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Development of a Pharmaceutical Database to support the Nonclinical Evaluation of Drug-Induced Cardiac Toxicity

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ABSTRACT

The Health and Environmental Sciences Institute (HESI) Cardiac Safety Committee designed and created a publicly accessible database with an initial set of 130 pharmacologically defined pharmaceutical agents with and without cardiotoxic properties. The database includes specific aspects about each compound that could be useful in evaluating hypotheses around mechanisms of drug-induced cardiac toxicity or development of novel cardiovascular safety assays. Data on the compounds was obtained from published literature and other online sources (e.g., DrugBank.ca) and was curated by at least 10 subject matter experts. The database includes applicable information such as the compound name, pharmacological mode of action, characterized cardiac mode of action, type of cardiac toxicity, known clinical cardiac toxicity profile, animal models used to evaluate the cardiotoxicity profile, routes of administration, and toxicokinetics (i.e., C_{max}). Data from both nonclinical and clinical studies is included for each compound. The user-friendly web interface allows for multiple ways to search the database and is also intended to provide a means for the submission of new data/compounds from relevant users. This will ensure that the database is constantly updated and remains current. Such a data repository will not only provide assistance for the HESI working groups in defining drugs for use in any future studies, but safety scientists can use the database as a vehicle of support for broader cardiovascular safety studies or exploring mechanisms of toxicity associated with certain pharmacological modes of action.

INTRODUCTION

The HESI Cardiac Safety Committee, a large, multisector, international, scientific collaboration works together to improve drug-induced adverse cardiovascular effects and outcomes. To achieve this, the Committee is often tasked with evaluating novel assays or testing approaches for cardiac safety. The Committee has conducted numerous research investigations and de novo experimental studies in diverse areas such as drug-induced effects on cardiac contractility (Guth et al., 2015; Pugsley et al., 2017), cardiac repolarization (Valentin et al., 2022), and changes in cardiac troponin levels in response to cardiac injury (Clements et al., 2010; Reagan et al., 2013) since it's inception in 2000. In order to test the model and/or hypothesis, these studies require the use of compounds with known cardiac effects. The Cardiac Compound Tool (CCT) Database Steering Team therefore identified a need for development of an online, structured compound resource (i.e., database) to compile data on multiple aspects informative to users.

METHODS

Components of the CCT database include compound name, clinical pharmacological category, pharmacological mode of action, cardiac mode of action, and relevant non-clinical and clinical endpoints (Table 1.)

The CCT database was compiled using a list of compounds derived from pharmaceuticals and drug development assays known to cause cardiac side effects in humans or animal models. Compounds were selected based on a comprehensive literature review as well as expert experience including knowledge of the mechanisms of drug action. Endpoints for both nonclinical and clinical studies are included, when possible, with nonclinical endpoints being limited to *in vivo* studies for the first version of the database. Further inclusion criteria were set to ensure sufficient available data on each drug with cardiotoxic information being prioritized. Data was initially compiled in Microsoft Excel before a web-based SQL application was built to provide a user-interface to search, categorize, and filter based on interest. Some compounds without reported cardiotoxicity have also been included as potential negative control test substances.

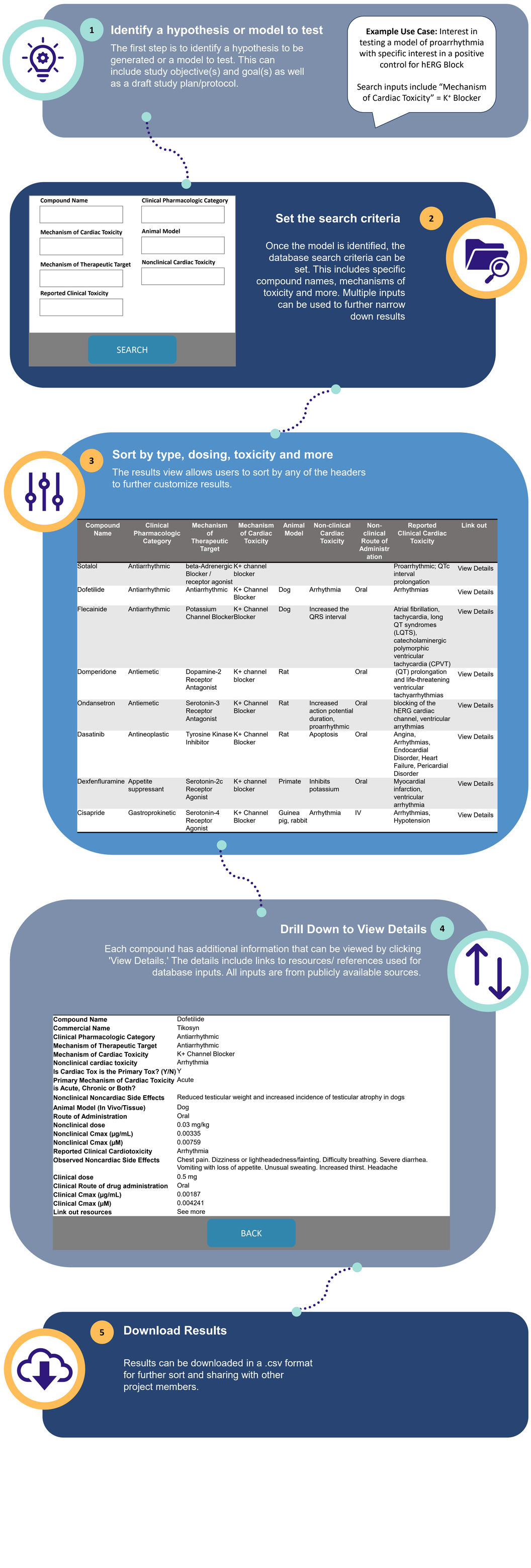
Once the database is made publicly available (anticipated Q4 2023), users will have the ability to suggest additional compounds for inclusion. The CCT Steering Team will review these suggestions at least annually and update the database accordingly.

Table 1. Components of the HESI Cardiac Compound Tool Database

CCT Database Column Header	Definition
Compound Name	Generic name of the compound
Commercial Name	Name Brand/Marketed Name of the compound
Clinical Pharmacologic Category	Clinical use/pharmacologic activity of the compound
Mechanism(s) of Therapeutic Action	The primary pharmacological mechanism of the compound related to clinical use
Mechanism(s) Responsible for Cardiac Toxicity	The primary mechanism of the compound related to any cardiotoxic effect
Reported Preclinical Cardiac Toxicity	The most common cardiac toxicity reported from preclinical studies
Is Cardiac Toxicity the Primary Toxicity? (Y/N)	Denotes whether or not the reported cardiac toxicity is the primary toxicity [in animal species] associated with the drug
Primary Onset of Cardiac Toxicity - Acute, Chronic or Both? (Nonclinical/Clinical)	Denotes whether the primary mechanism reported for the cardiac toxicity results from acute or chronic administration, or both
Observed Nonclinical Noncardiac Side Effects	Lists the major noncardiac toxicities observed in nonclinical studies
Animal Model (In Vivo/Tissue)	* Lists the animal model or tissue for which the nonclinical data included in the CCT Database was extracted
Nonclinical Route of Drug Administration	The nonclinical route of drug administration used in the animal model for data included in the CCT Database
Nonclinical dose	Dose of the drug administered to the animal model resulting in cardiac toxicity
Nonclinical C_{max} (µg/mL)	The nonclinical C_{max} derived from the reference dose literature for the animal model included in the CCT Database (calculated as micrograms per milliliter units)
Nonclinical C_{max} (µM)	The nonclinical C_{max} derived from the reference dose literature for the animal model included in the CCT Database (calculated as micromolar units)
Reported Clinical Cardiac Toxicity	The most commonly reported cardiac toxicity associated with clinical use
Is Cardiac Toxicity the Primary Toxicity? (Y/N)	Denotes whether or not the cardiac toxicity is the primary toxicity [in humans] associated with the drug
Observed Clinical Noncardiac Side Effects	Lists the major noncardiac toxicities associated with clinical use
Clinical dose	The most common clinical dose of drug administered to humans for data included in the CCT Database
Clinical Route of Drug Administration	The clinical route of drug administration used in humans included in the CCT Database
Clinical C_{max} (µg/mL)	The clinical C_{max} derived from the clinical dose literature included in the CCT Database (calculated as micromolar units)
Clinical C_{max} (µM)	The clinical C_{max} derived from the clinical dose literature included in the CCT Database (calculated as micrograms per milliliter units)
Row Completed?	Denotes whether or not the row containing data contains complete information
Link out resources	Denotes links to references and other resources used in the CCT Database for each drug

*Note that data from both *in vitro* and *in silico* models were not included in this first phase of the CCT Database but are anticipated to be added in subsequent revisions/updates

FIGURE 1. DATABASE SCHEMATIC



Compound Name	Clinical Pharmacologic Category	Mechanism of Therapeutic Target	Mechanism of Cardiac Toxicity	Animal Model	Non-clinical Cardiac Toxicity	Non-clinical Route of Administration	Reported Clinical Cardiac Toxicity	Link out
Sotalol	Antiarrhythmic	beta-Adrenergic Blocker / receptor agonist	K+ channel blocker				Proarrhythmic; QTc interval prolongation	View Details
Dofetilide	Antiarrhythmic	Antiarrhythmic	K+ Channel Blocker	Dog	Arrhythmia	Oral	Arrhythmias	View Details
Flecainide	Antiarrhythmic	Potassium Channel Blocker	K+ Channel Blocker	Dog	Increased the QRS interval		Atrial fibrillation, tachycardia, long QT syndromes (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT)	View Details
Domperidone	Antiemetic	Dopamine-2 Receptor Antagonist	K+ channel blocker	Rat		Oral	(QT) prolongation and life-threatening ventricular tachyarrhythmias	View Details
Ondansetron	Antiemetic	Serotonin-3 Receptor Antagonist	K+ Channel Blocker	Rat	Increased action potential duration, proarrhythmic	Oral	blocking of the hERG cardiac channel, ventricular arrythmias	View Details
Dasatinib	Antineoplastic	Tyrosine Kinase Inhibitor	K+ Channel Blocker	Rat	Apoptosis	Oral	Angina, Arrhythmias, Endocardial Disorder, Heart Failure, Pericardial Disorder	View Details
Dexfenfluramine	Appetite suppressant	Serotonin-2c Receptor Agonist	K+ channel blocker	Primate	Inhibits potassium	Oral	Myocardial infarction, ventricular arrhythmia	View Details
Cisapride	Gastroprokinetic	Serotonin-4 Receptor Agonist	K+ Channel Blocker	Guinea pig, rabbit	Arrhythmia	IV	Arrhythmias, Hypotension	View Details

Table 2. List of Pharmacological Mechanisms of Drug Action with Cardiac Effects

Adenosine Agonist/Antagonist
Adrenoceptor Agonist/Antagonist
Androgenic Hormone
Angiotensin Converting Enzyme Inhibitor (ACEI)
Angiotensin Receptor Blocker (ARB)
Anthracycline (Acute Type I Cardiotoxicity)
Anticoagulant
Anticonvulsant
Antihypercholestolemic
Antineoplastic (= Anticancer = Oncolytic = Chemotherapeutic)
Antiplatelet
Antiprotozoal
Anti-Vascular Endothelial Growth Factor (VEGF)
Antiviral
β- adrenoceptor antagonist (β-Blocker)
β- adrenoceptor agonist (β-Mimetic)
Dopaminergic Agonist
Inhibitor of Na^+/K^+ ATPase
Ca^{2+} channel blocker
Calcium sensitizer (Positive Inotrope)
Cholinoceptor Agonist
Cholinoceptor Antagonist
Acetylcholinesterase Inhibitor
Erythropoietin
Estrogen + progestin hormones
Ethanol
Fibrinolytic
Ganglionic Blocker (Ganglioplegic)
Glucocorticoid
Immunosuppressant
Potassium (K^+) Channel Activator/Blocker
Sodium (Na^+) channel Activator/Blocker
Nitrates (Isosorbide dinitrate; Nitroglycerin)
Non-Steroidal Anti-inflammatory Drug (NSAID)
Phosphodiesterase Inhibitor
Receptor Tyrosine Kinase Inhibitor Human Epidermal Growth Factor Receptor (HER2) Inhibitor (Chronic Type II Cardiotoxicity)
Renin Inhibitor
Tricyclic Antidepressant drug (TCA)

RESULTS & DISCUSSION

The database includes a total of 128 compounds with a diverse range of pharmacological mechanisms of action across a multitude of therapeutic categories. The list of included pharmacological mechanisms of drug action with cardiac effects is listed in Table 2.

Figure 1 depicts an example use case of the database to explore a hypothetical model of proarrhythmia using a hERG blocker as a positive control. Once a team is formed to develop the study assumptions and hypothesis, the database would be employed to find appropriate positive controls for the study. Several inputs allow users to tailor the search to their needs. In this use case, the search inputs are interested in mechanisms of cardiac toxicity (K^+ blocker) only. Initial search outputs contain 8 potential positive controls with a known K^+ blocker mechanism. The initial view does not include all components of the database, which can be found in the last column 'Link Out'. Selecting this opens the data for the compound of interest where all database inputs (e.g., from Table 1) are available to view. Resources used to compile the information are also linked in this view. Results can also be downloaded in a .csv format to allow for sharing with team members and further data manipulation.

The HESI CCT Database is an efficient workspace designed to reduce time spent searching for positive and negative controls to test CV-related hypotheses. It can streamline research processes and allow for greater collaboration on a given study topic of interest. The intent is for all users to benefit from data- and knowledge-sharing that could lead to greater insights into cardiovascular toxicity.

The authors recognize that the database is limited in a number of ways: it exclusively uses publicly available data, potentially overlooking more recent information on any given compound, and includes only in vivo data in this initial release. Despite this, it holds the potential for being a valuable resource of consolidated information and can be updated periodically to improve and enhance functionality.

FAQs

- Does the database include in vitro or in silico data? – *No but there's plans to include this information in a future version*
- Are you taking suggestions for new CCT compounds? – *Yes! We will have a form you can complete to suggest additional compounds.*
- Where did you get the Cmax data? – *Cmax data was pulled from existing literature and is referenced in the 'See More' for each compound. We know that Cmax may differ depending on the study but this is a starting point from publicly available sources.*
- When will the CCT Database be available? – *We are completing the final draft of a complimentary manuscript and plan to launch once the manuscript is accepted.*

ACKNOWLEDGEMENTS & DISCLAIMER

The authors would like to acknowledge the Cardiac Safety Committee and Steering Team for their input and expertise on selection of some of the compounds included in the database.

The opinions expressed here are that of the author and do not reflect the views of any organization or entity and they do not constitute an endorsement of any specific products. The chemicals and information included in this database are all available in the public domain. The intent is to use this information to better understand models of drug-induced cardiovascular toxicity and not intended to provide specific data on any one chemical.

Scan here to learn more about HESI Cardiac Safety and download a copy of the poster.