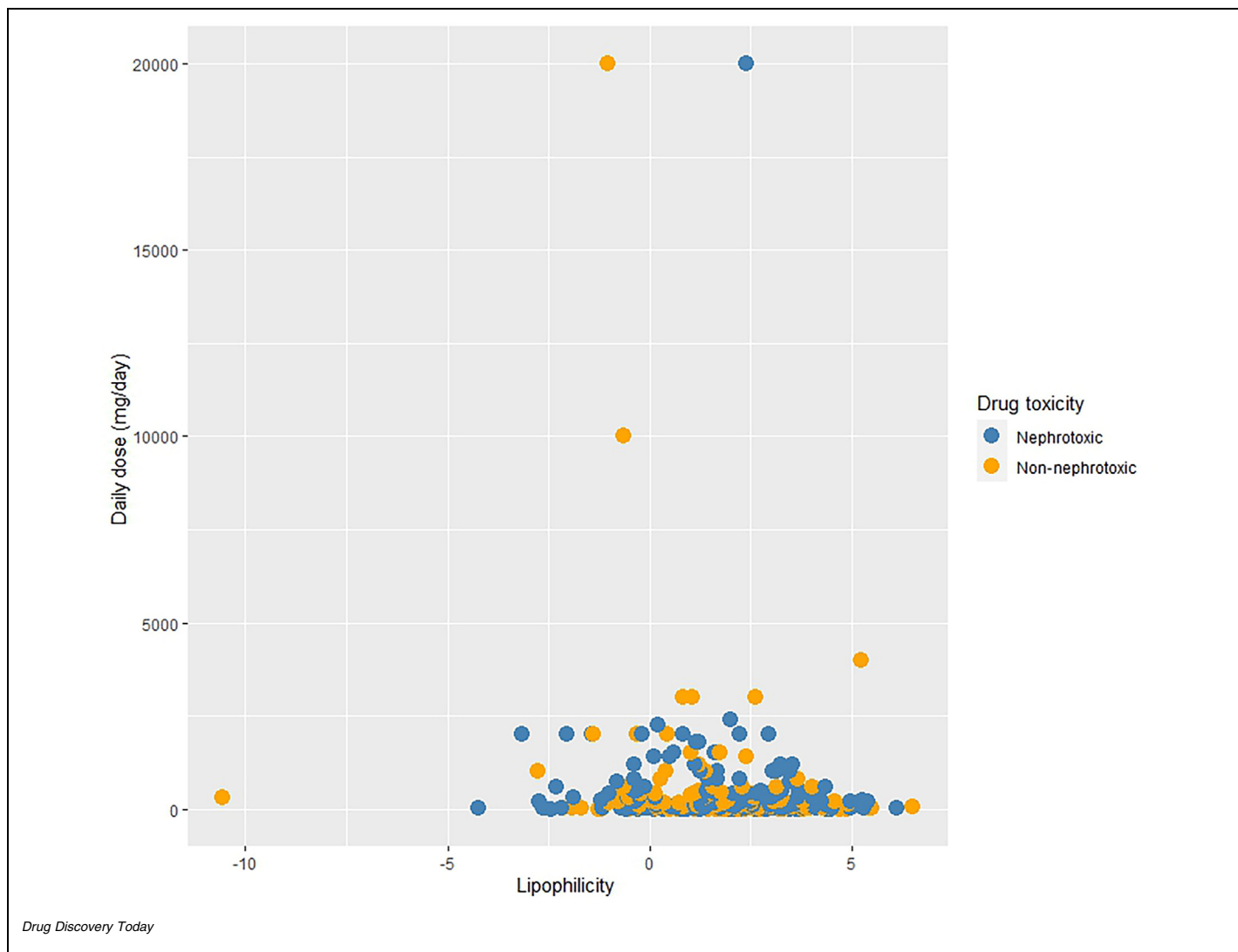
(a) A representation of the main anatomical classes of drug-induced renal injury list (DIRIL). (b) A representation of all the therapeutic classes represented by the drugs in DIRIL. (c) Provides a more in-depth look into the top six pharmacological classes.



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**FIGURE 3**

(a) Relationship between daily dose and nephrotoxicity. (b) Relationship between molecular weight and nephrotoxicity. (c) Relationship between lipophilicity and nephrotoxicity.



**FIGURE 4** Graph showing the relationship between drug daily dose (DDD) and lipophilicity for drug-induced renal injury list (DIRIL).

partition coefficient ( $\log P$ ), which we calculated using the free Mold2 software.<sup>(p36)</sup> Mold2 is an easily accessible software designed and produced by the National Center for Toxicological Research (NCTR) for the fast calculation of 777 descriptors from a 2D chemical structure.<sup>(p36)</sup> Lipophilic drugs tend to have a higher volume of distribution<sup>(p35)</sup> and a positive  $\log P$  value,<sup>(p37)</sup> whereas hydrophilic drugs tend to have a lower volume of distribution<sup>(p35)</sup> and a negative  $\log P$ .<sup>(p37)</sup> As seen in Figure 3c, there was no clear separation between the toxic and non-toxic drugs, meaning that for the drugs within DIRIL there is no clear relationship between lipophilicity or hydrophilicity and nephrotoxicity.

#### Consideration of the combination of drug properties and drug disposition

Different parameters can synergize to cause toxicity, as we previously described for the Rule-of-Two (RO2) method for drug-induced liver injury,<sup>(p28)</sup> where a daily oral dose of  $\geq 100$  mg combined with lipophilicity ( $\log P$ ) of  $\geq 3$  dramatically increases DILI frequency. Specifically, when tested on drugs with a severity classification of most- and no-DILI concern, the RO2 method yielded a 96% positive predictive value (ppv); and when applied to withdrawn and over-the-counter drugs it yielded a 93% ppv. However, as shown in Figure 4, there was no clear correlation between the combination of DD and  $\log P$ , at any value, and DIRI classification within DIRIL.

The Biopharmaceutics Drug Disposition Classification System (BDDCS) was proposed by Wu and Benet in 2005 as a methodology to predict drug disposition properties based on the extent of drug metabolism, permeability rate and aqueous solubility characteristics.<sup>(p38),(p39)</sup> The BDDCS has similar predictive potential to methodologies like RO2. Using several parameters, BDDCS indicated that drugs that fall within BDDCS Class 2 (extensively metabolized with low aqueous solubility) exhibited the highest rate of DILI risk, with a ppv of 90.2%.<sup>(p29)</sup> In 2015, Varma et al. published the Extended Clearance Classification System (ECCS) for identifying the predominant mechanisms of drug clearance.<sup>(p40)</sup> ECCS builds on the

BDDCS to provide further predictions of liver and kidney clearance and gut bioavailability.<sup>(p39),(p40)</sup> The BDDCS and ECCS systems are most useful in predicting drug disposition characteristics using the aqueous solubility, membrane permeability rate, molecular weight and charge of a drug before dosing information is provided.<sup>(p29),(p39)</sup> However, these methods were not effective in the classification of nephrotoxic potential based on DIRIL.

### Concluding remarks

DIRIL represents a highly curated set of molecules to facilitate research and development of NAMs for human DIRI. We plan to expand the size of the drug list, verify all toxicity classifications, further investigate the relationship between molecular weight and nephrotoxicity and perform QSAR analysis and modeling for DIRIL. DIRIL provides an opportunity to mitigate the risk of nephrotoxicity earlier in drug discovery and development.

### Disclaimer

This manuscript reflects the views of the authors and does not necessarily reflect those of the FDA. Any mention of commercial products is for clarification only and is not intended as approval, endorsement or recommendation.

### Conflict of interest

The authors declare no conflict of interest.

### CRedit authorship contribution statement

**Skylar Connor:** Writing – original draft, Methodology, Formal analysis, Data curation. **Ting Li:** Writing – review & editing, Formal analysis, Data curation. **Yanyan Qu:** Writing – review & editing, Formal analysis, Data curation. **Ruth A Roberts:** Writing – review & editing, Supervision, Conceptualization. **Weida Tong:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

### Data availability

the data is attached with the paper

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.drudis.2024.103938>.

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