Building Bridges Between Toxicity Testing in the 21st Century and Regulatory Decision-making Through Interactive Web Applications

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Abstract

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Building Bridges Between Toxicity Testing in the 21$^{st}$ Century and Regulatory Decision-making Through Interactive Web Applications (Under the direction of Matthew Martin and Ivan Rusyn)

Risk assessments and regulations are informed largely from animal studies, which are low throughput, costly, and time consuming. Gathering toxicity data for decisions on the large number of chemicals manufactured and used in commerce is a difficult task for current goals in chemical testing and safety decisions. Alternative approaches include computer models informed by existing toxicity data and computational toxicology like high throughput screening (HTS). Aggregating the large quantity of data produced through alternative methods is a difficult task with large gaps between the analysis and interpretation. The United States Environmental Protection Agency's (USEPA) Interactive Chemical Safety for Sustainability (iCSS) Dashboard project seeks to close the gap by enabling stakeholders, including decision-makers, to easily access and visualize computational toxicology data from USEPA's Toxicity Forecaster (ToxCast) project. The iCSS Dashboard is a web application that allows users to subset both HTS assays and chemicals to a manageable set for clearer visualization of the data, so the data is more accessible for understanding how computational toxicology can be applied to meet current goals in toxicity testing, screening, and risk assessments for chemical safety decision-making.

**Acknowledgements and Dedication**

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**Chapter 1 Literature Review of Computational Toxicology**

**Purpose**

Current risk assessments and regulatory decisions are based largely on toxicity data from clinical trials, epidemiological studies, and animal studies (Demchuk et al., 2008; Houck & Kavlock, 2008). Human data from clinical trials and epidemiological studies are most relevant to humans, but are low throughput and do not provide insight on the mechanisms underlying toxicity (Cogliano et al., 2008). While animal studies are amenable to higher throughput, extrapolation to humans can confound results and leaves a degree of uncertainty (Demchuk et al., 2008; Houck & Kavlock, 2008).

With large numbers of chemicals being manufactured each year and limited existing toxicity data, current approaches are not meeting the requirements for data to support informed decision-making. With current advances in alternative models both *in vitro* and *in silico* provide novel avenues for estimating toxicity (Gibb, 2008).

Computational approaches to toxicology provide a method to fill data gaps by developing computer models to predict the toxicity of new chemicals (Rusyn & Daston, 2010). Computational approaches have a significant impact on decision-making and decision support for toxicity of chemicals due to the inherent scalability from higher-throughput methods. Computational approaches produce a large amount of data in relatively short amounts of time. The high-throughput achieved with *in silico* approaches provides more information and can even be used to identify possible mechanisms of

toxicity (Collins, Gray, & Bucher, 2008; Demchuk et al., 2008; Dix et al., 2007; Gibb, 2008; Houck & Kavlock, 2008). Computational approaches

combine chemical information including physico-chemical and structural properties with *in vivo* and *in vitro* data, when available (Rusyn & Daston, 2010). For example, results from previous and ongoing traditional approaches, *in vitro* high-throughput screening (HTS) biochemical assays, and ultra high-throughput data from microarrays can be incorporated into computational approaches. Finally, existing computer models like chemical docking can also be incorporated to produce predictive toxicity models for preliminary decision-making and toxicity analysis of existing and unknown chemicals (Kirchmair et al., 2012).


**Data Sources**

**Aggregated Computational Toxicity Reference (ACToR)**

The Aggregated Computational Toxicity Reference (ACToR) is a United States Environmental Protection Agency (USEPA) project that includes databases and tools to access and analyze toxicity data. The ACToR project includes the ACToR database, Toxicity Reference database (ToxRefDB), and Toxicity Forecaster database (ToxCastDB) accessible through a web interface accessible at http://www.actor.epa.gov. The ACToR database a relational database adapted from the PubChem project where assay space and chemical space are linked through data. Currently data for over 500,000 chemicals from over 500 data sources resides in ACToR (R. S. Judson et al., 2012).

ToxCastDB, a subset of ACToR, contains data outputs from USEPAs Toxicity Forecaster (ToxCast) project (R. S. Judson et al., 2012). ToxCast captures HTS data to

produce a predictive model for prioritization of chemicals based on aggregated performance across the assays (Dix et al., 2007; Kavlock, Austin, & Tice, 2009; Rusyn & Daston, 2010). ToxCast currently consists of two phases of testing comprising over 1800 chemicals run across over 800 HTS assays ("EPA Releases Chemical Screening Data on 1,800 Chemicals/Agency improves access to chemical data and announces ToxCast Data Challenges," 2013). All of the ToxCast chemicals, assays and data are stored in ToxCastDB.

ToxRefDB, which is another subset of ACToR database (R. S. Judson et al., 2012), contains data from guideline *in vivo* studies incorporating data from sub chronic, chronic, developmental, and reproductive toxicity studies as well as cancer bioassays from rats, mice, and rabbits. ToxRefDB is used to supplement Toxicity Forecaster (ToxCast) project for validation and generate hypotheses for proposed mechanisms of toxicity (Martin, Judson, Reif, Kavlock, & Dix, 2009).

**Comparative Toxicogenomics Database (CTD)**

The Comparative Toxicogenomics Database (CTD) contains literature linking chemicals to gene and protein interactions. The interactions are also linked to corresponding disease outcomes creating a network of literature mapping chemicals to genes and genes to diseases. The literature is manually entered into the database so literature supporting each relationship is clearly defined. CTD functions as a hypothesis-generating tool focusing on environmental chemicals and their relationship to diseases (Davis et al., 2013; Davis et al., 2009; Mattingly, 2009).

**Carcinogenicity Potency Database (CPDB)**

The Carcinogenicity Potency Database (CPDB) is a collection of positive and

negative chronic cancer studies ranging back to the 1950s. CPDB serves as a uniform resource to locate and compare results from a multitude of studies on over 1050 chemicals. The aggregation of data in CPDB enables reporting of qualitative and quantitative information about the experiment, carcinogenic chemical ratios, associations between carcinogenic potency, and predictions of carcinogenicity in target organs across different species (Gold, Manley, Slone, Rohrbach, & Garfinkel, 2005; Gold et al., 1991).

**Chemical Effects in Biological Systems (CEBS)**

The Chemical Effects in Biological Systems (CEBS) database integrates toxicogenomics and proteomics data with gross observations, clinical chemistry, and other measurements from experiments in animals, cell cultures, and humans. Currently data for over 27 studies is available for search through the CEBS web interface, accessible at http://www.niehs.nih.gov/research/resources/databases/cebs/, either by study conditions or subject responses with a goal of viewing integrated data to hypothesize mechanisms associated with the observed biological responses (Waters et al., 2008).

**Distributed Structure-Searchable Toxicity (DSSTox)**

The Distributed Structure-Searchable Toxicity (DSSTox) database aggregates chemical structure data with toxic effects. Chemical structure data can be used in structure activity relationship (SAR) models to predict chemical toxicity. DSSTox serves as a central resource for this type of information to improve upon current SAR models and to incorporate chemical structure information into other predictive toxicity models (Richard & Williams, 2002).

**Models and Use of Computational Toxicology**

Computational toxicology has been used in many fields for predictive modeling and to supplement and support traditional toxicology findings. Within drug development, HTS has been used to discover chemicals best suited to treat a previously identified target where many different compounds are run against the same assay (Houck & Kavlock, 2008). Use of HTS assays for regulatory toxicity aims to discover or test known toxicity targets against chemicals in use (Gibb, 2008). HTS provides important mechanistic data to support postulated modes of action (MOA) (Houck & Kavlock, 2008; Rusyn & Daston, 2010) and molecular initiating events (MIE) to map out adverse outcome pathways (AOP). Below are summaries on models informed by computational toxicology including the USEPA's ToxCast project and Toxicity Testing in the 21st Century (Tox21) that have provided HTS data on numerous chemicals of interest.

**Toxicity Forecaster (ToxCast) and Toxicity Testing in the 21st Century (Tox21)**

The USEPA's ToxCast project has now released two phases of HTS data on over 1800 chemicals and over 800 assays providing chemical performance across assays at multiple concentrations ("EPA Releases Chemical Screening Data on 1,800 Chemicals/Agency improves access to chemical data and announces ToxCast Data Challenges," 2013). The data is analyzed and fitted to a concentration-response four-parameter hill curve where the chemical is either active or inactive based on the ability to fit a hill curve. To relay relative potency, concentration at half the maximum response ($AC_{50}$) is reported. For a single chemical, different assays can be grouped together based on target pathway and weighted scoring for an overall toxicity prioritization index

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(ToxPi) score can be calculated. Chemicals can then be prioritized based on ToxPi scores (Reif et al., 2013). Tox21 efforts are similar, but the chemical library is much larger consisting of over 10,000 chemicals across around 100 HTS assays (Gibb, 2008). For screening and regulatory purposes, toxicity of new chemicals can be predicted by using ToxCast and Tox21 data with QSAR and other structure related models (R. Judson et al., 2013).

**Quantitative Structure Activity Relationship (QSAR) and Read-Across**

Quantitative Structure Activity Relationship (QSAR) modeling uses congeneric chemicals to quantitatively predict properties and the biochemical activity of chemicals. Chemical analogs can be grouped together to highlight trends in similar qualitative and quantitative properties, even predicted properties from QSAR. The QSAR models associating one or many chemicals to certain toxic endpoints can be extended to assume the biochemical activity of a chemical with no toxicity data, this approach is called read-across. A chemical with no known bioactivity can have predicted properties based on structure relationships to chemicals with a wealth of toxicity data. The chemical properties can be used to match a group of analogs, such that the analogs have certain toxic endpoints therefore inferring unknown chemical has the same toxic endpoints (Barratt, 2003; Cherkasov et al., 2014; Patlewicz et al., 2013; Tropsha, 2012).

**Physiologically-Based Pharmacokinetic (PBPK) Models**

Physiologically-Based Pharmacokinetic (PBPK) models are compartmental models that attempt to predict adsorption, distribution, metabolism, and excretion (ADME) of chemicals from each of the compartments (or organs) of interest. PBPK models are used for the development of pharmaceuticals. PBPK models have also been

used in risk assessment and exposure models. Data from computational approaches can be used to develop and refine PBPK models and support different AOPs by defining specific MOA and MIE ultimately mapping to larger biological responses and disease. PBPK models are used in regulatory toxicology for predicting safe levels of exposure, and understanding metabolism and distribution of chemicals in living organisms (Andersen, 2003).

**Threshold of Toxicological Concern (TTC)**

Thresholds of Toxicological Concern (TTC) were originally developed in the 1980's by the United States Food and Drug Administration (FDA) to establish safe levels of exposure to chemicals found in food products that have little to no toxicity data available. The TTC approach requires the unknown chemical's structure to find analogs and determine safe exposure levels based on the analogs' available toxicity data and the intake level of the unknown chemical. TTC is similar to read-across except outputs from TTC are generated through a decision tree that asks questions about the properties and exposure of each chemical. The output of the decision tree can be a toxicity endpoint along with a threshold, or require further information before any type of decision can be made (Kroes, Kleiner, & Renwick, 2005; Munro, Renwick, & Danielewska-Nikiel, 2008). Since the development and use of TTC in food products, TTC models are being developed and considered for use in risk assessments of environmental chemicals (Dewhurst & Renwick, 2013).

**Challenges**

Although computational approaches to toxicology solve problems of throughput and time efficiency, the data needs even further extrapolation to humans than animal studies. Animal studies have been, and continue to be, instrumental in the discovery of disease targets, toxic endpoints, and reference doses for risk assessments. However, animals are not always sufficient to provide data relevant to humans (Ennever & Lave, 2003). Mechanistic data from *in vitro* studies and computer models face the same criticism due to an even higher level of extrapolation from a single molecule, cell, or culture to a larger biological response or disease.

A wealth of data is being produced, and advanced statistical methods are available for analyzing the large datasets. The large uncertainty inherently associated with HTS due to the nature of reporting and result interpretation remains a challenge for the use of these data. Ultimately, the combination of human, animal, HTS, and computational data is extremely powerful.

Computational approaches to toxicology produce a wealth of heterogeneous data related to existing data across multiple disciplines. Proper access, storage, and management of the data are essential for analysis and incorporation into the approaches mentioned above. Currently, no one source of toxicity data exists due to the difficultly in developing and managing a data model to effectively capture and manage the large quantity of data along with the complex relationships between the data.

**Current Work**

  The Chemical Safety for Sustainability (CSS) project is an interdivisional project at the USEPA aiming to improve how chemicals are evaluated. The Interactive Chemical Safety for Sustainability (iCSS) Dashboard is a web application that serves as a portal to access USEPAs ToxCast data. iCSS is currently a beta release providing access to all assay information including descriptions as well as chemical information and the summary hit calls of all chemicals across all the assays. The goal of iCSS is to facilitate the communication between scientists and regulators by creating an easier way to interact and visualize the data for interpretation.

**Chapter 2 Introduction: Bridging the Gap**

Computational toxicology approaches are not traditionally used for decision-making due to the gap between analysis and interpretation of data for regulatory purposes. Through the CSS project, many efforts are being made to develop new models and incorporate computational data into existing models for decision support and new screening processes. A key goal of the project is to facilitate communication between different fields so that bridging the gap in understanding between different sources of data is easier. The Interactive Chemical Safety for Sustainability (iCSS) Dashboard project is key to achieving the CSS goals by providing a portal for easier access to data from the ToxCast project as well as tools to aid in understanding the analysis for interpretation.

Feedback obtained from ongoing discussions with USEPA program offices and stakeholders, including decision-makers, about ToxCast is consistent: the data is difficult to understand due to the quantity of data, lack of descriptions surrounding the assays, and lack of explanations and examples of how to interpret the results. iCSS addresses feedback by providing an interactive web application with modes allowing users to subset assays and chemicals independently based on descriptions surrounding each assay and chemical for a more manageable data set. The performance of each chemical across an assay is summarized into a single summary activity call. All the data supporting the activity call is not reported through iCSS but is available in the data files. Only reporting the summary activity calls dramatically reduces the amount of data a user must mine.

Interpretation of the data solely from the beta release is difficult because the Prioritization mode is not yet implemented. Ultimately, incorporating Toxicological Priority Index (ToxPi) into iCSS will allow aggregation of assays, so performance of a chemical across subsets of assays can be scored and compared for ranking. Ultimately, with continued development, iCSS will provide users a way to logically navigate large sets of data to gain insight into toxicity mechanisms of chemicals.

**Chapter 3 Materials and Methods**

**Dataset**

The dataset for the beta release of iCSS is from the most recent release of ToxCast that includes 1858 chemicals and 821 assays. The chemicals are from ToxCast phases I and II and e1k. A custom database, iCSSDB, was created to meet the specific needs of the application. Summary hit calls including tested and modeled responses each as individual coordinate pairs; concentration at 50% maximum response (AC50); concentration at the maximum response ($E_{max}$); and hill curve parameters, bottom of curve (B), top of curve (T), and slope of curve (W) are accessible through iCSS. The assay descriptions are from ToxCast Assay Annotation, an ontology surrounding the ToxCast assays and adapted from BioAssay Ontology (Phuong, 2014). Figure 1 is an example of the hierarchy used in ToxCast Assay Annotation to describe an assay and link a specific assay endpoint to a summary hit call. The chemical descriptors consist of general properties surrounding each chemical adapted from data in DSSTox. No documentation is currently accessible through the application for each assay annotation and chemical descriptor.

The iCSSDB is a MySQL relational database. Separate tables for chemicals and assays with a one-to-many relationship link to tables with descriptors: assay selection parameters and chemical selection parameters. An aggregate table with a chemical and assay pair linked to the summary hit calls, tested responses, modeled responses, and hill

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curve fits. The database is a MyISAM storage engine, so there's no foreign key links or transaction safety. The public facing database is read only. The data is accessible through the web application or through the 5 data services described in Table 1.

**Figure 1** Assay, Assay Component, Assay Endpoint Example from ToxCast Assay
Annotation
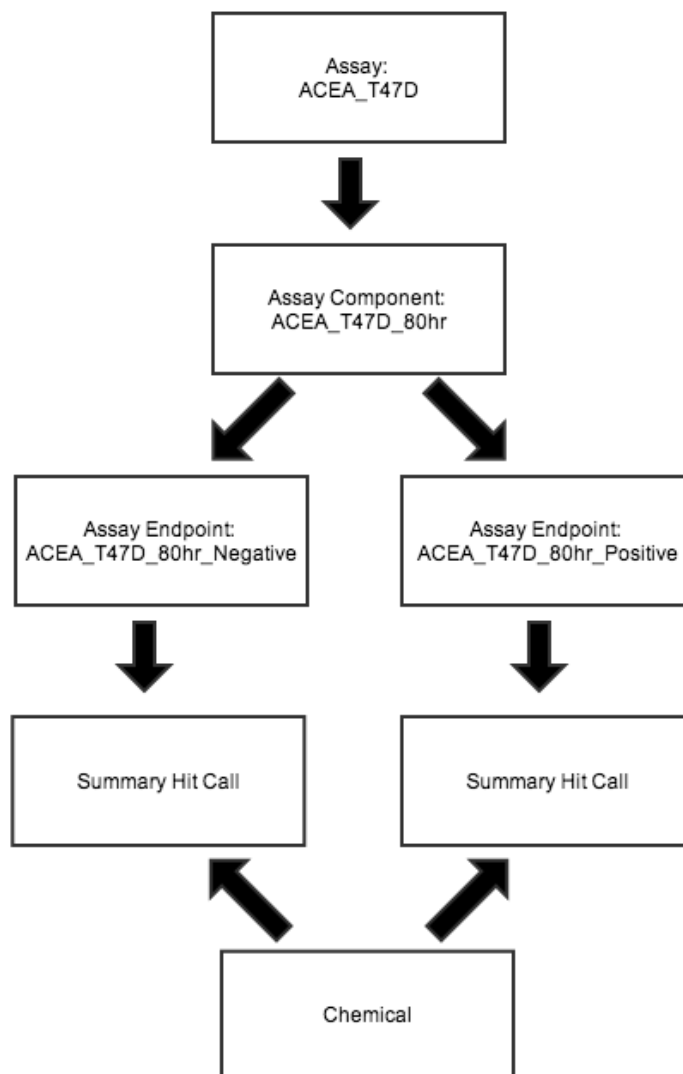


**Figure 1: Assay, Assay Component, Assay Endpoint Example from ToxCast Assay Annotation**

This figure describes the hierarchy to represent the ToxCast assays with an assay as the

most generic descriptor to an assay component to an assay endpoint. An assay can have

one to many assay components; an assay component can have one to two assay

endpoints; and each assay endpoint and chemical has a summary hit call.

**Frameworks**

Sencha's Ext JS 4.2.x is JavaScript-based framework used to develop the front-end client. Ext JS 4.2.x provides standards for developing an application supporting a model view controller (MVC) architecture. MVC is a common architecture used for development of many different applications. Conceptually, the model is the data to be displayed through a view, and controllers that keep the model and views synchronized by managing interactions by the user through the view. More details about the MVC architecture specific to the front end are provided below in the first Architecture section and generically represented in Figure 3-A.

Zendframework 2.0 is a php framework that also utilizes MVC architecture. The middle-ware that brokers information from the backend database to the client via data services (Table 1) is provided through Zendframework 2.0. The data model is abstracted through an object relational mapper (ORM), and business logic is applied to the corresponding objects for efficient representation on the client.

**Architecture**

**Front-End**

The major base classes in Ext JS 4.2.x are Model, Store, Proxy, Component and Controller. The Model class stores one piece of data like a single assay or single chemical. Figure 2 provides an example of a model for an Assay Endpoint. A Store is a collection of Models and has built-in methods for manipulation of the Models within the Store like sort. Using master/slave communication, Models from the master Stores can be subset into slave Stores. Master/slave communication is a conceptual design where a

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master object serves as the authoritative source and manages all aspects of corresponding slave objects. For example, the master Chemical Store has information for all 1858 chemicals, but chemicals can be excluded from viewing forming a smaller subset of chemicals. A slave Chemical Store is created that only contains Models for the smaller subset of chemicals. The client only interacts directly with the view that has the slave store registered with it. As decisions are made for subsets of chemicals, the changes are first written to the master Store then the slave store is subsequently reloaded with the changes.

A Proxy manages how a Store is loaded with Models. Within the context of iCSS, the Proxy loads Models from locally stored data. Asynchronous JavaScript and XML (AJAX) calls are made by the Ext JS global AJAX method to data services, and the JavaScript Object Notation (JSON) response is stored locally within an object that is read into the store through custom load methods.

The Component class represents any type of visualization on the client like a grid or dropdown menu as an object that is instantiated on the client and mapped to hypertext markup language (HTML) that is rendered on the client screen. A user interacts with the data through the Component objects, and Controllers capture the interactions of the user. The interactions, like a click, are called events. Each event has a callback function that is fired once the event is triggered. A specific Controller is registered to a Component or Components listening to specific events and firing callbacks to appropriately update objects.

**Figure 2** Assay Endpoint Model Example

Model: Assay Endpoint

{"data_id":"ATG_ERa_TRANS","analysis_direction":["positive"],"assay_design_type":["inducible reporter"],"assay_design_type_sub":["mRNA induction"],"assay_footprint":["microplate: 24-well plate"],"assay_format_type":["cell-based"],"assay_format_type_sub":["cell-based"],"assay_function_type":["reporter gene"],"chemicals_tested":[1857],"hit_count":[442],"percent_active":[24],"assay_source_name":["ATG"],"biological_process_ target":["regulation of transcription factor activity"],"cell_format":["cell line"],"cell_free_component_source":["NA"],"cell_growth_mode":["adherent"],"cell_short_name":["HepG2"],"content_readout_ type":["multiplexed"],"detection_technology":["RT-PCR and Capillary electrophoresis"],"detection_technology_type":["Fluorescence"],"detection_technology_type_sub":["Fluorescence intensity"],"intended_signal_direction":["gain"],"intended_target_family":["nuclear receptor"],"intended_target_family_sub":["steroidal"],"intended_target_gene_id":["2099"],"intended_target_gene_symbol":["E SR1"],"intended_target_type":["protein"],"intended_target_type_sub":["transcription factor"],"normalized_data_type":["percent_activity"],"organism":["human"],"technological_target_gene_id":["2099"],"technolog ical_target_gene_symbol":["ESR1"],"technological_target_type":["rna"],"technological_target_type_sub":["mRNA"],"tissue":["li ver"],"_individual_assay":["ATG_TRANS"],"_individual_assay_component":["ATG_ERa_TRANS"],"_individual_assay_comp onent_endpoint":["ATG_ERa_TRANS"]}

View: One row in the Assay Selection Grid

| Assay Endpoint | Ty | Analysis Direction | Design Type | Format Type | Biological Process T | Cell Format | Chemicals Tested | Hit Count | % Active |
|---|---|---|---|---|---|---|---|---|---|
| ATG_ERa_TRANS | | positive | inducible reporter | cell-based | regulation of tr... | cell line | 1857 | 442 | 24 |

**Figure 2: Assay Endpoint Model Example**

A model within the context of application architecture is different than a statistical model or any other model mentioned in the literature review. The example model in this figure is data for an Assay Endpoint represented in JavaScript Object Notation (JSON), a data format used for communication between the client and server. The data, or model, can then be used in a view for displaying within the client. In this example, the model is one row within the Assay Selection Grid.

**Middle Ware**

ZendFramework 2.0, similar to Sencha's Ext JS, is an MVC architecture that

populates a server side object model from the data model, which is the schema for

iCSSDB. The abstraction from the data model to the object model is accomplished with

Doctrine, an object relational mapper (ORM). Business logic, like paging, is applied to

the result sets from the database to load the object model in an appropriate format for the

client.

Communication between the frontend client and backend databases is

accomplished through data services. Within the context of iCSS, data services are

platform independent applications that respond to a request through a url and pass a

JSON response to the requester. Table 1describes the available data services that load

data for the application.

**Figure 3** Software Architecture with Focus on Model View Controller Front-End
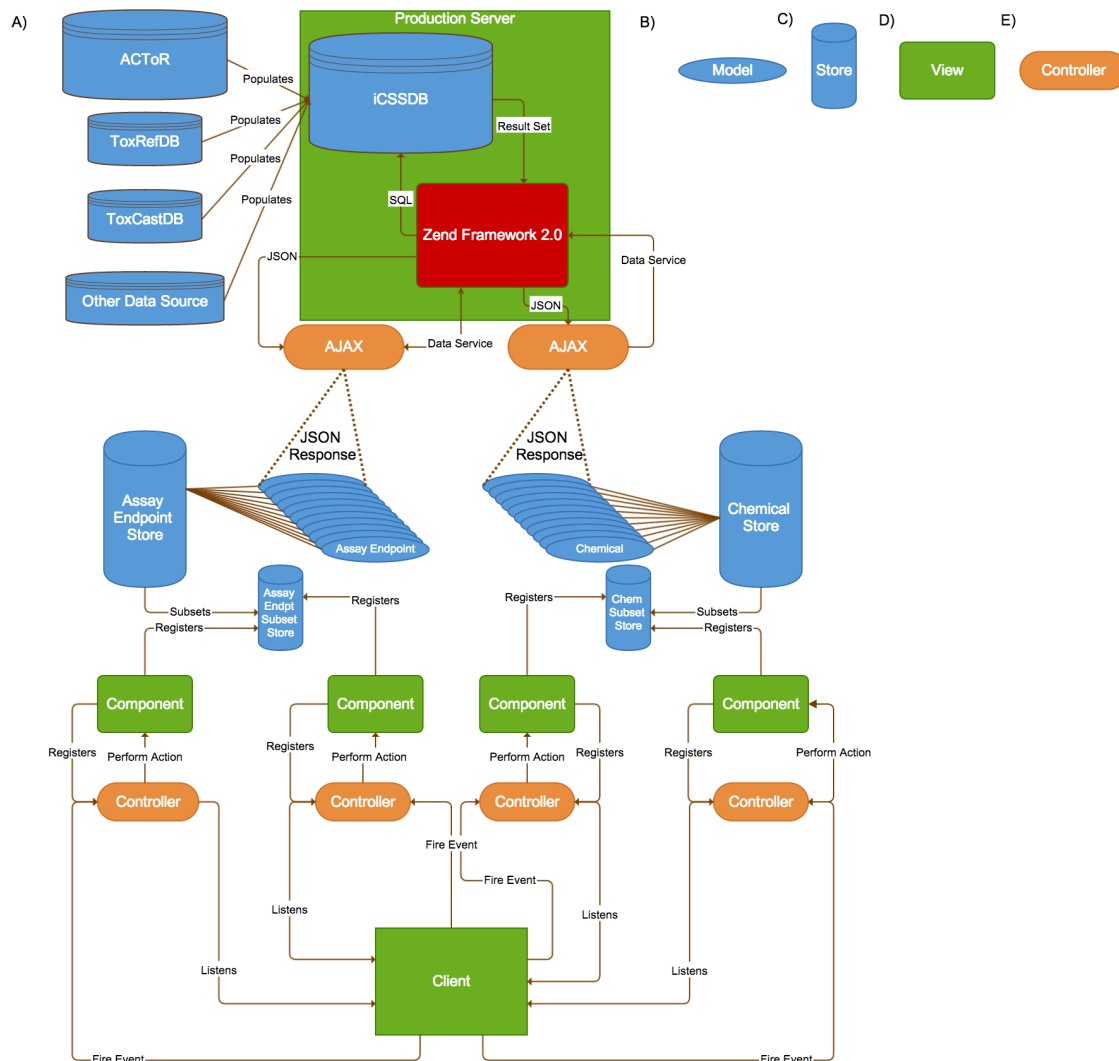


**Figure 3: Software Architecture with Focus on Model View Controller Front-End**

Model View Controller (MVC) architecture is an application design concept that separates the data from the visualization. (A) The basic architecture of the web application displayed as a flow from the backend databases to the middleware Zend Framework 2.0 (MVC architecture) to the frontend Sencha Ext JS (MVC architecture) to the client. (B) A model represents data for visualization. (C) A store aggregates a collection of models and performs specific actions requested from the client (view). (D)

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The view is a graphic display of a model or store. (E) A controller listens to requests from views and performs a specific action.

**Table 1** List of Data Services

| Name | Example | Parameters |
|---|---|---|
| **Assay Selection** | http://actor.epa.gov/dashboard/data-service/data-selection/index?page=1&itemsPerPage=4&field=analysis_direction&name=negative | page<br>parameter_field<br>parameter_name<br>parameter_value<br>ItemsPerPage<br>sort<br>meta |
| **Chemical Selection** | http://actor.epa.gov/dashboard/data-service/chemical-selection/index?page=1&name=PISA&vMin=0&vMax=555.5 | page<br>parameter_field<br>parameter_name<br>parameter_value<br>ItemsPerPage<br>sort<br>meta |
| **Assay Explorer** | http://actor.epa.gov/dashboard/data-service/data-explorer/index?itemsPerPage=10000&assay_endpoint=ACEA_T47D_80hr_Positive&page=1&activity_call=active | page<br>assay_endpoint<br>activity_call<br>ItemsPerPage<br>sort<br>meta |
| **Chemical Explorer** | http://actor.epa.gov/dashboard/data-service/chemical-explorer/index?itemsPerPage=10000&casrn=100-01-6&page=1&activity_call=active | page<br>casrn<br>activity_call<br>ItemsPerPage<br>sort<br>meta |
| **Concentration Response** | http://actor.epa.gov/dashboard/data-service/conc-response/index?casrn=80-05-7&assay_name=ATG_ERa_TRANS&page=1 | page<br>casrn<br>assay_name |

**Table 1: List of Data Services**

The parameter descriptions and constraints are listed in Table 2.

**Table 2** List of Data Service Parameters

| Parameter | Description |
|---|---|
| page | Any number < 1 results in page 1 being provided. Any number > MaxPages results in MaxPage number being provided. If page is not in the query string, page 1 is provided |
| parameter_field | Any alphanumeric value is accepted. Note the space, comma and underscore |
| parameter_name | Any alphanumeric value is accepted. Note the space, comma and underscore |
| parameter_value | If vMin>vMax a 404 error is given |
| ItemsPerPage | You may request any number of items per page. The default is 25. |
| sort | The name of the column to be sorted [ASC|DESC] *case sensitive. |
| meta | If meta=1 is set, a list of data_id's will be the only thing returned. |
| assay_endpoint | Any alphanumeric value is accepted. Note the space, comma and underscore |
| activity_call | Any alphanumeric value is accepted. Note the space, comma and underscore. |
| casrn | Any alphanumeric value is accepted. Note the space, comma and underscore |
| assay_name | Any alphanumeric value is accepted. Note the space, comma and underscore |

**Table 2: List of Data Service Parameters**

The data service parameters are appended to the base uniform resource locator (URL) of

the data service for communication between the server and client.

**Chapter 4 Results**

**Interactive Chemical Safety for Sustainability (iCSS) Dashboard Beta Release**

The beta release of the application is currently public and accessible at

http://actor.epa.gov/dashboard. The beta release serves as a browser of the ToxCast

assays and chemicals as well as the summary hit calls for each chemical across the

assays. Chemicals and assays can be subsetted by annotations surrounding the assays and

chemicals. Full assay descriptions as well as data from result sets with replicates, not only

summary activity calls, are available in the ToxCast data files downloadable at

http://www.epa.gov/ncct/toxcast/data.html.

Below, summaries of each mode and a specific use case are detailed. Most users

only want to see the summary hit calls on either a single chemical or small subset of

chemicals rather than looking at a single assay. The application does not follow a specific

workflow, but the recommended first step is to identify a subset of assays for viewing

summary activity calls by chemical within the Assay Selection mode because selecting a

subset of assays first can significantly decrease the amount of data to view at once.

**Home**

Home mode is the default mode and serves as the landing page of iCSS where general information about the application as well as ToxCast and other resources like workshops and events (Figure 4-B). The link to the full ToxCast data (Figure 4-D) is also provided along with the email link (Figure 4-C) for questions and feedback. Currently no history is logged for the application so refreshing the page or closing the browser will provide the user with a new session and bring the user back to the Home mode clearing all previous actions.
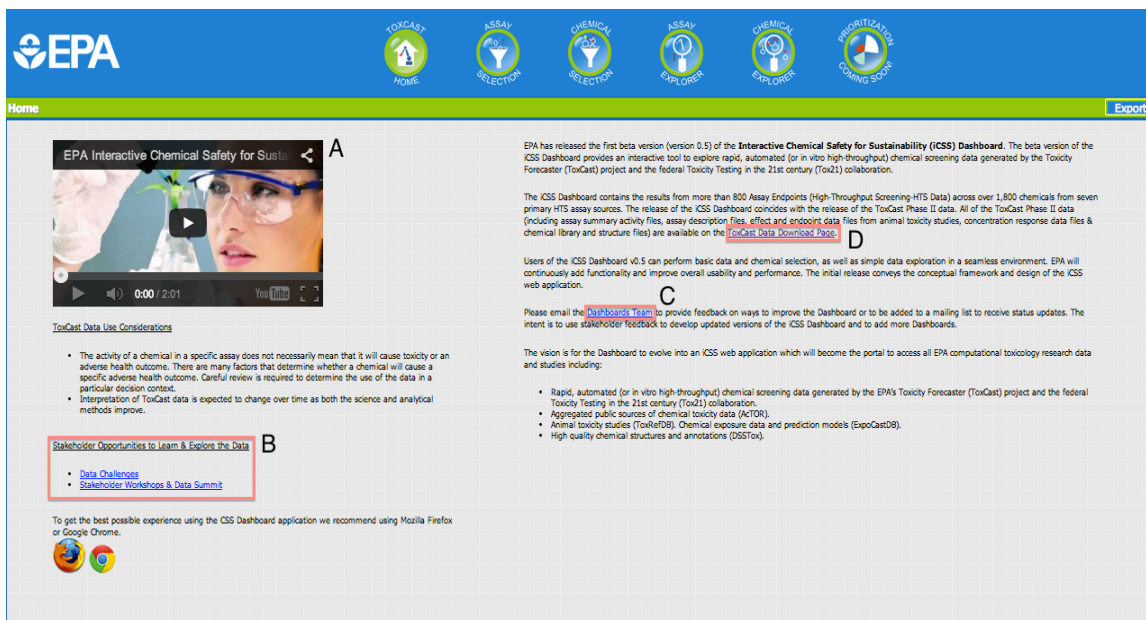
**Figure 4** Home Mode



**Figure 4: Home Mode**

Home mode is the default mode that serves as the landing page for the application. (A) A short video provides a high level overview of the major goals of the ToxCast project. Also provided are (B) links to information about stakeholder workshops and data challenges, the (C) email to contact the iCSS team for feedback and questions, and the (D) ToxCast data files download link.

**Assay Selection**

  Assay Selection mode is the recommended first mode to access, although any mode is accessible because no set workflow is implemented. Assay selection provides a list of all of the assays with all of the assay descriptions from ToxCast Assay Annotation database. Subsets of assays are grouped by the descriptors. A single assay or an existing subset of assays can be selected, added to a current subset, or removed from a current subset.

**Use Case**

  To select only the estrogen assays, select the field, "intended_target_gene_symbol" from the first drop down menu (Figure 5-B). Next, type "ESR1" into the second drop down menu (Figure 5-C) and click "ESR1" to select the symbol of the gene. The result will be 17 assays all involved with the estrogen receptor. To select only the 17 assays, press the "Select Only" button (Figure 5-D). If a subset of assays already exists, and the 17 estrogen assays need to be added to the subset, then press the "Add to Selection" button (Figure 3-E). Ultimately, the numbers of assays that have been selected will be updated according to the button selected and the numbers will be reflected in both Chemical and Assay Selection modes as well as the green information bar just below the mode buttons at the top of the page (Figure 5-A). The updated selection can be seen by navigating to the Assay Explorer mode and viewing the currently selected assays in the Assays Only Grid on the left side of the page (Figure 7-A).

Figure 5 **Assay Selection Mode**



**Figure 5: Assay Selection Mode**

(A) The green information bar displays the current mode, number of chemicals selected for a subset, and the number of assays selected for a subset, and has the "Export" button. (B) The drop down menu listing the higher level, parent assay annotations. (C) A second drop down menu listing the lower level, child assay annotations. The second drop down menu is populated with the child annotations of the parent selected from B. (D) The "Select Only" button subsets the current result set of assays. (E) The "Add to Selection" button adds the current result set of assays to the existing subset.

**Chemical Selection**

The Chemical Selection mode is very similar to the Assay Selection mode except this mode allows the user to select subsets of chemicals. Chemical descriptors from DSSTox are used to subset the chemicals just as the assay descriptions from ToxCast Assay Annotation database are used to subset the assays.

**Use Case**

To select only the phenols from the full chemical set, first select "Chemical_Super_Category" from the first drop down menu (Figure 6-B). Next, type "phenol" into the next drop down menu (Figure 6-C) and click "phenol" to select the chemical super category. These selection parameters produce a result set of 95 chemicals that are phenols according to the "Chemical_Super_Category" criteria of a phenol. To create a subset of only the phenols, press the "Select Only" button. The green information bar at the top of the page (Figure 6-A) that also contains the assays selected information will update according to the selection of chemicals. The subset of chemicals will be reflected in the Chemical Explorer mode in the Chemicals Only Grid on the right hand side of the page (Figure 8-A).

**Figure 6 Chemical Selection Mode**



**Figure 6: Chemical Selection Mode**

(A) The green information bar displays the current mode, number of chemicals selected for a subset, and the number of assays selected for a subset, and has the "Export" button.

(B) The drop down menu listing the higher level, parent chemical annotations. (C) A second drop down menu listing the lower level, child chemical annotations. The second drop down menu is populated with the child annotations of the parent selected from B.

(D) The "Select Only" button subsets the current result set of chemicals. (E) The "Add to Selection" button adds the current result set of chemicals to the existing subset.

**Assay Explorer**

Assay Explorer mode allows the user to select a single assay from the Assays Only Grid (Figure 7-A) to populate the Assay Explorer Grid (Figure 7-B) with the summary hit calls for the selected assay across all the chemicals that have been subsetted in Chemical Selection mode (or all of the chemicals if no chemical subset has been selected). The Assays Only Grid is searchable and sortable by assay endpoint and is not case sensitive. Only the subset of assays, or all the assays if no subset was selected, appear in the Assays Only Grid. With the summary hit calls loaded into the Assay Explorer Grid, a row can be selected to draw the concentration response plot (Figure 7-C) for that particular chemical and assay summary hit call. The concentration response plots reflect the parameters used to draw the hill curve (B, T, W, AC50, $E_{max}$) provided in the Assay Explorer Grid along with individual points used to produce the modeled response. The units for all of the concentrations reported are micro-Molar (uM). Currently, the units are only available through the concentration response plots but will be added to the Assay Explorer and Chemical Explorer Grids in the coming updates.

**Use Case**

Continuing with the subset of 17 estrogen assays along with 95 phenols from the above use cases, the user will only be able to choose one of the 17 assays from the Assays Only Grid. By clicking on the "ATG_ERa_TRANS" assay endpoint from the grid, the Assay Explorer Grid is populated with the summary hit calls for "ATG_Era_TRANS" across only the 95 phenols. Both inactive and active hit calls are populated, but only active hit calls are loaded if the checkbox on the top of the Assay Explorer Grid is checked. The Assay Explorer Grid is not searchable, but each column

can be sorted by clicking on the header of the column. By clicking the "CASRN" column on the summary hit call grid with the "actives only" checkbox checked, the rows are sorted ascending by CASRN. Selecting the second chemical, 4-Nonylphenol (CASRN 104-40-5), the concentration response plot (Figure 7-C) is drawn below the summary hit call grid. The parameters to fit the model and reasoning for the active hit call can be seen in the concentration response plot that is drawn. The logAC50 value in the Assay Explorer Grid is mapped to the grid to see that within the modeled curve the logAC50 is 0.84 uM.

**Figure 7** Assay Explorer Mode
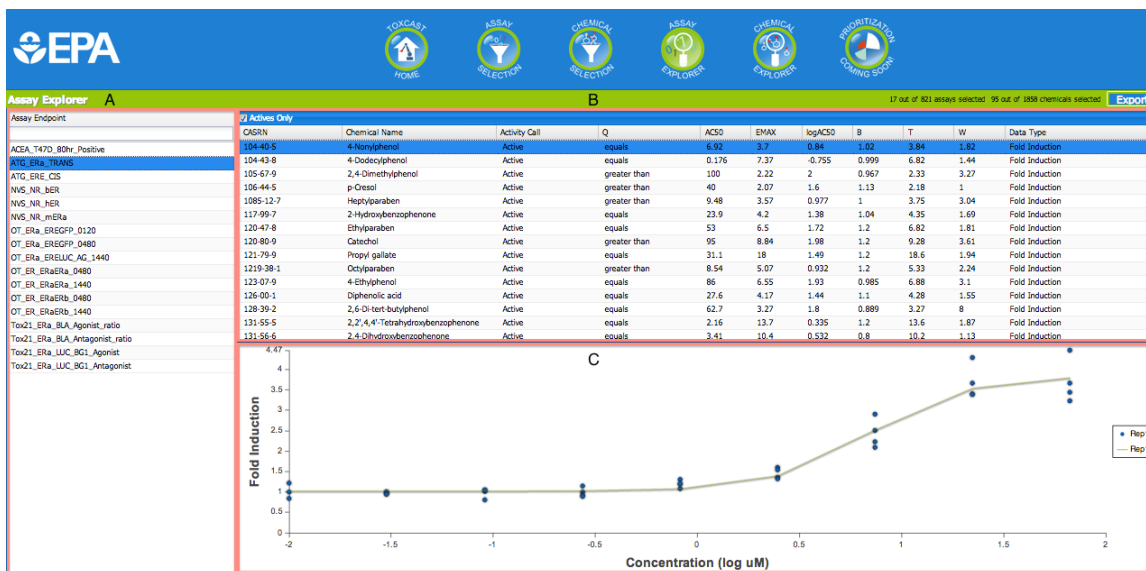


**Figure 7: Assay Explorer Mode**

(A) The Assays Only Grid displays only the subset of assays selected from Assay Selection mode. The grid is searchable and sortable by Assay Endpoint. (B) The Assay Explorer Grid displays summary hit calls across all chemicals from the chemical subset from Chemical Selection mode for a single assay that is selected from A. (C) The concentration response plot is drawn once a row from B is selected.

**Chemical Explorer**

Most users are interested in the performance of either a single chemical or a small subset of chemicals across the ToxCast assays. The Chemicals Only Grid (Figure 8-A) is searchable by either CASRN or chemical name and is not case sensitive. The recommended search is by CASRN since chemical names are not unique, but uniqueness of CASRN is preserved within the ToxCast chemicals. The CASRN search matches any CASRN within the subset of chemicals selected from Chemical Selection mode, but hyphens must be included in the search. For example, to find Bisphenol A (80-05-7) by CASRN "-05-", "80-0", or "80-05-7" will have Bisphenol A in the results; Alternatively, "8005" or "057" will not have Bisphenol A in the results. Searching by chemical name does not search synonyms, but only the exact chemical name within iCSSDB. With updates, the chemical search will include synonyms, including alternate CASRNs. Once a chemical is selected from the Chemicals Only Grid, the summary hit calls for the selected chemical across all of the assays or the subset of assays from the Assay Selection mode populate the Chemical Explorer Grid (Figure 8-B). Once a specific row from the Chemical Explorer Grid is selected, the concentration response plot (Figure 8-C) corresponding to the summary hit call is drawn below the Chemical Explorer Grid.

**Use Case**

Using the subset of 17 estrogen assays and 95 phenols from the above Assay Selection mode and Chemical Selection mode use cases, within the Chemicals Only Grid in Chemical Explorer mode only the 95 phenols are visible. Each column, "CASRN" and "Chemical Name", is searchable and sortable. Use the same chemical, 4-Nonylphenol, example from the previous use case on Assay Explorer mode. 4-Nonylphenol is found by

typing the CASRN "104-40-5" into the text box below the "CASRN" column header.

Clicking on 4-Nonylphenol populates the Chemical Explorer Grid with the hit calls

across the 17 estrogen assays selected from Assay Selection mode. To view only the

assays that are active, check the "actives only" checkbox located within the header within

the Chemical Explorer Grid. The grid is reloaded with 6 assays including

"ATG_ERa_TRANS" from the Assay Explorer mode use case. Selecting

"ATG_ERa_TRANS" will draw the same concentration response plot seen in the use

case from Assay Explorer mode. The same fit parameters match the curve drawn for a

simpler visualization of the hit call.

**Figure 8** Chemical Explorer Mode
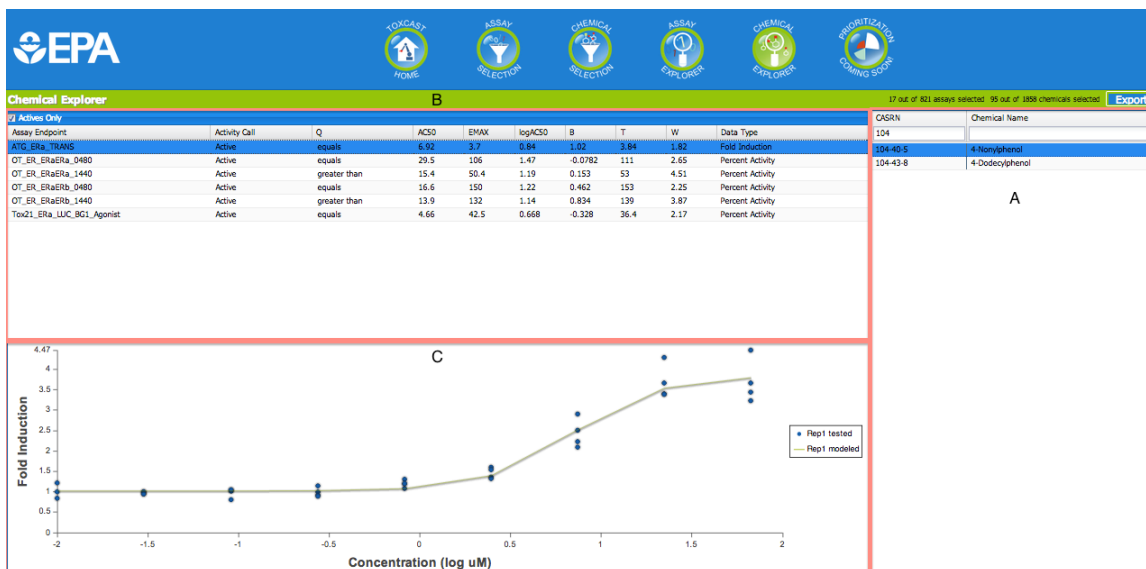


**Figure 8: Chemical Explorer Mode**

(A) The Chemicals Only Grid displays only the subset of chemicals selected from Chemical Selection mode. The grid is searchable and sortable by CASRN and chemical name. (B) The Chemical Explorer Grid displays summary hit calls across all assays from the assay subset from Assay Selection mode for a single chemical that is selected from A. (C) The concentration response plot is drawn once a row from B is selected.

**Export**

The summary hit call data seen in both Assay Explorer Grid and Chemical Explorer Grid

is available for export. When the "Export" button is clicked, the export prompt (Figure 9)

is presented to the user before the data is generated and downloaded. The prompt informs

the user of the number of chemicals and assays the export will contain. Once the user

clicks the "OK" button, the file containing the summary hit calls for the subset of

chemicals and subset of assays from Chemical Selection mode and Assay Selection mode

respectively will be generated and downloaded to the client as a comma separated values

(CSV) file. Table 3 contains a small excerpt from the export file generated from the

above use cases.

**Figure 9** Export Prompt
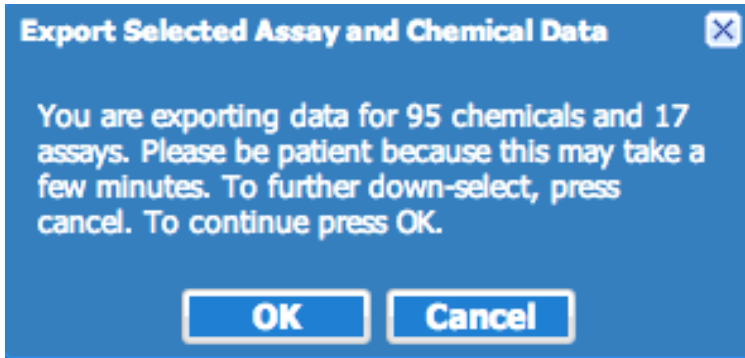


**Figure 9: Export Prompt**

The export prompt is shown after the "Export" button is clicked. The prompt displays the number of chemicals and assays within their respective subsets to inform the user exactly what the generated export file will contain. With a larger number of chemicals and assays, the export file will take a longer time to generate and download.

**Table 3** Excerpt from Export of Summary Hit Calls of 95 Chemicals and 17 Assays

| Assay Endpoint | Chemical Name | CASRN | Activity Call | AC 50 | Emax | Log AC 50 | B | T | W |
|---|---|---|---|---|---|---|---|---|---|
| ACEA_T47D_80hr_Positive | Sodium phenolate | 139-02-6 | Active | 25.7 | 34.1 | 1.41 | 0.187 | 35.8 | 1.84 |
| ACEA_T47D_80hr_Positive | 2-Hydroxy-4-methoxybenzophenone | 131-57-7 | Inactive | 1000 | 31.6 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | Phenolphthalin | 81-90-3 | Inactive | 1000 | 11.1 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | 3-tert-Butylphenol | 585-34-2 | Inactive | 1000 | 15.6 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | 2,3,6-Trimethylphenol | 2416-94-6 | Inactive | 1000 | 6.48 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | 4-Phenylphenol | 92-69-3 | Active | 8.31 | 110 | 0.92 | -9.32 | 116 | 2.49 |
| ACEA_T47D_80hr_Positive | p-Cresol | 106-44-5 | Inactive | 1000 | 15.7 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | Phenol | 108-95-2 | Inactive | 1000 | 3.06 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | Thymol | 89-83-8 | Inactive | 1000 | 8.19 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | tert-Butylhydroquinone | 1948-33-0 | Inactive | 1000 | 7.89 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | 2,3-Dimethylphenol | 526-75-0 | Inactive | 1000 | 18 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | 4-(Butan-2-yl)phenol | 99-71-8 | Active | 9.68 | 118 | 0.986 | 0.891 | 123 | 1.6 |
| ACEA_T47D_80hr_Positive | Butylated hydroxytoluene | 128-37-0 | Inactive | 1000 | 3.88 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | Bisphenol B | 77-40-7 | Active | 0.239 | 152 | -0.622 | -0.324 | 140 | 2.32 |
| ACEA_T47D_80hr_Positive | 2,5-Di-tert-butylbenzene-1,4-diol | 88-58-4 | Inactive | 1000 | 13.4 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | Octylparaben | 1219-38-1 | Active | 1.1 | 114 | 0.0409 | 2.91 | 119 | 1 |
| ACEA_T47D_80hr_Positive | 3,3?,5,5?-Tetraiodothyroacetic acid | 67-30-1 | Inactive | 1000 | 1.42 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | Octyl gallate | 1034-01-1 | Inactive | 1000 | 4.84 | 3 | 0 | 0 | 1 |
| ACEA_T47D_80hr_Positive | Isopropyl-o-cresol | 499-75-2 | Inactive | 1000 | 12 | 3 | 0 | 0 | 1 |

**Table 3: Excerpt from Export of Summary Hit Calls of 95 Chemicals and 17 Assays**

The table is a very small excerpt from the export file generated after all steps from the use cases were taken. Columns excluded from this excerpt are Q and Data Type. Q is a qualifier that represents uncertainty surrounding the AC50 such as "less than" or "equals". Data Type is the response unit and is either "Fold Induction" or "Percent Activity".

**Chapter 5 Discussion, Limitations, Conclusion, and Future Directions**

**Discussion**

Research in toxicology is being driven towards computational approaches because current goals in risk assessment and regulation are not being met by traditional methods in toxicology. Computational approaches produce large amounts of data in a short amount time, but large gaps exists between analysis and interpretation of data. Currently several large sources of computational toxicology data exists and are largely accessible through web applications. Although the data is accessible, criticism remains the same: too much data exists to mine and examples of how the data has been analyzed, can be used and subsequently interpreted are lacking. To further utilize computational data within regulations these concerns must be addressed.

Through continued, open communication with stakeholders and decision-makers, including USEPA program offices, feedback is being assessed to develop applications to meet the needs of all stakeholders wanting to use these data. The iCSS project incorporates feedback to facilitate the communication between interested groups for clearer interpretation of data from computational approaches to toxicology. The iCSS Dashboard is comprised of ToxCast data summarizing activity of over 1,800 chemicals across over 800 HTS assays. Through the four modes currently implemented in the beta release, users can subset assays and chemicals independently for a smaller, targeted, and manageable set of data. The concentration response plot across

each chemical and assay intersection summarizes the activity with the parameters to fit a four-parameter hill curve. The summary hit calls for the subset of chemicals and assays can be exported for further review and serve as a reference when looking though the ToxCast data files for all the result sets with replicates.

ToxCast assays can be aggregated together into data classes to produce a biological read across model by scoring a chemical's performance across each data class and ranking the chemicals. Using Toxicity Priority Index (ToxPi), data classes and the corresponding scores can be visualized for a clearer understanding of a chemical's performance across specific subsets of assays. For example, estrogen, androgen, thyroid, and steroidogensis are data classes for ranking chemicals according to endocrine disruption potential. Each chemical can be scored across these data classes to be ranked based on individual endpoints (estrogenic, androgenic, thyrogenic, and/or steroidogenic) or collectively against all endpoints (overall endocrine disruption potential), which is the ToxPi score. Individually, the assays do not provide information about the overall toxicity endpoints, but aggregating the assays together in data classes provides a more holistic view of a chemicals behavior across specific toxicity pathways because each assay provides information about chemical performance across a snapshot of a toxicity pathway. Prioritization mode for iCSS, which is currently not implemented, would utilize data classes and ToxPi for biological read across using ToxCast assays and chemicals.

Implementing the prioritization mode, which is a key task mentioned in future directions, will allow users to incorporate computational toxicity data into chemical safety decisions. For example, using the endocrine disruption example above, the Endocrine Disruptor Screening Program (EDSP) could use biological read across to

expedite and support Tier 1 screening decisions, which identifies chemicals with the potential to be an endocrine disruptor. Information from the biological read across would also provide information for Tier 2 screening decisions, which identify a chemical's specific endocrine disruption endpoints, by narrowing down the specific endocrine pathways that could possibly be affected to result in the endpoint.

Ultimately, implementing Prioritization mode will help translate chemical performance across assays to toxicity endpoints bridging the gap between analysis and interpretation of computational toxicity data because the large amount of data can be collectively quantified and visualized. With clearer interpretations of chemical performance combined with effective features to subset assays for aggregation into data classes, which is also a task mentioned in future directions, iCSS will become a more effective tool for hazard characterization for chemical safety decisions to increase the user base. Increasing the user base not only drives the development of the application through demand and feedback, but, also, helps validate ToxCast and any other data and models incorporated through updates and future versions.

**Limitations**

The major limitations faced with the development and release of the beta version of iCSS surround user needs, data needs, and technological needs. Although user feedback from workshops promoting ToxCast and iCSS is positive, users are still having trouble navigating the application. Even with one-on-one sessions to answer specific questions, users are still confused about navigating the application as well as how the data can be used. Most of the feedback is about the lack of descriptions surrounding an

assay. Descriptions in sentence form are available through the data files, but currently, no sentence descriptions are available for each assay endpoint through iCSS. Documentation surrounding the data and how to use it is lacking and has contributed to the gap between analysis and interpretation of the data. Despite having annotations from ToxCast Assay Annotation available for each assay in Assay Selection mode, users have a difficult time interpreting the annotations because no documentation is provided through iCSS. For example, users have trouble understanding the difference between technological and intended targets. The technological target is the target being measured from the assay, and the intended target is the target that describes the biological process being captured. For example, the assay endpoint ATG_ERa_TRANS has a technological target of mRNA and an intended target of transcription factor with both targets mapped to the gene ESR1 (gene id 2099). Both targets along with the gene effectively describe the biological process that is captured within the assay: measuring mRNA from transcription of the gene ESR1 describes transcription factor regulation of the gene ESR1.

Users have also commented that they are not able to use the application because iCSS cannot perform a specific function they need. For example, many users would like to export only the active summary hit calls for a subset of assays and chemicals. Also, users would like to export all the descriptions, or annotations, for a subset of assays and a subset of chemicals. The only export currently available is all of the summary hit calls for the subset of assays and subset of chemicals from Assay Selection and Chemical Selection modes.

iCSS is currently limited to only ToxCast data due to the difficulty in creating, updating, and managing a data schema built within a relational database. Incorporating

data from other sources like ToxRefDB would break the current schema for iCSSDB. Storing heterogeneous data within a schema is extremely difficult due to the inherent complexity of the data itself, but also the complex relationships between data from multiple sources. Other solutions for storing heterogeneous data are available, like graph databases that do not require a schema, but are currently not in use because of the time required to map existing data into an entirely new backend then rebuild the middleware for support to the client.

A technological need, along with alternative database solutions to support other data sources, is browser support for older versions of Mozilla Firefox and Internet Explorer. Currently, iCSS browser support is limited to only the most recent versions of Google Chrome and Mozilla Firefox. Developing a web application to work across all platforms is a huge task because the application needs to be compatible with the user base's browsers including the correct version. Each browser uses JavaScript and styles in different ways, so development to meet all users' needs is challenging.

**Conclusion**

In conclusion, the development and release of iCSS is a significant step towards facilitating the communication between stakeholders interested in computational toxicology. Updates and development of newer versions will be driven by continued discussions with stakeholders to meet any needs required for improvements in chemical testing and safety decisions.

**Future Directions**

Through continued development driven by ongoing communication between stakeholders, including USEPA program offices and decision-makers, future versions will include a prioritization mode, data from other sources driving the development of a new schema or schema free solution, other features and tools to create a better user experience and effectively navigate the large amount of data, and documentation including examples detailing specific use cases for the application.

The first major step in development is implementing Prioritization mode. As mentioned in the discussion, Prioritization mode will incorporate data classes, aggregates of assays by toxicity pathways or endpoints, and ToxPi to score, rank, and visualize chemical performance across assays for clearer interpretation of the data.

Incorporating data from other sources like ToxRefDB Exposure Forecaster Database (ExpoCastDB) and ACToR requires a new schema for iCSSDB because the schema is currently specific to ToxCast data. Creating a schema to represent heterogeneous data is difficult because relationships between the data cannot be efficiently stored within a tabular structure. A new schema that captures all the data and relationships between the data and able to be quickly queried is needed to maintain usability of the application. Other solutions exist like graph databases, which do not have schemas and efficiently store extremely large amounts of data along with capturing complex relationships. The first goal is create a schema to support data from both ToxCast and ToxRef. A graph solution is further away because a specific graph database needs to be chosen, and the security review for external access to the database can take a long time.

Other features currently in development are history support, user logs, better tools to navigate the data like 2D structure similarity search, and a more user-friendly interface. With history support, users can more effectively navigate the application by undoing actions. Currently, if the page is refreshed or the user clicks the back button, the application will restart losing all progress. History support will prevent any loss of progress or premature exiting of the application. User logs would save all the actions from a session and be available for export along with any other information from the application, so another user can replicate the process to observe the same data. Tools specific for navigating the assay space and chemical space are currently in development. For example, the 2D structure similarity search allows users to find chemicals of a similar structure to compare performance across assays. The new tools will be implemented in user friendly visualizations with interactions like drag-and-drop rather than large tables and drop down menus with basic interactions.

Lastly, further documentation surrounding ToxCast Assay Annotation and specific use cases are currently in progress. Sentence descriptions about the assays, currently available only through the ToxCast Data files, are being added as tooltips for consistent access to descriptions of assays in all modes. Both written and video examples of specific cases of how to accomplish specific tasks through iCSS are also in progress. All the documentation will be available through links on the Home mode.

**Chapter 6 Practicum Report**

In partial requirement for the Master of Science in Public Health, I completed my practicum at USEPA's Office of Chemical Safety and Pollution Prevention, Office of Pollutions Prevention and Toxics, Information Management Division (USEPA/OCSPP/OPPT/IMD) under direction of Matthew Leopard, the director of IMD. The goal of the practicum was to work with members of OPPT involved with the Toxic Substances Control Act (TSCA) in order to expand my knowledge of risk characterization of chemicals. In order to look at data submitted to TSCA for risk characterization, I had to get clearance for Confidential Business Information (CBI). I was denied clearance because I was not a Federal employee, but I was still able to meet the competencies required for completion of the practicum requirement. Summarized below are descriptions of how each competency was met.

OPPT has a public web application called ChemView that allows users to search for data used to support toxicity endpoint decisions on a particular chemical. Due to my background and work on iCSS, I provided feedback on all aspects of the development of ChemView including how to improve the interface and incorporate other data into the application. I attended three meetings where these topics were addressed. The first meeting was a high level overview of the future directions of ChemView as well as a review of recent feedback from demonstrations with Division Directors within OPPT. I did not actively participate in discussions in this meeting, however, I learned a lot about the development of the ChemView. I also learned a lot about the data accessible through

ChemView, so I was able to participate in discussions in other meetings. The next meeting was with the contractors, who gave me a brief overview of the software architecture and then focused on how the data is displayed. Adding computational toxicology data is a high goal for ChemView, so I was able to talk to the developers about the use of computational toxicology data as well as how it relates to the toxicity data provided through ChemView, which is data from traditional toxicology approaches and/or environmental and ecotoxicology studies. The last meeting was with again with OPPT Division Directors and focused mainly on how to use computational toxicology data and how to incorporate it into ChemView. I was able to effectively communicate the use of ToxCast data to support risk characterizations of chemicals because of the knowledge gained through the other meetings as well through reading documentation detailing TSCA methodologies. Through these meetings I completed the Communication and Informatics, Diversity and Culture, and Leadership competencies.

I also met with scientists involved with the receipt and storage of data provided to TSCA. Through these meetings, I was given demos of the data available through ChemView and was walked through the various regulations and decisions placed on the chemicals. I was able to actively participate in the meetings with these scientists because I already had enough background knowledge to ask informed questions and the meetings were very relaxed. I was able to refer to documents detailing TSCA methodologies for questions, but also for discussion points on how challenges to the methodologies are being addressed. I met the environmental sciences and systems thinking competency by reviewing the TSCA program with these scientists.

**Table 4** Competencies Met for Practicum

| Competency | How to meet competency | How Competency was Met |
|---|---|---|
| Communication and Informatics | Use information technology tools effectively in core public health functions such as retrieval of institutional and online public health data and dissemination of public health information | Successfully used ChemView as a tool for accessing information surrounding a chemical's toxic endpoint |
| | Engage in collective information sharing, discussion and problem solving | Actively participated in meetings discussing data needs from different research programs for a more successful risk characterization process |
| Diversity and Culture | Show effective and productive skills in working with diverse individuals including co-workers, partners, stakeholders, and/or clients | |
| Leadership | Create a climate of trust, transparency, mutual cooperation, continuous learning, and openness for suggestion and input with co-workers, partners, other stakeholders, and/or clients | Opened up communication with OPPT about future collaborations with TSCA for continued support of computational toxicology data |
| | Develop knowledge of one's individual strengths and challenges, as well as mechanisms for continued personal and professional development | Discovered my expertise has been shifted towards the computer science field and need to expand my knowledge about regulatory toxicology |
| Program Planning | Identify needed resources for public health programs or research | Learned more about the data used for risk characterizations and chemical safety decisions |
| Systems Thinking | Identify characteristics of a system | Worked across multiple offices within a highly structured agency, which is a system |
| | Respond to identified public health needs within their appropriate contextual setting | Attended meetings that addressed the needs of different communities: scientists and the general public |
| Environmental Sciences | Describe federal and state regulatory programs, guidelines and authorities that control environmental health issues | Reviewed TSCA methodologies with those who collect TSCA data |
| | Specify current environmental risk assessment methods | |
| | Specify approaches for assessing, preventing and controlling environmental hazards that pose risks to human health and safety | |

**Table 4 : Competencies Met for Practicum**

The practicum is a partial requirement for completion of a Master of Science in Public Health. The competencies met for the practicum along with brief descriptions of how each competency is completed are described in this table.

## References

Andersen, M. E. (2003). Toxicokinetic modeling and its applications in chemical risk assessment. *Toxicol Lett, 138*(1-2), 9-27.

Barratt, M. D. (2003). QSAR, Read-across and REACH. *Altern Lab Anim, 31*(5), 463-465.

Cherkasov, A., Muratov, E. N., Fourches, D., Varnek, A., Baskin, II, Cronin, M., . . . Tropsha, A. (2014). QSAR Modeling: Where Have You Been? Where Are You Going To? *J Med Chem*. doi: 10.1021/jm4004285

Cogliano, V. J., Baan, R. A., Straif, K., Grosse, Y., Secretan, B., & El Ghissassi, F. (2008). Use of mechanistic data in IARC evaluations. *Environ Mol Mutagen, 49*(2), 100-109. doi: 10.1002/em.20370

Collins, F. S., Gray, G. M., & Bucher, J. R. (2008). Toxicology. Transforming environmental health protection. *Science, 319*(5865), 906-907. doi: 10.1126/science.1154619

Davis, A. P., Murphy, C. G., Johnson, R., Lay, J. M., Lennon-Hopkins, K., Saraceni-Richards, C., . . . Mattingly, C. J. (2013). The Comparative Toxicogenomics Database: update 2013. *Nucleic Acids Res, 41*(Database issue), D1104-1114. doi: 10.1093/nar/gks994

Davis, A. P., Murphy, C. G., Saraceni-Richards, C. A., Rosenstein, M. C., Wiegers, T. C., & Mattingly, C. J. (2009). Comparative Toxicogenomics Database: a knowledgebase and discovery tool for chemical-gene-disease networks. *Nucleic Acids Res, 37*(Database issue), D786-792. doi: 10.1093/nar/gkn580

Demchuk, E., Ruiz, P., Wilson, J. D., Scinicariello, F., Pohl, H. R., Fay, M., . . . De Rosa, C. T. (2008). Computational toxicology methods in public health practice. *Toxicol Mech Methods, 18*(2-3), 119-135. doi: 10.1080/15376510701857148

Dewhurst, I., & Renwick, A. G. (2013). Evaluation of the Threshold of Toxicological Concern (TTC)--challenges and approaches. *Regul Toxicol Pharmacol, 65*(1), 168-177. doi: 10.1016/j.yrtph.2012.03.007

Dix, D. J., Houck, K. A., Martin, M. T., Richard, A. M., Setzer, R. W., & Kavlock, R. J. (2007). The ToxCast program for prioritizing toxicity testing of environmental chemicals. *Toxicol Sci, 95*(1), 5-12. doi: 10.1093/toxsci/kfl103

Ennever, F. K., & Lave, L. B. (2003). Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Regul Toxicol Pharmacol, 38*(1), 52-57.

EPA Releases Chemical Screening Data on 1,800 Chemicals/Agency improves access to chemical data and announces ToxCast Data Challenges. (2013). [Press release]. Retrieved from http://yosemite.epa.gov/opa/admpress.nsf/bd4379a92ceceeac8525735900400c27/38b102d67c6b9ee385257c4400732725!OpenDocument

Gibb, S. (2008). Toxicity testing in the 21st century: a vision and a strategy. *Reprod Toxicol, 25*(1), 136-138. doi: 10.1016/j.reprotox.2007.10.013

Gold, L. S., Manley, N. B., Slone, T. H., Rohrbach, L., & Garfinkel, G. B. (2005). Supplement to the Carcinogenic Potency Database (CPDB): results of animal bioassays published in the general literature through 1997 and by the National Toxicology Program in 1997-1998. *Toxicol Sci, 85*(2), 747-808. doi: 10.1093/toxsci/kfi161

Gold, L. S., Slone, T. H., Manley, N. B., Garfinkel, G. B., Hudes, E. S., Rohrbach, L., & Ames, B. N. (1991). The Carcinogenic Potency Database: analyses of 4000 chronic animal cancer experiments published in the general literature and by the U.S. National Cancer Institute/National Toxicology Program. *Environ Health Perspect, 96*, 11-15.

Houck, K. A., & Kavlock, R. J. (2008). Understanding mechanisms of toxicity: insights from drug discovery research. *Toxicol Appl Pharmacol, 227*(2), 163-178. doi: 10.1016/j.taap.2007.10.022

Judson, R., Kavlock, R., Martin, M., Reif, D., Houck, K., Knudsen, T., . . . Dix, D. (2013). Perspectives on validation of high-throughput assays supporting 21st century toxicity testing. *ALTEX, 30*(1), 51-56.

Judson, R. S., Martin, M. T., Egeghy, P., Gangwal, S., Reif, D. M., Kothiya, P., . . . Richard, A. M. (2012). Aggregating Data for Computational Toxicology Applications: The U.S. Environmental Protection Agency (EPA) Aggregated Computational Toxicology Resource (ACToR) System. *Int J Mol Sci, 13*(2), 1805-1831. doi: 10.3390/ijms13021805

Kavlock, R. J., Austin, C. P., & Tice, R. R. (2009). Toxicity testing in the 21st century: implications for human health risk assessment. *Risk Anal, 29*(4), 485-487; discussion 492-487. doi: 10.1111/j.1539-6924.2008.01168.x

Kirchmair, J., Williamson, M. J., Tyzack, J. D., Tan, L., Bond, P. J., Bender, A., & Glen, R. C. (2012). Computational prediction of metabolism: sites, products, SAR, P450 enzyme dynamics, and mechanisms. *J Chem Inf Model, 52*(3), 617-648. doi: 10.1021/ci200542m

Kroes, R., Kleiner, J., & Renwick, A. (2005). The threshold of toxicological concern concept in risk assessment. *Toxicol Sci, 86*(2), 226-230. doi: 10.1093/toxsci/kfi169

Martin, M. T., Judson, R. S., Reif, D. M., Kavlock, R. J., & Dix, D. J. (2009). Profiling chemicals based on chronic toxicity results from the U.S. EPA ToxRef Database. *Environ Health Perspect, 117*(3), 392-399. doi: 10.1289/ehp.0800074

Mattingly, C. J. (2009). Chemical databases for environmental health and clinical research. *Toxicol Lett, 186*(1), 62-65. doi: 10.1016/j.toxlet.2008.10.003

Munro, I. C., Renwick, A. G., & Danielewska-Nikiel, B. (2008). The Threshold of Toxicological Concern (TTC) in risk assessment. *Toxicol Lett, 180*(2), 151-156. doi: 10.1016/j.toxlet.2008.05.006

Patlewicz, G., Ball, N., Booth, E. D., Hulzebos, E., Zvinavashe, E., & Hennes, C. (2013). Use of category approaches, read-across and (Q)SAR: general considerations. *Regul Toxicol Pharmacol, 67*(1), 1-12. doi: 10.1016/j.yrtph.2013.06.002

Phuong, J. (2014). Structured Application of Biological Ontologies to Annotate High-Throughput Screening Assays and their Targets of Activity.

Reif, D. M., Sypa, M., Lock, E. F., Wright, F. A., Wilson, A., Cathey, T., . . . Rusyn, I. (2013). ToxPi GUI: an interactive visualization tool for transparent integration of data from diverse sources of evidence. *Bioinformatics, 29*(3), 402-403. doi: 10.1093/bioinformatics/bts686

Richard, A. M., & Williams, C. R. (2002). Distributed structure-searchable toxicity (DSSTox) public database network: a proposal. *Mutat Res, 499*(1), 27-52.

Rusyn, I., & Daston, G. P. (2010). Computational toxicology: realizing the promise of the toxicity testing in the 21st century. *Environ Health Perspect, 118*(8), 1047-1050. doi: 10.1289/ehp.1001925

Tropsha, A. (2012). Recent trends in statistical QSAR modeling of environmental chemical toxicity. *EXS, 101*, 381-411. doi: 10.1007/978-3-7643-8340-4_13

Waters, M., Stasiewicz, S., Merrick, B. A., Tomer, K., Bushel, P., Paules, R., . . . Fostel, J. (2008). CEBS--Chemical Effects in Biological Systems: a public data repository integrating study design and toxicity data with microarray and proteomics data. *Nucleic Acids Res, 36*(Database issue), D892-900. doi: 10.1093/nar/gkm755