Public data sources to support systems toxicology applications

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Abstract
Public databases provide a wealth of freely available information about chemicals, genes, proteins, biological networks, phenotypes, diseases, and exposure science that can be integrated to construct pathways for systems toxicology applications. Relating this disparate information from public repositories, however, can be challenging because databases use a variety of ways to represent, describe, and make available their content. The use of standard vocabularies to annotate key data concepts, however, allows the information to be more easily exchanged and combined for discovery of new findings. We explore some of the many public data sources currently available to support systems toxicology and demonstrate the value of standardizing data to help construct chemical information pathways.

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Keywords
Public database, Systems toxicology, Data standard, Chemical, Gene, Disease.

Introduction

Systems toxicology assembles information into pathways to describe a xenobiotic toxicant interacting with a mediator in a living system to set into motion a series of biological events that ultimately result in an outcome [1]. The toxicant is typically a chemical; the biological mediator can be any type of macromolecule but is often studied as a gene-encoded product (e.g. receptor, transporter, transcription factor, enzyme); the series of biological events can be wide ranging and include alterations in transcripts, protein expression patterns, metabolic pathways, interaction networks, and/or biological processes; and the outcome can be the perturbed biological system trying to return back to a normal state (resilience) or a new, and potentially, adverse state due to toxicity [2]. The toxicant may trigger multiple different pathways simultaneously by interacting with different biological mediators, complicating understanding about the specific connectivity between individual events, mediators, and outcomes. As well, in the real world, humans are typically exposed simultaneously to mixtures of chemicals and drugs, further complicating understanding of toxic mechanisms of actions [3,4].

The goal of systems toxicology is to discern and organize exposure and toxicogenomic events to help formalize an understanding for drug therapy, risk assessment, exposure hazards, and toxicity to humans [5−9]. Creating, testing, and validating systems toxicology pathways *de novo* can be an onerous task because they require information from diverse disciplines and data types, including environmental science, exposure biology, chemistry, structural biology, pharmacokinetics, genomic influences, evolutionary biology, genetic and protein networks, high-throughput data sets (transcriptomics, proteomics, metabolomics, and so on), biological processes, cellular and tissue physiology, phenotypes, diseases, medicine, epidemiology, global health, statistics, and computational modeling, among others. The intricacies of such events make it difficult for any one laboratory on its own to investigate and resolve a complete pathway without leveraging external data resources.

Conveniently, a surfeit of public databases applicable to systems toxicology readily provides information about many of these key interactions and pathway steps. These public data, made freely available and unrestricted to all people in all places at any time, can be leveraged to help generate information frameworks. Combining diverse information from a variety of resources is made easier when public databases use standardized terms, stable accession identifiers (IDs), and cross-reference IDs. Here, we review and explore a variety of public repositories that can be used and applied in the construction of systems toxicology pathways, with comparisons to how this is done at Comparative

Toxicogenomics Database (CTD; http://ctdbase.org/), a public toxicology resource that advances understanding about environmental chemical exposures and their effects on human heath [10,11].

Finding public databases for systems toxicology

The primary literature can be perused to discover the most appropriate public databases for systems toxicology applications. Database: *The Journal of Biological Databases and Curation* (https://academic.oup.com/database) and the annual 'Database issue' of *Nucleic Acids Research* (https://academic.oup.com/nar) are popular journals where articles report new or updates to existing public databases and describe their resource, data standards, content, and features. As well, toxicology review articles are good sources for learning about public databases for systems toxicology applications [2,8,12−18]. In addition to print, researchers can use online catalogs to search for databases relevant to systems toxicology. The *NAR Molecular Biology Database Collection* (http://www.oxfordjournals.org/nar/database/a/), for example, features a categorized list of all the database resources featured in the *Nucleic Acids Research* annual reviews [19], and a search with 'chemical' retrieves over 65 available public repositories. One of the most extensive and comprehensive online catalogs is *FAIRsharing* (https://fairsharing.org/databases/), a manually curated resource of data standards and databases that implement the BioDBcore guidelines for core database descriptors [20,21]. Currently, over 1200 repositories are listed at *FAIRsharing*, and each entry is annotated with subject and knowledge domain tags, allowing users to filter their searches; for example, a basic query with 'chemical' retrieves over 430 public resources, which can be further refined to include domains such as 'protein interaction,' 'phenotype,' and 'disease' to filter for resources geared toward systems toxicology. Searches for taxonomy, related databases, and data standards discover similarly themed and constructed public repositories. The accuracy, reliability, and effectiveness of this community-driven catalog, however, are dependent upon database creators reviewing and updating their entry page at the portal.

We surveyed over a hundred databases from selected articles and websites to identify those that are relevant to systems toxicology. To focus on current and truly public databases, we eliminated repositories that had since been decommissioned or now required a paid subscription, creation of a login account, licensing agreement, or software download and installation. In Supplemental Table 1, we provide a detailed matrix of these public databases with a short description, an updated hyperlink, a citation article, and nine sortable data fields applicable to systems toxicology: exposure information, chemical data (including drugs), gene data

(including proteins, mRNA, and so on), chemical−gene interactions, protein−protein interactions, pathway/network data, phenotypes/diseases, anatomy, and human population−level information.

Leveraging public data
Data standards, terms, and accession IDs

An important quality of any good public databases is the practice of defining the data object with a primary term and a stable accession ID, and then supplementing the primary term with a list of synonyms, abbreviations, and cross-reference accession IDs for the same data object in other public databases [22]. Use of controlled vocabularies and ontologies to represent and annotate data is critical, and many vocabularies exist for a wide variety of biological topics and are freely available for use at the OBO Foundry [23]. Choosing the most appropriate vocabulary for a biocuration initiative can be challenging; considerations include whether a particular vocabulary or ontology adequately addresses the specific content with respect to both breadth and depth for the resource's goal. The stable accession ID allows information to be easily stored, identified, and exchanged with other databases. Database cross-reference links collate the same terms from various controlled vocabularies and act as a Rosetta stone to translate and unambiguously resolve terms and accession IDs from different vocabularies to the same biological concept. Using shared data standards, terms, and accession IDs helps disparate databases speak the same language and enables their content to adhere to the FAIR principle, allowing information to be Findable, Accessible, Interoperable, and Reusable [24], which in turn increases the value of the data by making it a more readily shareable asset [25].

The scientific literature

One of the most resourceful and ubiquitous data standards in public databases is the PubMed identifier (PMID), a short numerical accession ID to represent a published scientific document. PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) is a user-friendly portal developed by the National Center for Biotechnology Information (NCBI) that assigns a unique PMID to over 28 million citations in life sciences, medicine, molecular biology, behavioral sciences, and chemistry [26]. The PMID simplifies the process of describing and communicating complex article citations and allows other public databases to associate their curated content to original source articles, providing both traceability and interoperability for bioinformatics analysis. Most scientific abstracts at PubMed are additionally indexed using Medical Subject Headings (MESH), an exhaustive, wide-ranging thesaurus of controlled terms that tag scientific documents with descriptors summarizing the principle concepts addressed in research articles [27]. MESH terms cover a vast knowledge landscape with over 275,000 terms arranged in hierarchical tree

branches (https://meshb.nlm.nih.gov/treeView), several of which are highly relevant to systems toxicology, including 'Chemicals and Drugs,' 'Phenomena and Processes,' 'Anatomy,' and 'Diseases'. Importantly, MESH terms also have unique accession IDs (MESH:ID). Thus, a corpus of scientific articles can be represented as a series of PMIDs, with each PMID associated with a set of MESH:IDs indexing the content of each article. Compiling PMIDs that maximize the number of shared MESH:IDs efficiently organizes articles related to each other, allowing the literature to be triaged and meta-analyzed; for example, in a subset of documents, if one chemical MESH term consistently co-occurs with another chemical MESH term, then there is a potential relationship between the two toxicants [28].

Comparing and integrating data types relevant to systems toxicology

Other types of data, beyond article information, are represented in repositories integrating various types of vocabularies, ontologies, terms, and accession IDs. As evaluated in Supplemental Table 1, four of the key concepts in systems toxicology include chemicals (toxicant), gene-encoded products (typically, biological mediators that interact with the toxicant), phenotypes (i.e. induced events before the clinical manifestation of a disease), and diseases (toxic outcomes of a systems toxicology pathway).

We compared the data standards (primary terms, accession IDs, and cross-referencing IDs) used to annotate and represent these four concepts from six databases with content highly relevant to systems toxicology: CTD [10]; PharmGKB, a pharmacogenomics knowledge base of genetic variants and drug responsiveness [29]; DrugBank, a drug therapeutic target resource [30]; the human metabolome database (HMDB) [31]; Reactome, a pathways database [32]; and the Monarch Initiative, a multispecies, semantically integrated genotype–phenotype platform [33]. The data standards used to curate and report information for

Figure 1
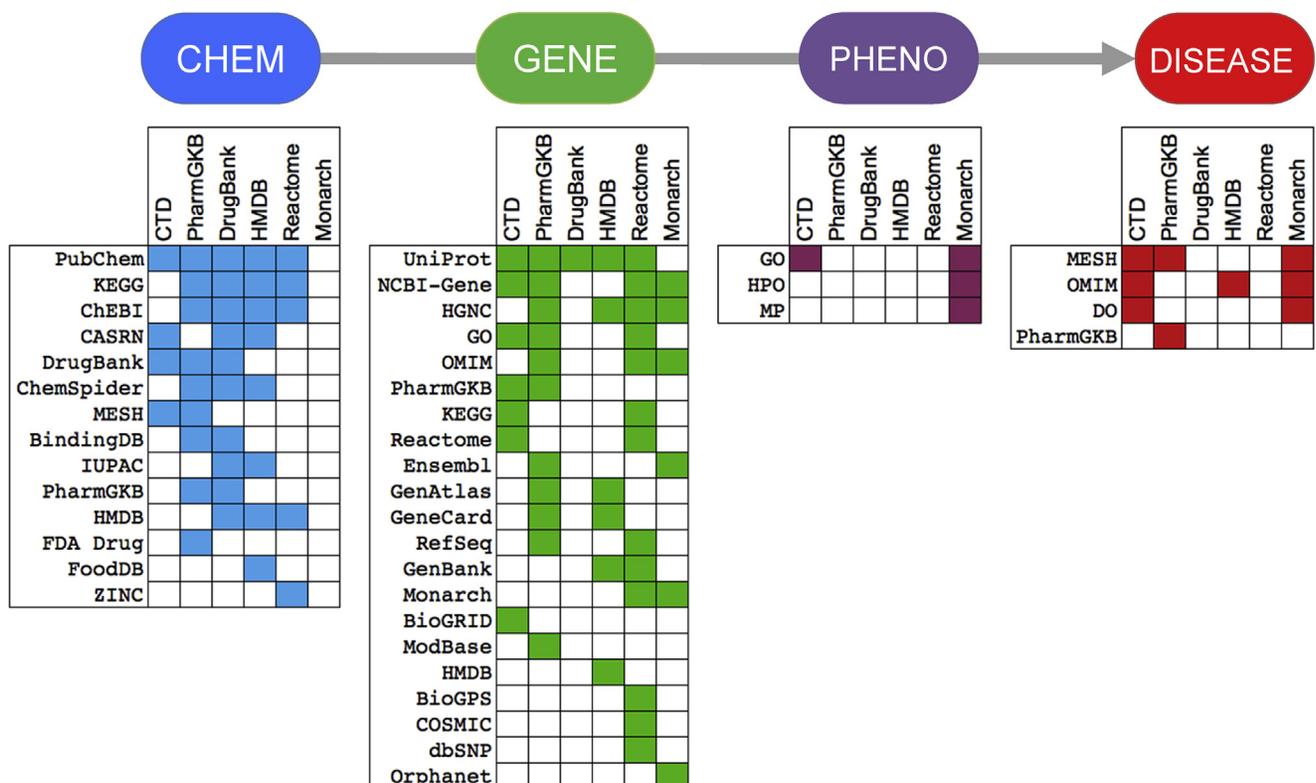
Four key components of a systems toxicology pathway include the toxicant chemical (CHEM), the interacting biological mediator (GENE), a series of predisease events (PHENO), and an adverse outcome (DISEASE). The data standards (identifying and/or cross-referencing terms and accession IDs) used by six top public resources for each key component are listed, and shared data types between the resources are highlighted by color in each grid. For example, PubChem, CASRN, and ChEBI terms/IDs are frequently used to depict chemical data at multiple public resources (blue blocks), while UniProt and NCBI Gene terms/IDs are used for genes (green blocks), and so on. This shared use of common data standards allows seemingly disparate databases to combine information. For simplicity, not all the data standards from all six resources are shown. Data standards listed in the grids are described in Supplemental Table 1. CASRN, Chemical Abstracts Service Registry Number; ChEBI, Chemical Entities of Biological Interest; NCBI, National Center for Biotechnology Information; CTD, Comparative Toxicogenomics Database; HMDB, human metabolome database; IDs, identifiers, MESH, Medical Subject Headings; GO, Gene Ontology; DO, Disease Ontology.

these four components vary greatly from database to database (Figure 1). Many resources create their own database-specific accession ID but also associate their content with cross-referencing accession IDs. Cross-referencing accession IDs facilitate data harmonization and interoperability. For example, at HMDB, the chemical arsenic trioxide has a unique accession ID (HMDB:0015300) but is also annotated with a Chemical Abstracts Service Registry Number (CASRN:1327-53-3) that in turn can be used to find arsenic trioxide at CTD, which is also represented by a unique MESH accession ID (MESH:D000077237).

Due to their different scientific objectives, these public databases do not necessarily have information pertaining to all four key components; some (e.g. Monarch) do not contain chemical data, while others (e.g. DrugBank, HMDB, Reactome) invoke phenotype and disease information but in a free-text format which limits computational possibilities. However, by combining and integrating data from disparate public resource, these public database groups have the opportunity to glean new information and fill in 'knowledge gaps'. For instance, while the Monarch database does not contain direct chemical information, it does share data standards for gene, phenotype, and disease information with CTD. Leveraging those shared connections allows CTD chemical information to be brought into the Monarch framework (Figure 2). Thus, in Monarch, the human

gene HMOX1 (NCBIGene:3162) is associated with five phenotypes and 26 diseases, while in CTD, human HMOX1 (NCBIGene:3162) is associated with 13 phenotypes, 63 diseases, and directly interacts with 628 chemicals that affect the expression, activity, localization, mRNA stability, ubiquitination, and DNA methylation of HMXO1 products. By integrating the content from both databases, potentially new combinations of chemical–phenotype and chemical–disease connections are discovered at both resources. Similarly, CTD phenotype and disease data can be brought into DrugBank by shared gene data standards, and new chemical–gene interactions can be expanded at both repositories (Figure 2). Integrating and harmonizing data across different platforms facilitates discovery of new connections at each individual resource and accommodates the rapid construction and expansion of potential systems toxicology pathways.

Integrating CTD public data to make systems toxicology pathways

Since 2004, CTD has leveraged the use of in-house curated content and public data integration to make numerous types of novel, putative discoveries [34]. CTD uses professional biocurators [35] to read the toxicology literature and manually curate chemical-gene-phenotype-disease-exposure interactions in a structured format using standardized, controlled vocabularies, ontologies, and accession IDs (e.g. Figure 1)

Figure 2
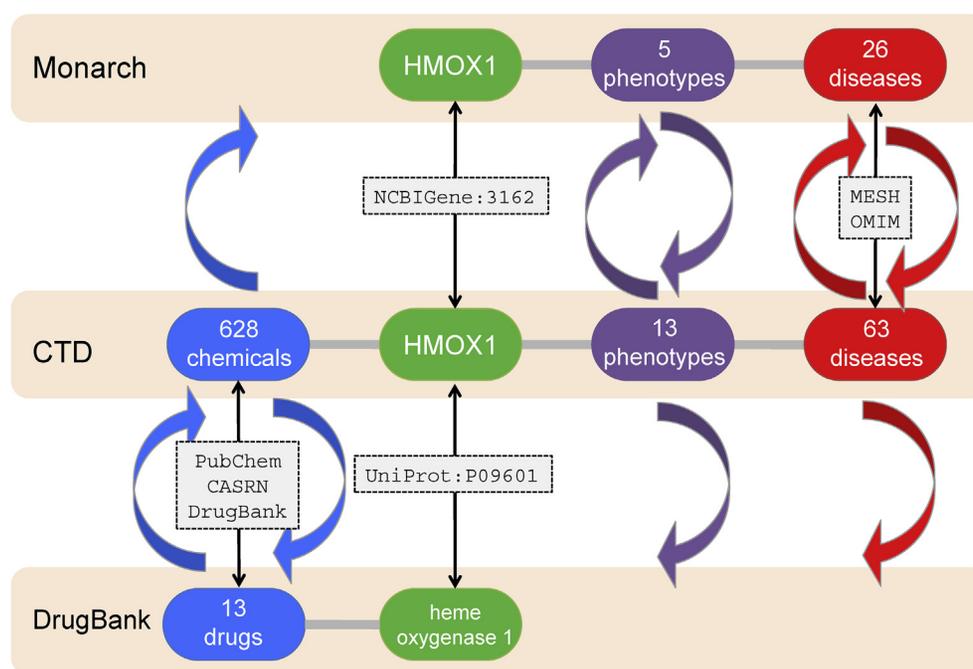
Shared data standards for the human gene HMOX1 (NCBIGene:3162 and UniProt:P09601) between three different public resources (Monarch, CTD, and DrugBank) allow novel chemical (blue arrows), phenotype (purple arrows), and disease (red arrows) information to be integrated and brought into each repository, expanding knowledge at each individual resource, as well as expanding and improving systems toxicology pathways. CTD, Comparative Toxicogenomics Database; CASRN, Chemical Abstracts Service Registry Number; MESH, Medical Subject Headings.

adapted from other public databases [36]. This curation process has resolved and harmonized a tremendous amount of diverse, disparate data from more than 130,000 scientific articles published in over 4850 different journals, going as far back as 1946, and making all of the information traceable, interoperable, and cohesive for developing testable hypotheses [37]. In total, CTD biocurators have used common data standards to annotate contextualized toxicological relationships for 1.8 million chemical−gene, 182,000 chemical−phenotype, 213,000 chemical−disease, and 38,100 gene−disease interactions for over 15,800 chemicals, 47,100 genes, 4600 phenotypes, 7100 diseases, 590 different species, and 810 anatomical sites (http://ctdbase.org/about/dataStatus.go), all publicly available to any user.

CTD direct interactions, in turn, are integrated to generate inferred relationships supportive of systems toxicology: if chemical C1 interacts with gene G1 (C1-G1), and independently gene G1 is associated with disease D1 (G1-D1), then chemical C1 can be said to have an inferred relationship to disease D1 via gene G1 (C1-G1-D1) [38]. Similarly, phenotype P1 can be inferred to disease D1 (P1-C1-D1) if chemical C1 has a directly curated relationship with each [39]. Common data nodes allow binary relationships to be linked together, and simple linear pathways emerge: C1-G1-P1-D1. When additional curated relationships are added for chemical 1 (C1) with other genes (G2, G3) and phenotypes (P2, P3), more complex and interconnecting systems toxicology pathways can be constructed (Figure 3). Additionally at CTD, these data are integrated with real-world environmental exposure and human biomarker measurements [11,40], connecting laboratory experimental data with human population-level results. These computationally generated predictive adverse outcome pathways assemble and organize intricate information for biologically plausible pathways [41]. Toward that end, CTD content has been

Figure 3
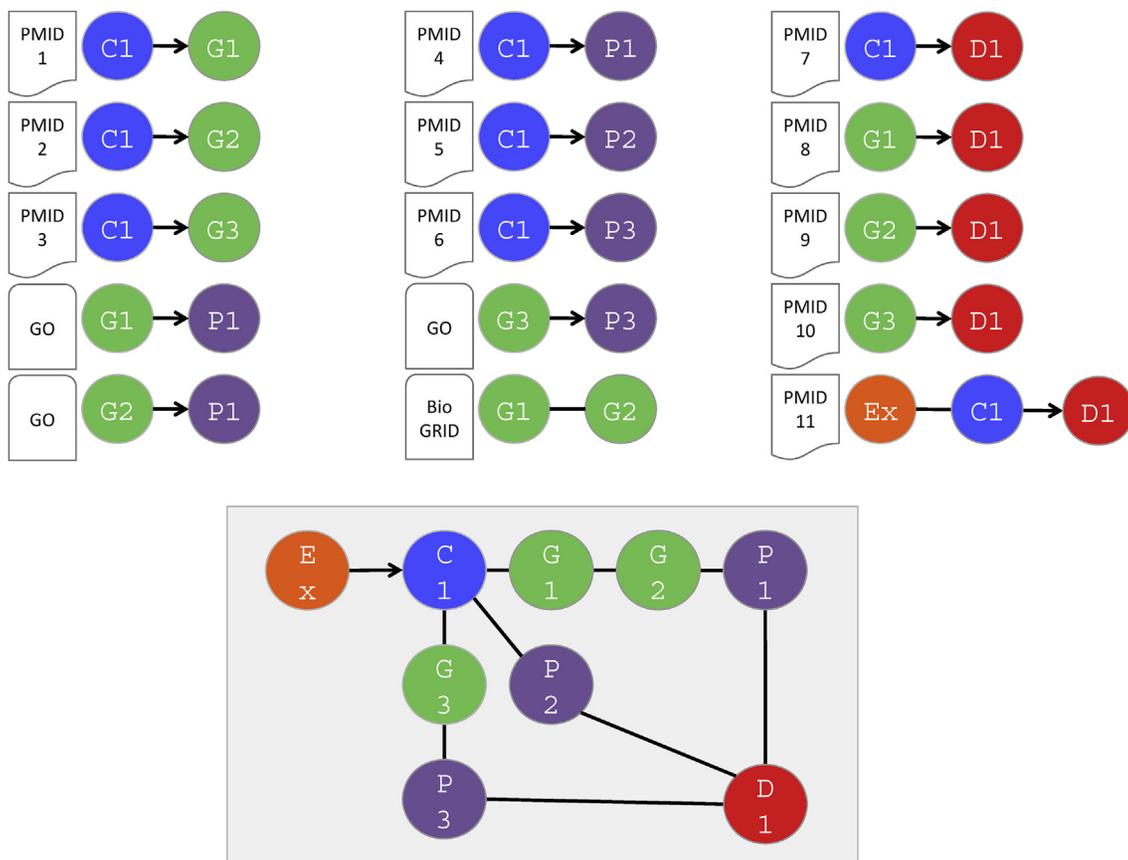
Integrating data from various public resources helps construct information pathways for systems toxicology. CTD manually curates the toxicology literature (PMID1-11) to capture contextualized relationships between chemicals (C1, blue), genes (G1-3, green), biological process phenotypes (P1-3, purple), diseases (D1, red), and exposure events (Ex, orange). As well, CTD imports Gene Ontology (GO) data (connecting genes to biological process phenotypes) and BioGRID data (for gene−gene interactions) from other public databases (Supplemental Table 1). Integrating these independent data modules generates a potential systems toxicology pathway (bottom box), linking an initial exposure event to a toxicant−mediator interaction, connecting genes and phenotypes, and resulting in a disease. Common accession terms and shared data standards allow systems toxicology pathways to be generated programmatically.

integrated in several recent independent bioinformatics studies to generate predictive systems toxicology pathways for pesticide-associated reproductive disorders [15], cadmium-induced neurological phenotypes related to Alzheimer disease [39], arsenic-induced alterations in glucose phenotypes preceding diabetes [39], AHR gene networks connected to glaucoma [42], piperonyl butoxide–induced pathway modulations associated with liver cirrhosis [43], chemical-induced androgen receptor activation leading to infertility [44], and lead exposure disrupting cortical plasticity in neurodevelopment [45], among others.

Evaluating other public data standards
CTD's approach
Ultimately, data exchange between different resources for systems toxicology applications could be even more seamless if all public databases used the same standards and vocabularies. To keep abreast of data standards, CTD frequently reviews available ontologies and controlled vocabularies used by other public resources, determining their suitability for migration from our existing curation. For example, CTD's initial phenotype-related curation was completed as part of a CTD–Pfizer collaboration [46] and used terms from the 'Phenomena and Process' branch of MESH; new and existing phenotype curation was later migrated to terms in the Gene Ontology [47] to enable biocurators to more accurately represent the outcomes reported in the toxicology literature and improve interoperability with other external data sets [39]. Other vocabularies that CTD is very interested in monitoring and potentially migrating to include the Disease Ontology [48] and Monarch Disease Ontology [33] for disease content and Chemical Entities of Biological Interest [49] for chemical terms.

To aid in this analysis, CTD developed an in-house tool called the Computational Vocabulary Evaluation Tool (CVET) to computationally evaluate proposed vocabularies. When contemplating converting to a new vocabulary, the most important question is how would it affect existing CTD curation? Consequently, rather than evaluating complete vocabularies against one another, the tool focuses on existing curation coverage, that is, what percentage of CTD existing curation would be lost due to conversion? CVET uses an algorithm to evaluate each curated term. First, does the proposed vocabulary provide a direct cross-reference accession ID to the curated term? This is considered by CTD as the most effective means of resolving a term because it is essentially the vocabulary provider unambiguously mapping their term to another vocabulary. Next, CVET runs through a series of comparisons looking to see if there is a term in the proposed vocabulary that directly matches the CTD curated term (term–term), a synonym in the proposed vocabulary that directly matches the CTD

curated term (synonym-term), a term in the proposed vocabulary that directly matches a synonym for the CTD curated term (term-synonym), or a synonym in the proposed vocabulary that directly matches a synonym for the CTD curated term (synonym–synonym). As imagined, attempting to match terms across controlled vocabularies can be complicated. Even using clear, unambiguous cross-references computationally can yield results that must be manually reconciled. Consequently, CTD biocurators manually determine the appropriate mapping, in some cases referencing the source material to identify the term that most closely reflects the authors' intent on the basis of the context in which it was used. Using CVET, CTD currently is able to achieve a 53% curated chemical term match to Chemical Entities of Biological Interest, a 62% curated disease term match to Disease Ontology, and an 88% curated disease term match rate to Monarch Disease Ontology. CTD will continue to periodically monitor and evaluate these and other promising vocabularies to improve our content for systems toxicology applications.

Acknowledgements

Conflicts of interest statement
Nothing declared.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.cotox.2019.03.002.

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