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Research article

Development of a pharmaceutical database as an aid to the nonclinical detection of drug-induced cardiac toxicity

Donald De Alwis [a], C. Michael Foley [b], Eugene Herman [c], Adam P. Hill [d], Peter K. Hoffmann [e], Yasunari Kanda [f], Emily Kaushik [g], Jennifer Pierson [a,*], Raechel Puglisi [a], Hong Shi [h], Xi Yang [i], Michael K. Pugsley [j]

[a] Health and Environmental Sciences Institute, Washington, DC 20005, USA
[b] Abbvie Inc., North Chicago, IL 60064, USA
[c] National Cancer Institute, Bethesda, MD 20892, USA
[d] Victor Chang Cardiac Research Institute, Sydney, NSW, Australia
[e] Cat Island, Beaufort, SC 29907, USA
[f] National Institute of Health Sciences (NIHS), Kawasaki, Japan
[g] Takeda Pharmaceuticals Company Ltd., Cambridge, MA 02139, USA
[h] Bristol-Myers Squibb Co., Princeton, NJ 08543, USA
[i] RTI International, Washington, DC 20005, USA
[j] Cytokinetics, South San Francisco, CA 94080, USA

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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 128 pharmacologically defined pharmaceutical agents, many with known cardiotoxic properties. The database includes specific information about each compound that could be useful in evaluating hypotheses around mechanisms of drug-induced cardiac toxicity or for development of novel cardiovascular safety assays. Data on each of the compounds was obtained from published literature and online sources (e.g., DrugBank.ca and International Union of Basic and Clinical Pharmacology (IUPHAR) / British Pharmacological Society (BPS) Guide to PHARMACOLOGY) and was curated by 10 subject matter experts. The database includes information such as 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 toxicokinetic parameters (i.e., Cmax). Data from both nonclinical and clinical studies are included for each compound. The user-friendly web interface allows for multiple approaches 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 aid the HESI working groups in defining drugs for use in any future studies, but safety scientists can also 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.

1. Introduction

Safety issues are one of the most important factors responsible for drug withdrawal from clinical use, accounting for at least one-third of all drug discontinuations (Kennedy & Niebergall, 1997; Ray, Murray, Hall, Arbogast, & Stein, 2012). In this regard, cardiovascular toxicity has been reported to be one of the most common adverse safety effects (Redfern et al., 2010), and is estimated to be responsible for at least 45% of all safety related, post-approval, drug withdrawals from clinical use (Stevens & Baker, 2009). Despite this apparently large effect post-approval, cardiovascular toxicity is responsible for only approximately 9% of total drug withdrawals that occur during phase one of clinical trials (Sibille,

* Corresponding author at: HESI, Washington, DC 20005, USA.
E-mail addresses: Michael.Foley@abbvie.com (C.M. Foley), eugene.herman2@nih.gov (E. Herman), a.hill@victorchang.edu.au (A.P. Hill), kanda@nihs.go.jp (Y. Kanda), Emily.Kaushik@takeda.com (E. Kaushik), jpierson@hesigloba.org (J. Pierson), rpuglisi@hesiglobal.org (R. Puglisi), hong.shi@bms.com (H. Shi), xyang@rti.org (X. Yang), mpugsley@cytokinetics.com (M.K. Pugsley).

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Deigat, Janin, Kirkesseli, & Durand, 1998), and is frequently not noted until a drug is introduced into clinical practice. Such data indicate that there is a considerable opportunity to develop screening methodologies that can more accurately predict the risk of adverse cardiovascular effects in clinical populations much earlier during the conduct of nonclinical studies and early clinical trials, i.e., Phase I studies.

The cardiovascular system is susceptible to drug-induced adverse effects since the complex network of pathways that control its normal function can be easily perturbed by potential off-target effects of drugs. As a result, many cardiovascular and non-cardiovascular drugs have been shown to cause a broad spectrum of both indirect and direct effects that can range from mild to severely toxic to myocardial tissue and the cardiovascular system. Among these, some cardiac drugs may induce functional and structural alterations by interfering directly with highly specific biochemical processes that are essential to the integrity of the heart and vascular tissue. Other agents, whose primary therapeutic action is directed toward non-cardiac tissues, have also been noted to cause adverse cardiovascular effects. Examples include anticancer, central nervous, genitourinary system, gastrointestinal, antihistaminic, anti-inflammatory, and anti-infective agents (Mamoshina, Rodriguez, & Bueno-Orovio, 2021). Finally, drugs can also cause myocardial toxicity without having a direct effect on any cardiovascular processes. For example, substances targeting the kidney can provoke biochemical changes of sufficient magnitude to alter normal cardiovascular activity (Hoffmann & Pugsley, 2024). This prevalence of cardiovascular toxicity has negative effects on how a drug can safely be prescribed clinically as well as necessitating the need for additional pre/and or post approval monitoring.

For more than a decade, the Health and Environmental Sciences Institute (HESI) Cardiac Safety Committee has worked in this field with a mission to 1) improve public health by reducing unanticipated drug-related cardiovascular adverse effects, 2) develop innovated approaches to support early detection and prediction of adverse cardiovascular effects and 3) identify improved means to evaluate the resulting cardiovascular toxicity and pathobiology. To achieve this, the Committee is often tasked with evaluating novel assays or testing approaches for cardiac safety. Since its inception in 2000, 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). While the committee is adept at designing and conducting studies involving multiple study sites, the issue the group always confronts lies in the fact that the committee utilizes non-proprietary compounds to test the hypothesis under investigation in the model; however, this process only starts after conduct of a labor-intensive literature and database search.

Several online databases can be searched since they are related to general toxicology principles (Toropov, Toropova, Raska Jr., Leszczynska, & Leszczynski, 2014). However, these databases, by nature, do not specifically address cardiac and/or cardiovascular toxicity nor do they collate the associated research information that is usually required. The HESI Cardiac Compound Tool (CCT) Database Steering Team therefore identified a need for an online, structured compound resource (i.e., database) to compile data on multiple aspects informative to users. A series of descriptive terms were identified to begin to compile the CCT database including aspects such as the type of adverse cardiac event, mechanism of the pharmacological drug target and impact on cardiovascular function, and other relevant pharmacological and pharmacokinetic characteristics. These terms comprise many of the column headers included in Table 1. To this end, an extensive variety of compounds with demonstrated translation to clinical outcomes were selected that also included compound information from past Cardiac Safety Committee efforts. Based on this initial set of compounds, we have built a freely accessible, searchable database that defines the cardiotoxic actions of a set of compounds together with supporting literature that characterizes those effects. The database web interface is intended to support ongoing submission of new data/compounds from users, ensuring that the database always remains current. Such a

Table 1
Components of the HESI Cardiac Compound Tool Database - Column Headers and Definitions.

CCT Database Column Header	Definition
Compound Name	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 Nonclinical Cardiac Toxicity	The most common cardiac toxicity reported from nonclinical 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 Non-clinical 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
Non-clinical 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 micrograms per milliliter units)
Clinical C_{max} (μM)	The clinical C_{max} derived from the clinical dose literature included in the CCT Database (calculated as micromolar 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

repository will not only aid with the HESI working groups but could also provide support for broader cardiovascular safety and assay investigations.

2. Methods

The components of the CCT database include such details as compound name, clinical pharmacological category, mechanism(s) of therapeutic action, mechanism(s) responsible for cardiac toxicity, and relevant nonclinical and clinical endpoints (Table 1). The CCT database also includes information on the nonclinical and clinical doses with which cardiac toxicity results and the associated maximal plasma concentration (Cmax) associated with the cardiac toxicity. The Cmax value was selected for use since the nonclinical studies for which the database was developed are primarily acute in nature. Fig. 1 provides an overview of the CCT database generation workflow that was established by the CCT sub team.

2.1. Compound selection for inclusion in the database

The current CCT database was compiled as a list of 128 compounds that were primarily derived from a comprehensive literature review but also based on the experience of subject matter experts. This final list of 128 compounds was derived from a much larger list of compounds evaluated based upon previously conducted pharmaceutical and drug development assays known to assess cardiac side effects and/or toxicities in both humans and/or nonclinical animal models. The initial compound list was generated by an international panel of expert researchers on the CCT sub team within the HESI Cardiac Safety Committee (i.e., industry toxicologists, safety pharmacologists, contract service providers, academics, and regulatory authorities), with the support of HESI management staff. These CCT panelists are renowned researchers with many years of expertise in cardiac and cardiovascular safety pharmacology, cardiac physiology, and cardiac toxicology who have considerable 'real-world' knowledge and are well versed in the scientific practice of drug safety profiling. The summarized compound list was supplemented by previous literature reviews conducted by HESI staff on pharmacological cardiac toxicity in addition to previous literature on known drug targets (Gaulton et al., 2017; Guth et al., 2015; Vargas et al., 2015).

2.2. Nonclinical and clinical database endpoints

The nonclinical and clinical endpoints that were selected for inclusion in the CCT database were initially developed primarily based upon the pharmacological mechanism of action and the agreed upon primary cardiac mechanism of action associated with the characteristic toxicity profile of the compound. The overview also included details on the clinical pharmacological category. The literature was then mined, and a validated nonclinical model consistently utilized and reported in the literature by cardiovascular scientists was selected, evaluated, and used for each compound. This information was collected to define the primary versus any potential secondary toxicities, the animal model used, dose administered, dosing route (primarily oral), the maximum plasma concentration (Cmax) achieved by the compound post dose in the nonclinical animal model where the Cmax value was presented in both units of μg/mL as well as μM concentrations, and significant cardiac but also noncardiac side effects. These same database endpoints were defined for the clinical study data provided.

Cardiac side effects were defined as target or non-target effects of the compound when administered at the dose derived from the nonclinical animal model that resulted in cardiotoxicity. While cardiotoxicity was the primary effect, compound effects on the circulatory system were also included if directly affected by adverse cardiac function. Nonclinical in vivo models were primarily, but not exclusively, limited to rats and dogs since these are the main species selected as the rodent and nonrodent toxicology and safety pharmacology species in nonclinical safety evaluations. Additionally, these species are used in studies to characterize the pharmacological mechanism of action. Other nonclinical animal species (i.e., ferret, pig, monkey, guinea pigs and rabbit) may be used to evaluate compound safety and/or pharmacology. However, their use was limited in the current database to characterize electrophysiological-associated cardiac toxicities involving effects on cardiac ion channels which are more relevant in the guinea pig or rabbit than the rat in the conduct of cardiac safety studies. Additionally, in vitro cardiac assays were not included in this first iteration of the CCT database, however there are plans to include validated assays in a future version (see "Continued Database Expansion" for details).

2.3. A complete review of the literature

The literature review was conducted by utilizing a combination of key words and short phrases that permitted a search of databases including Google Scholar and PubMed. Information on cardiac effects was primarily gathered by the key word search of the compound name, followed by a combination of a long list of terms that included "cardiotoxicity", "cardiac toxicity", "cardiac side effects", "cardiac and adverse effect", and/or "cardiac effects." Cardiac mechanisms of action of compounds were categorized using a peer-reviewed list (Mladěnka et al., 2018) in conjunction with a list derived from both Goodman and Gilman's: The Pharmacological Basis of Therapeutics (Brunton, Knollman, & Hilal-Dandan, 2017) and Integrated Pharmacology (Page, 2002). Nonclinical endpoints were identified by keyword searching the compound name, followed by the nonclinical model of interest that defined the cardiac toxicity. These searches were conducted sequentially, rat models from the list of studies were assessed followed by dog models. The pharmacokinetic (PK) data for nonclinical and clinical tests were found by keyword searching the compound name followed by the term "Cmax". The adverse (or side) effects were found by reviewing all the gathered literature for adverse non-cardiac effects, and then subsequent searches were conducted with Google Scholar using the compound name, followed by the model and "adverse effect".

Pharmacological information for the developing compound list was derived primarily from DrugBank.ca which is an open-access database of molecular drug information led by researchers at the University of Alberta (Wishart et al., 2018). Missing data for any of the database endpoints were filled by searching Drugs.com, an online pharmaceutical encyclopedia populated using IBM Watson Micromedex, Cerner

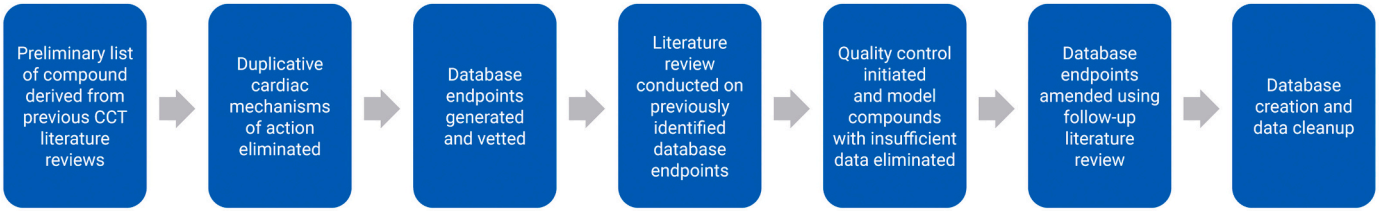

Fig. 1. An overview of the CCT database generation workflow beginning with development of a preliminary list of compounds from previous program literature reviews using standard literature search methods and ending with the actual creation of the CCT database.

Multum, Micromedex, American Society of Health-System Pharmacists, U.S. Food and Drug Administration (FDA), PubChem National Center for Biotechnology Information (U.S. National Library of Medicine) and Wolters Kluwer.

2.4. Quality control of data inclusion in the CCT database

HESI CCT experts convened monthly during and after a preliminary literature review was conducted to assess the database for content quality and relevance. This was followed by curation by these same subject matter expert reviewers who discussed any potential missing terms and eliminated non-specific terms. Inclusion and exclusion criteria for compounds and database endpoints are summarized below in sections 2.6 and 2.7, and existing compounds in the early database were eliminated using a consensus-driven approach. This approach included active engagement and collaboration among the expert reviewers, who synthesized evidence from multiple sources and their own experience utilizing many of these drugs in their own studies to come to an agreed upon decision. Nonclinical models of interest were narrowed to rats and dogs given the predominant use of these species in both toxicology and safety pharmacology studies and the lack of consistent research using other model organisms (e.g., pigs, ferrets, and monkeys). Some experimental compounds that are only used in a nonclinical setting, i.e., they are important pharmacological tool compounds but lack traditional clinical data correlates were included for database for completeness. These compounds are usually used to validate a nonclinical assay and therefore many publications are available for review and use in the construction of the database. CCT committee members prioritized compiling a list of compounds with diverse mechanisms of action, and similar compounds were eliminated for this preliminary database version. Additional compounds were identified during subsequent literature reviews, and these compounds will be included in the next database update.

2.5. Creation of the CCT database

The data resulting from the literature search was gathered in Microsoft Excel and then inputted into the web-based SQL application, from which the graphic user interface was generated. The database includes a search feature in which users can create a custom search query to categorize and filter the database compounds using cardiotoxic endpoints of interest. For each compound included in the database, a specifically curated literature article that is relevant to the nonclinical species, cardiotoxic mechanism and PK data. The user can use this reference citation as a starting point to conduct an independent search if desired as the citation provides a point of focus at reducing the time needed to conduct secondary literature searches. An important feature is that the information provided within the CCT database is referenced since the database was constructed from manually curated study information from public literature sources. This promotes database flexibility so that it can also be used as a research tool similar to the South Africa Natural Product Database (SANPDB) developed by Hatherley et al. (2015). Since the possible reference list for each compound is very extensive, the most relevant nonclinical and clinical literature reference decided upon for inclusion by the subteam members is provided for each compound. These references for each compound are included as a DOI or PMID in the database. The database can be accessed online here https://hesiglobal.org/cctdatabase/.

2.6. Inclusion criteria for compounds in the CCT database

A series of criteria were established for inclusion of compounds in the CCT database. Selected was the most representative compound of a given pharmacological class of drugs with a primary cardiotoxic effect. At a minimum for inclusion was the requirement that a sufficient literature base on each drug that had been evaluated for the proscribed cardiotoxic effect had been published in investigations in both nonclinical animal species and humans. The published nonclinical cardiotoxic effects were included irrespective of the animal model conditions (anesthetized, restrained, unrestrained, or conscious), the drug study protocol, or the methodology utilized to characterize the cardiotoxic effect. Similarly, the human cardiotoxicity data were included regardless of the study design used, the duration of the clinical study, clinical sample size and population enrolled, data collection method, or the method used to evaluate the cardiotoxic effect data. If the significance of the animal and human cardiotoxicity findings was reported in the published literature, it was included.

2.7. Exclusion criteria for compounds in the CCT database

A series of criteria were established for exclusion of compounds in the CCT database. These criteria excluded compounds for which data could only be found for the reported cardiotoxic effect in a single species (either animal or human). Compounds for which only animal studies but not human studies report cardiotoxicity were excluded as they would not make a good tool for testing a model for translation. Human case reports were excluded if found for the cardiotoxic effect since these studies are not controlled and may involve unknown background medications in patients that manifest cardiotoxicity. Radiological contrast agents used in medical imaging and other clinical diagnostic pharmaceutical agents were excluded since they would not be routinely evaluated in a HESI nonclinical study and because they lack nonclinical correlates. Any duplicative cardiac mechanisms of action causing the cardiac toxicity were eliminated from inclusion in the database. Monoclonal antibodies and other biological modalities were not considered for inclusion in this first version of the CCT database since the primary objective was for use by HESI safety scientists in cardiac studies that involve small chemical molecules.

2.8. Continued database update and expansion

HESI plans to update the “HESI CCT Database” annually with additional identified cardiotoxic compounds. The open-access format allows database users to suggest compounds for inclusion, which are reviewed on a rolling basis by the Cardiac Compound Tool subcommittee. These requests can be made by navigating to the “Click here to suggest a new compound in the database” on the HESI CCT website (https://hesiglobal.org/cctdatabase/). An annual revision of the database will not only allow for the review of new potential compounds for inclusion with novel cardiotoxicity profiles, but also a revision of existing database compounds. Additional data that may be relevant to previously included compounds may be added as new research methods and models emerge. Similarly, the CCT database subgroup will consider expanding the current database to include data from in vitro cellular and electrophysiological models that support the cardiotoxicity mechanisms described for the list of included compounds. Fig. 2 describes the overview of the annual database revision workflow.

3. Results

The 128 compounds that currently comprise the CCT database provide users with a diverse range of pharmacological mechanisms of action across a multitude of therapeutic areas including oncology, cardiovascular, central nervous system, respiratory, gastrointestinal and hematological systems. The complete listing of current pharmacological categories of drugs represented in the CCT is found in Table 2. While we believe that the literature search utilized was comprehensive, we recognize there are likely additional drugs associated with cardiac toxicities of interest to safety scientists. It is acknowledged that there are a multitude of additional mechanisms that are not captured in this current version of the CCT. However, there will be the possibility to update, on an annual basis, the CCT with additional compounds that manifest

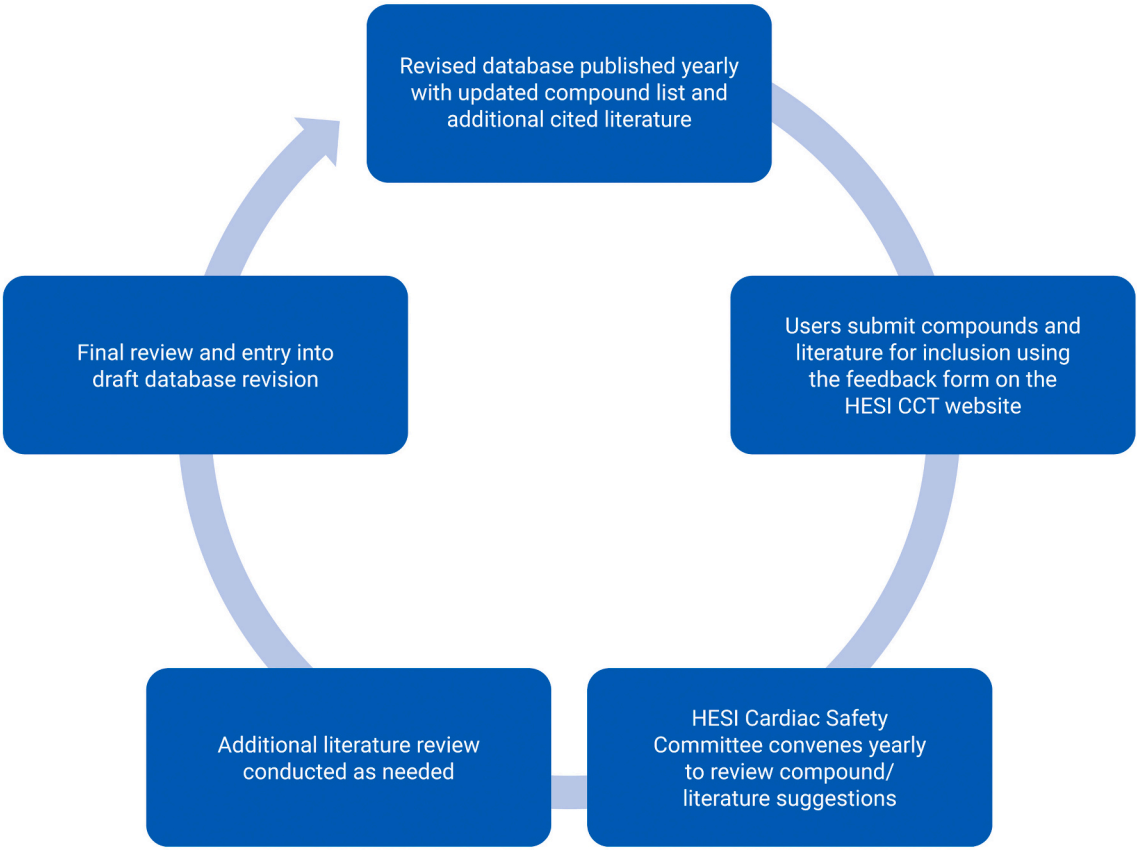

Fig. 2. An overview of the annual database revision workflow.
Note. Database users are encouraged to submit novel compounds and relevant literature for potential inclusion in database updates. All submissions are reviewed annually by HESI Cardiac Safety Committee members and submissions are either returned for further data details or advanced for inclusion in the updated CCT database.

cardiotoxicity not currently captured in this initial version of the database.

The key nonclinical and clinical mechanisms associated with cardiac toxicity of compounds included in the CCT database are summarized in Table 3. The totality of the literature search findings and interpretation of the resulting data for the compound and its associated cardiac toxicity were reviewed and evaluated by the subject matter experts within the HESI Cardiac Safety Committee. Thus, these individuals were primarily responsible for defining the cardiac toxicity associated with each CCT compound. It should be recognized that no mechanism and/or toxicity are absolute and perhaps with time these could change with any of the compounds within the CCT database due to utilization of additional methods and models that provide additional potential mechanisms. However, the group is confident that the cardiac toxicity defined, at this time, is likely the most complete mechanism responsible.

3.1. A case study from the CCT database

There are many ways that this CCT database could be utilized by individuals interested in cardiotoxicities associated with drugs used clinically, those interested in mechanisms responsible for adverse/toxic effects on the heart, and even by other groups within the HESI Cardiac Safety Committee. A case study representing one example of how the Committee plans to use this database moving forward is presented below.

A hypothetical study proposal to investigate the effects of a novel potassium channel (K+) blocker was submitted to HESI and was accepted as a project by the HESI Cardiac Safety Committee (Fig. 3). The Cardiac Safety Committee forms a study group comprised of interested individuals with a broad subject matter expertise to identify the hypothesis of interest as it relates to K+ channel blockers and explore test compound options existing in the database, rather than conducting an extensive, labor-intensive literature search. Using the CCT database, multiple inputs allow users to tailor the search to their needs so the study group members would directly filter for compounds to use as positive control(s) in the study with a specific mechanism of K+ blockade in the heart. Initial search outputs contain 7 potential positive controls with a known K+ blocker mechanism (Fig. 3). By doing this, additional data are retrieved from the database including the animal model evaluated, the route of administration of the compounds and relevant clinical information regarding the effects in humans. The strength of the database includes the ability of the individual to narrow down the focus of the search to only include compounds given orally in the nonclinical animal of interest, the dog. This is easily done with the filter and search feature. 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.

Prior to publication of this type of database, a significant effort by multiple individuals was required to research any drug cardiotoxicity of interest. For example, K+ channel blockers in the example above would require review of copious numbers of publications on this topic, ~1399 relevant articles published between 2018 and 2023 on PubMed alone to find not only relevant nonclinical but also importantly, clinical information, on the cardiotoxic mechanism of interest. All of this information

Table 2
A List of Pharmacological Classes of Drug Action with Cardiac Effects.

Pharmacological Categories
Adrenergic/Antiadrenergic
Analgesic (Opioid)
Anorectic
Antacid
Antianginal
Antiarrhythmic
Antibiotic
Anticoagulant
Antidepressant
Antidiabetic
Antiemetic
Antifungal
Antihistamine
Antihypertensive
Anti-inflammatory (NSAID)
Antineoplastic
Anthelmintic
Antipsychotic
Antiviral
Artificial Sweetener
Bronchodilator
Cardiac Myosin Inhibitor
Cholinergic/Anticholinergic
Corticosteroid
Dietary Supplement
Flavor Enhancer
Gastroprokinetic
Hormone Modulator
Immunosuppressant
Insecticide
Laxative
Local Anesthetic
Proinflammatory
Sodium Channel Activator
Stimulants (CNS)
Thrombolysis
Vasodilator
Vasopressor
Veterinary Medication

is captured in the CCT database providing for a rapid, reliable search that can facilitate inquiries into a given mechanism of action relevant to the cardiac toxicity of interest. The database results can then be rapidly shared with colleagues allowing for discussion, and development of a strategy for investigation.

4. Discussion and conclusion

The creation of this CCT database resulted from the realization that the continuous need to conduct literature searches on topics associated with cardiac safety was a very arduous and inefficient process. Such a search is generally required prior to the discussion of cardiac safety topics by the HESI Cardiac Safety Committee. The standard literature-based review can take up to a year to extensively examine the topic of interest and usually relies on a few members of the committee using different search systems to generate a list of relevant manuscripts. The breadth of the literature review typically includes a review of the published nonclinical and human clinical safety data. Thus, the database is comprised of a variety of drugs and/or mechanisms that can be used to determine not only whether nonclinical findings are important but also whether human data provides a reliable basis for use in cardiac safety evaluations. Compilation of this information will help scientists test new and existing nonclinical models to better understand if the results are comparable to clinical outcomes. Tool compounds play a crucial role in evaluating nonclinical models to predict clinical outcomes in assessing cardiac risk by providing mechanistic insights, enabling pharmacological profiling, and validating the translational relevance of nonclinical models.

As far as the authors are aware, this CCT database appears to be the first of its kind. While many databases have been developed, most are specific to the topic of interest. For example, van Ree et al. (2021) developed the Comprehensive Protein Allergen Resource (COMPARE) which is a database that provides a transparent and consistent mechanism to identify protein allergens. The collaborative scientific group was coordinated by HESI and tasked to develop the database. Like the CCT database, COMPARE is data-driven and clinical-research based that utilizes an independent panel of experts to evaluate and document data input. Kuhn, Letunic, Jensen, and Bork (2016) also developed the Side-Effect Resource (SIDER) database of drugs and adverse drug reactions (ADR). In its current release, SIDER 4, it contains 1430 drugs, 5880 ADRs and 140,064 drug-ADR pairs. Recently the database was expanded to included data from Package Inserts of marketed drugs that include the frequency of side effects developed. Unlike our CCT database, SIDER 4 obtained data from European charity organizations, national drug registries and structured product labels provided by the FDA and used Named-Entity Recognition, a dictionary-based approach to curate the data (Kuhn et al., 2016). Unlike data in the CCT database, the authors created a dictionary of ADR and diseases and pooled synonyms using natural language processing methods. In SIDER 4 there has been a 40% increase in data compared to previous versions. It is hoped that the CCT database will be updated annually in such a manner and provide users with access to the most relevant drug cardiac safety studies in a single location.

While there is considerable information available in the literature that assesses the potential cardiotoxic effects of many chemicals and natural products, it remains a very laborious/protracted task to find such literature and, most importantly, evaluate the validity of the study findings based on the standard principles of research used in the conduct

Table 3
Some Key Nonclinical and Clinical Mechanisms Associated with Cardiac Toxicity.

Nonclinical Cardiac Toxicity	Clinical Cardiac Adverse Effects
Apoptosis	Angina
Arrhythmias (Supraventricular/ Ventricular)	Arrhythmias (Supraventricular/Ventricular)
Bradycardia (Type I/II AVB)	Arterial Stenosis
Cardiac Fibrosis	Atherosclerosis
Dromotropy (Positive/Negative)	Bradycardia (Type I/II AVB)
Edema	Cardiac Valve Disorder (Stenosis/ Insufficiency)
Hypertrophy	Cardiac Fibrosis
Heart Failure (HFpEF/HFrEF)	Coronary Artery Disease
Hemorrhage	Edema
Hypertension	Endocardial Disease (Endocarditis/ Fibroelastosis)
Hypotension	Heart Failure (HFpEF/ HFmrEF/HFrEF)
Inflammation (Vascular)	Hypertension
Inotropy (Positive/Negative)	Hypotension
Myocardial Ischemia/Infarction	Inotropy (Positive/Negative)
Necrosis	Myocardial Infarction (STEMI/NSTEMI)
Reactive Oxygen Species	Pericardial Disease (Effusion/Pericarditis/ Tamponade)
Tachycardia	Pulmonary Arterial Hypertension
Valvular (Fibrosis)	Vascular Disease (Arterial/Venous Thrombosis) Vasculitis

Notes
AVB = Atrio-Ventricular Block.
HFmrEF = Heart Failure with Mildly Reduced Ejection Fraction.
HFpEF = Heart Failure with Preserved Ejection Fraction.
HFrEF = Heart Failure with Reduced Ejection Fraction.
NSTEMI (Non-STEMI) = Non-ST-Elevation Myocardial Infarction (a partial block of a coronary artery).
STEMI = ST-Elevation Myocardial Infarction (a complete block of a coronary artery).

of drug safety studies. These important principles include the study design used in the evaluation, data analysis methods, statistical design, and data interpretation. Because of these numerous uncertainties in the published public domain, the curated data in the CCT database should be of use to numerous research scientists.

5. Current limitations of the CCT database

While the database was originally envisioned to assist the HESI Cardiac Safety Committee in their mission to characterize cardiac adverse effects, the authors acknowledge that there are many additional potential uses for this cardiac-related information. The authors encourage suggestions for additional uses and welcome input from the greater scientific community. The CCT Database is not an exhaustive list of all compounds that could be useful tools for investigating cardiac toxicity and HESI will be seeking recommendations for compound additions for future versions of the database. Such recommendations should be submitted to using the fillable from at the end of the database along with at least one supporting reference for the drug and cardiac toxicity that manifests. The database will be updated at least annually, reflecting ongoing continuous drug characterization of cardiac toxicities as novel pharmacological mechanisms related to novel drug modalities are developed. This will provide additional utility to the database to continually monitor safety assessment development of validated novel methods and models that are used to characterize and define cardiotoxicity resulting from drug administration.

The authors recognize that the database is limited in several 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.

6. Future modifications to the CCT database

The CCT database enables drug safety experts to focus on cardiac safety topics by using tools in a database that simplifies the repetitive and tedious literature review. To remain relevant, it would be useful for users to set up alerts when the database is updated by generating a user-friendly interface that can help assist in the organization, assessment and reporting of articles with curated drug safety data. This consideration would be implemented in an updated version of the database.

Recently, concerns around drug-induced changes in blood pressure have grown, in part, due to increased understanding of the importance of sustained changes of even relatively small increases in blood pressure increasing the risk of severe cardiovascular adverse events (Food and Drug Administration, 2022; Lewington et al., 2002; MacMahon et al., 1990). As new data are published molecules that produce drug-associated changes in blood pressure will require a centralized database necessary to compile the critical hemodynamic data. The addition of this valuable information to the CCT database could serve as useful aid to facilitate future studies in order to understand the translation of drug-associated hemodynamic changes from nonclinical to clinical.

Drug-induced cardiotoxicity can occur after either acute (< 24 h) or chronic (weeks to months) exposure. Distinct cardiovascular toxicities may be observed depending upon whether an acute or chronic exposure occurs. These cardiac adverse effects can be functional or structural in nature and can manifest themselves as impairments of cardiac rhythm, contractility, coronary perfusion and valvular function. The CCT database is currently focused on compounds with acute cardiac toxicities, such as changes in hemodynamics and arrhythmias. In some cases, drug-induced cardiotoxicity is observed following chronic exposure, without an immediate observation of structural damage or electrical disturbances, so-called occult cardiotoxicity (Hoffmann & Pugsley, 2024). Therefore, while different nonclinical studies have their own advantages and limitations with respect to identifying and assessing drug-induced cardiotoxicities, the CCT database will be expanded to include chronic toxicological effects that manifest in the heart.

7. Summary

The HESI CCT database provides users with a rigorously developed resource for use in evaluating drugs with distinct mechanisms causing cardiac toxicity. The database is data driven and provides both nonclinical and clinical data that profiles the cardiac toxicity of interest. The 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.

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CRediT authorship contribution statement

Donald De Alwis: Writing – original draft, Validation, Software, Methodology, Data curation. **C. Michael Foley:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization. **Eugene Herman:**

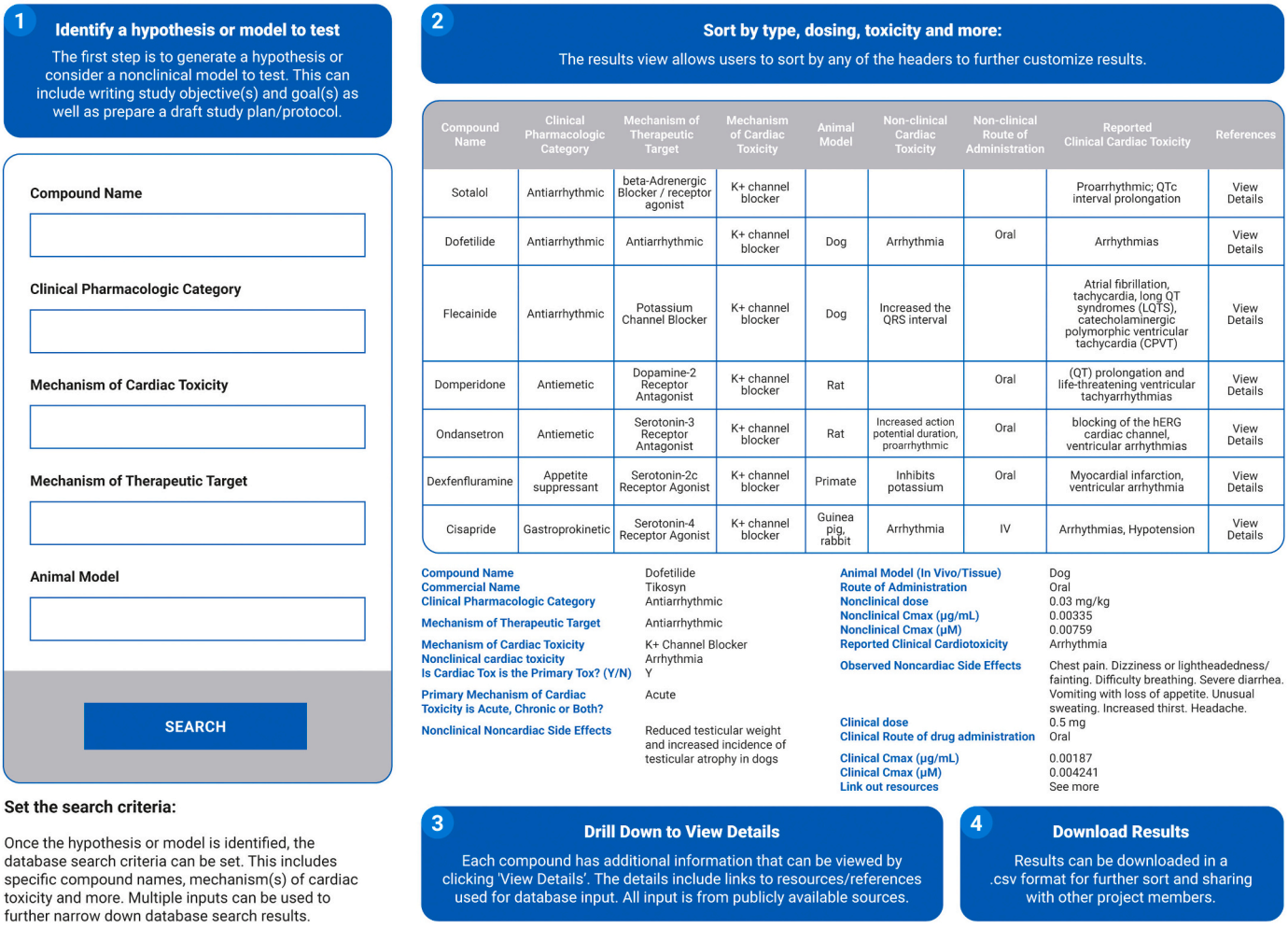

Fig. 3. An outline of a use case example from the CCT database that overviews the data for a cardiac K+ channel blocking drug.
Note. The first step (1) is the identification of a hypothesis or model to test which establishes the search criteria within the CCT database. For this example, a novel potassium channel (K+) blocker is to be investigated in the heart and a search output provides 7 possible positive control compounds for use. The results view (2) allows users to customize the database results. Users can 'View Details' (3) which provides important information on the parameter of interest, i.e., nonclinical and clinical noncardiac side effects as well as toxicokinetic information (i.e., Cmax concentrations). All search findings can be downloaded (4) for further discussion or data analysis.

Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Adam P. Hill:** Writing – review & editing, Validation, Methodology, Data curation, Conceptualization. **Peter K. Hoffmann:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Yasunari Kanda:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Emily Kaushik:** Writing – review & editing, Validation, Methodology, Data curation. **Jennifer Pierson:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Data curation, Conceptualization. **Raechel Puglisi:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Data curation. **Hong Shi:** Writing – review & editing, Validation, Methodology, Data curation. **Xi Yang:** Writing – review & editing, Validation, Methodology, Data curation. **Michael K. Pugsley:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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