Data management solutions to support ENTACT and Non-targeted Analysis

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2. *ORISE Participant*
3. *NERL, U.S. EPA*

ENTACT, Summer 2018

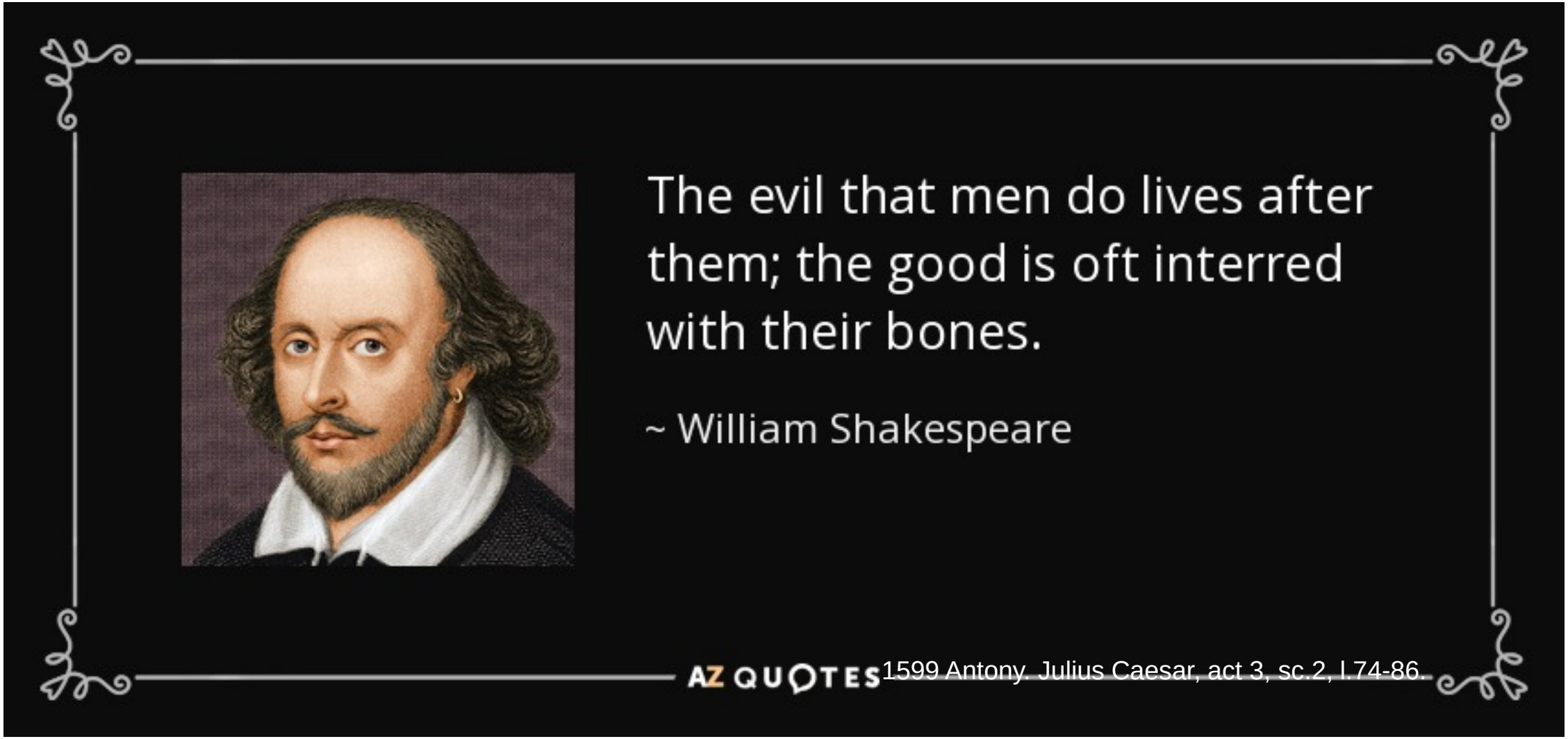
15 August 2018, RTP, NC

Office of Research and Development

Who am I?

- Name: Christopher M. Grulke
- Undergraduate Education:
  - BSE Chemical Engineering
- Job 1: Research Informatics at Pfizer
- Graduate Education
  - PhD, Pharmaceutical Sciences
  - Focus: QSAR modeling
- Current Position at EPA:
  - Title: Computational Chemist
  - Duties: Research (Chem)informatics so one
- Analytical Chemistry Background: 0
- Interest in Formal Presentation Formats: 0

Onward to Evil



From https://www.azquotes.com

Lets Start the “Evil”

- Evil Act I (completed 2 years ago)
  - Yes, I designed the mixtures
  - Yes, there were some mistakes in the mixtures
  - Yes, I wanted to make them even more complicated
  - Yes, you can blame me for everything
- Evil Act II (starting now)
  - Yes, I am going to talk about databases
  - Yes, It may get a bit boring
  - Yes, I will have all of the data
  - No, You can’t take a nap
- Evil Act III (only if I can convince Elin and Jon)
  - Yes, I want to make new mixtures to really cause problems

Goals for “Evil Mixtures”

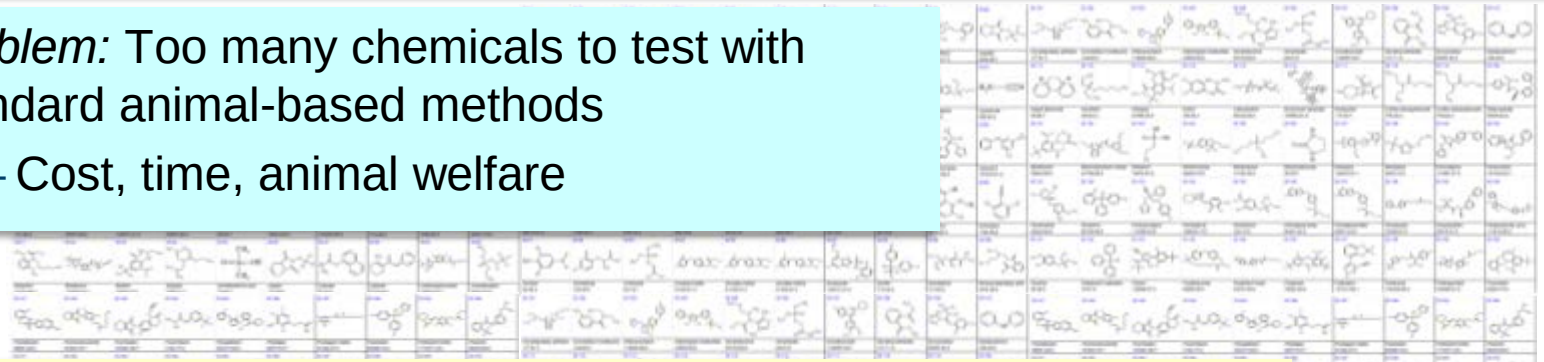
Question(s):

- **What is the relationship between NTA identification (methods) and chemical space detected?**
- Are there chemicals that cannot be detected
- If mixtures are bigger, is detection frequency less?
- If I put the same chemical in a different mixture, can they find it?
- If I put the same chemical in a bigger mixture, can they find it?
- If I put the same chemical in a mixture with an isobaric chemical, can they find it?
- If I throw in some bad QC chemicals, can they find them?
- What if I toss an ill-defined chemical in the mixture?
- Hmmm, polymers are fun…
- Maybe I should vary concentration…
- ...

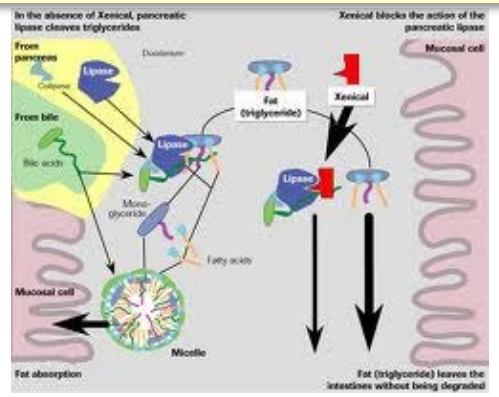
ToxCast Goals

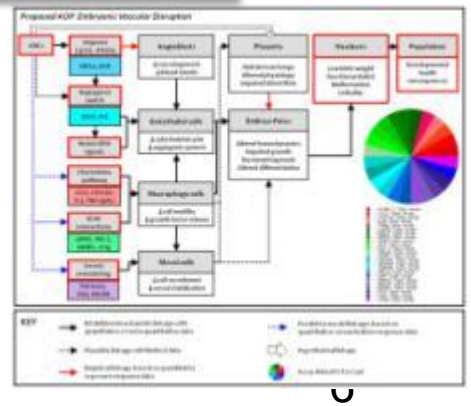
Problem: Too many chemicals to test with standard animal-based methods

– Cost, time, animal welfare



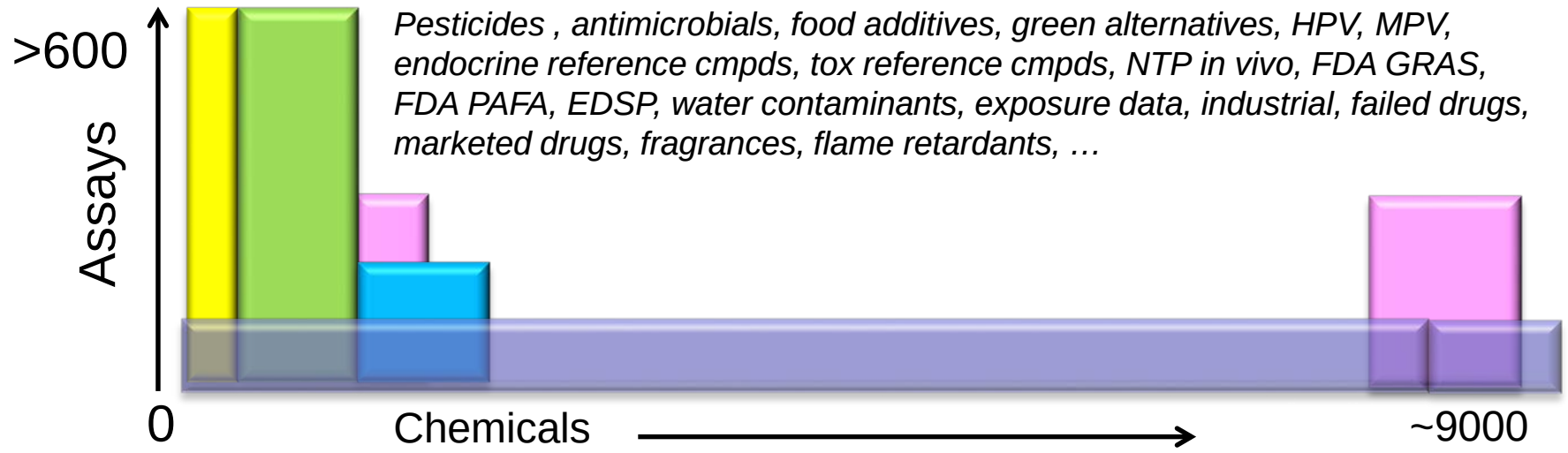
- Use high-throughput screening (HTS) assays to probe possible target & pathways linked to toxicity
- Use large chemical library to probe molecular initiating events, modes of action, adverse outcome pathways
- Develop models to predict in vivo toxicity outcomes





ToxCast & Tox21 Inventories: Chemicals, Data & Timelines

Set	Chemicals	Assays	Endpoints	Completion	Available
ToxCast Phase I	293	~600	~700	2011	Now
ToxCast Phase II	767	~600	~700	03/2013	Now
ToxCast E1K	800	~50	~120	03/2013	Now
Tox21	~9000	~80	~150	Ongoing	Ongoing
ToxCast Phase III	~900	~300	~300	Ongoing	Ongoing



Organizing Our Chemical Library Processes

EPA

1: EPA Orders New Chemical

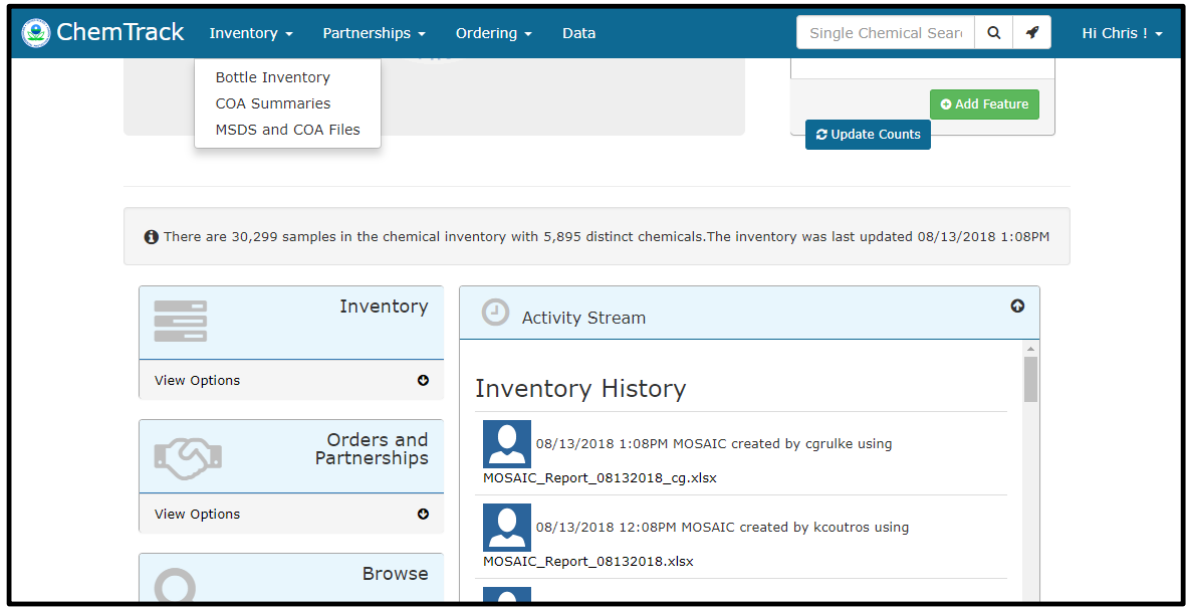
2: CC Procures Chemicals

3: CC Sends EPA
a. COA/MSDS
b. Inventory Report

4: EPA Submits Order

5a: EVOTEC Sends Plate Map

Chemical Contractor (CC)



5b: EVOTEC Ships Plates

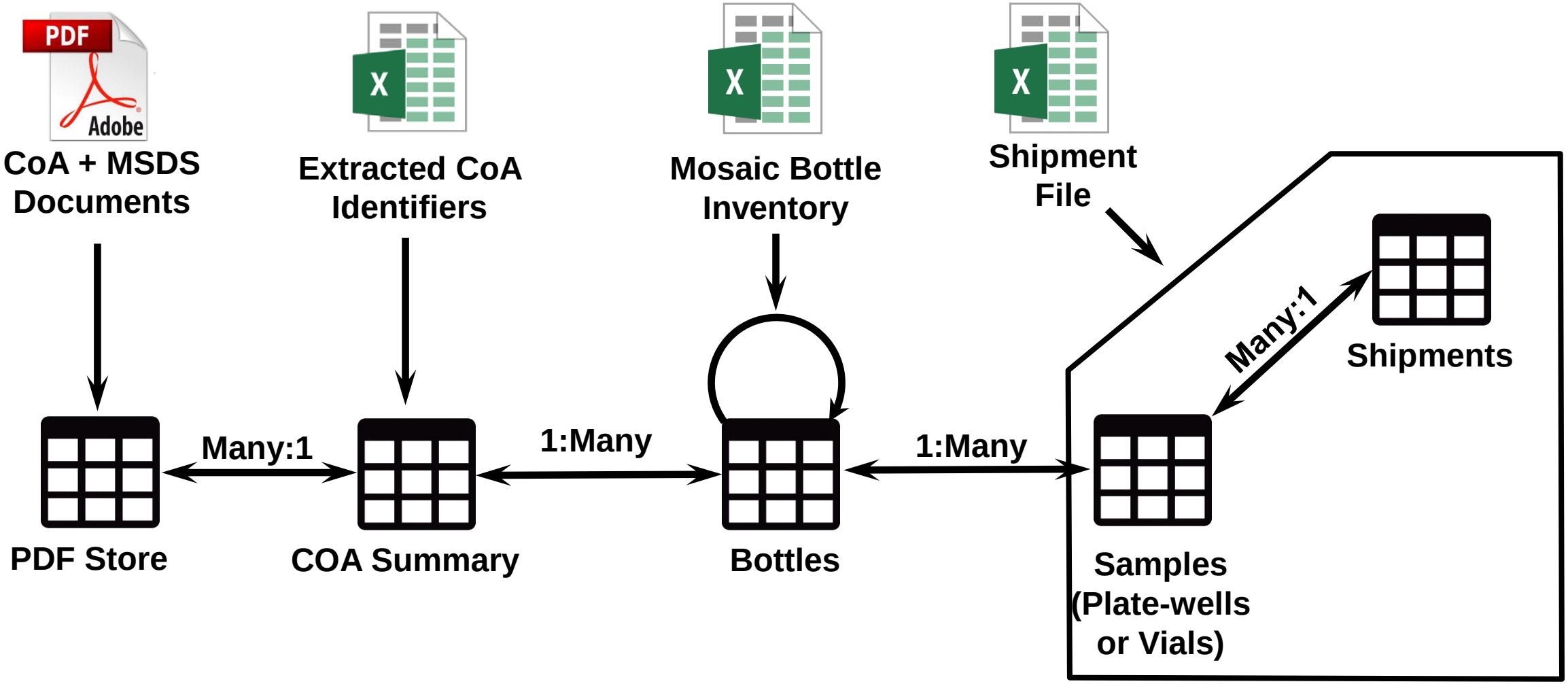
6: EPA Sends Blinded Plate Map

7: Partner Sends Data

8: EPA Sends Unblinded Plate Map

Screening Partner

ChemTrack Simple Data Model



ChemTrack Bottles

ChemTrack | Inventory | Partnerships | Ordering | Data | Single Chemical Search | Hi Chris !

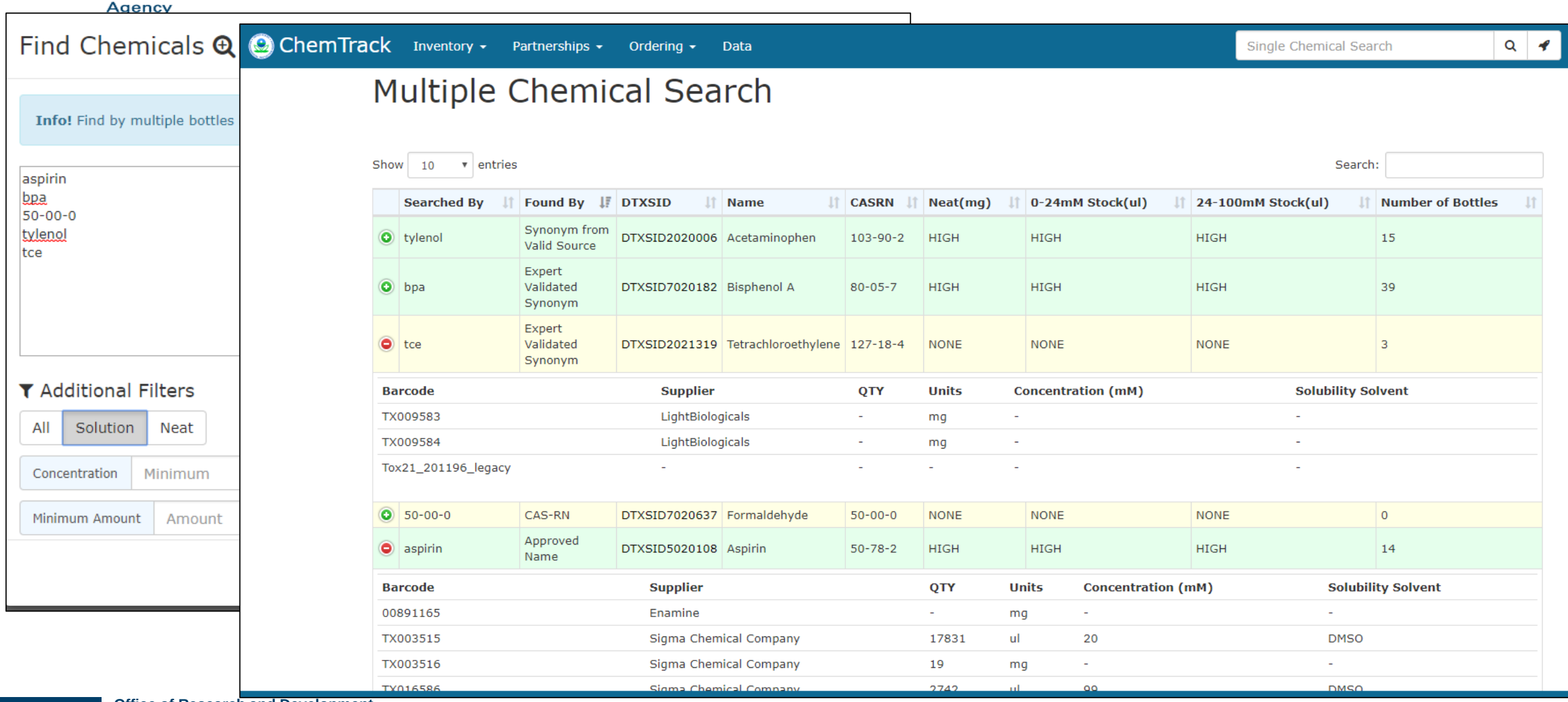
Uploaded MOSAIC Files 25 | Mapped & Available Bottles 29850 | Unmapped Bottles 449 | External Bottles 98 | Add New MOSAIC | Create External Bottle

Mapped & Available Bottles

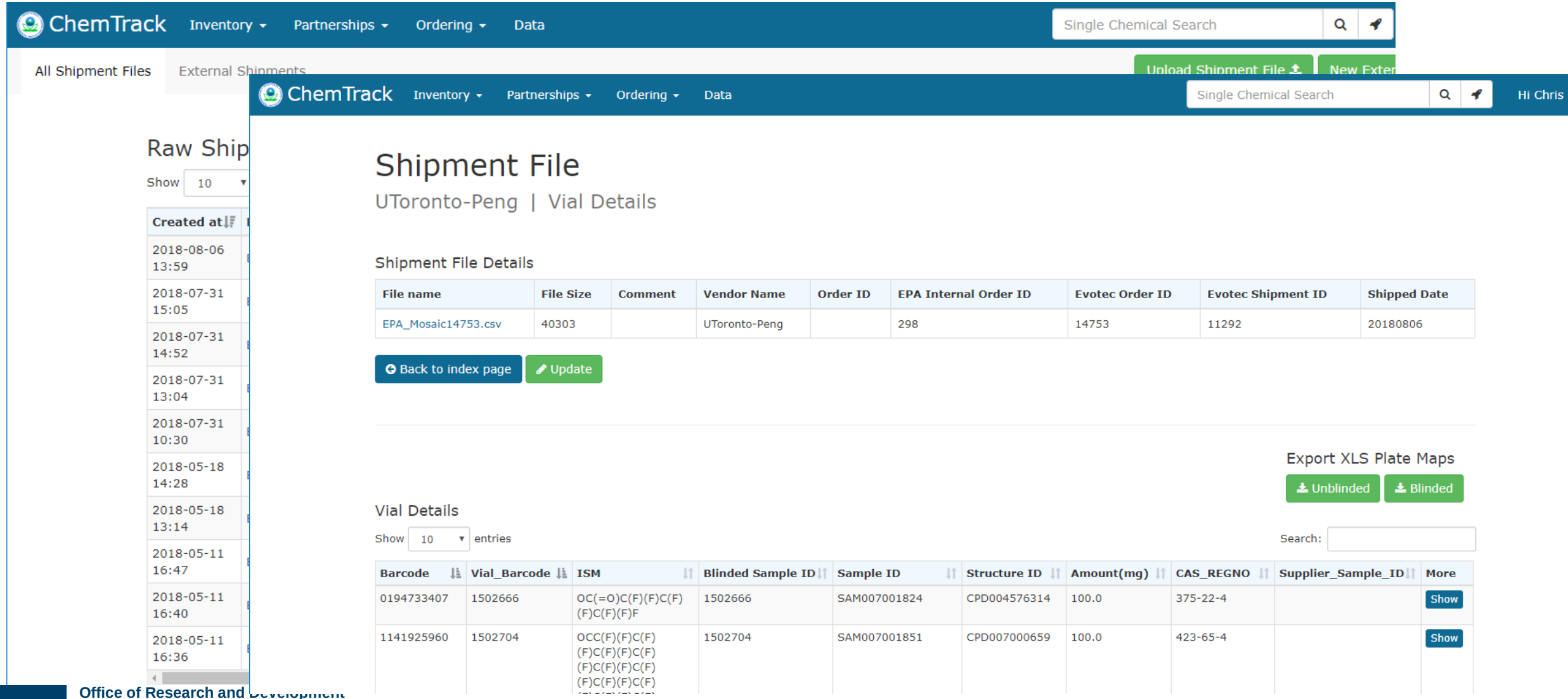
Show 10 entries | Search:

Barcode Type	Barcode	COA Summary	Compound Name	CAS	QTY Available	Units	Vendor	SAM	CPD	Can Plate?	Comment	
INVALID_SUPTX0013222_INVALID	ALID_SUPTX0013222_INVALID	2660	Aluminium phthalocyanine chloride	14154-42-8	1000	mg	Sigma Chemical Company	SAM004888816	CPD003650672	Yes		Edit
INVALID_SUPTX0013294_INVALID	ALID_SUPTX0013294_INVALID	2735	Nickle(III) carbonate basic hydrate	12607-70-4	250000	mg	Sigma Chemical Company	SAM004888887	CPD003650704	Yes		Edit
EPA_Vial_Source_Storage	BF00079587	18768	Pentabromophenol	608719	178	mg	Sigma Chemical Company	SAM006061824	CPD001224527	Yes		Edit
EPA_Vial_Source_Storage	BF00079581	18774	Phthalic anhydride	85-44-9	193	mg	Sigma Chemical Company	SAM006061820	CPD001252223	Yes		Edit
EPA_Vial_Source_Storage	BF00079583	18772	TRIPOLI	7631-86-9	196	mg	Sigma Chemical Company	SAM006061823	CPD001252283	Yes		Edit
EPA_Vial_Source_Storage	BF00079582	18773	4,4'-Methylenebis(2-chloroaniline)	101144	188	mg	Sigma Chemical Company	SAM006061819	CPD001307314	Yes		Edit
EPA_Vial_Source_Storage	BF00079585	18770	4-sec-Butyl-2,6-di-tert-butylphenol	17540-75-9	188	mg	Sigma Chemical Company	SAM006061825	CPD004560495	Yes		Edit
EPA_Vial_Source_Storage	BF00079584	18771	Creosote	8001-58-9	178	mg	Sigma Chemical Company	SAM006061821	CPD004757028	Yes		Edit
EPA_Vial_Source_Storage	BF00079586	18769	tert-Amyl methyl ether	994-05-8	194	mg	Sigma Chemical Company	SAM006061822	CPD004757029	Yes		Edit
EPA_Vial_Source_Storage	BF00079580	18775	3,3'-	91-94-	188	mg	Sigma Chemical	SAM006061826	CPD004757030	Yes		Edit

ChemTrack Search

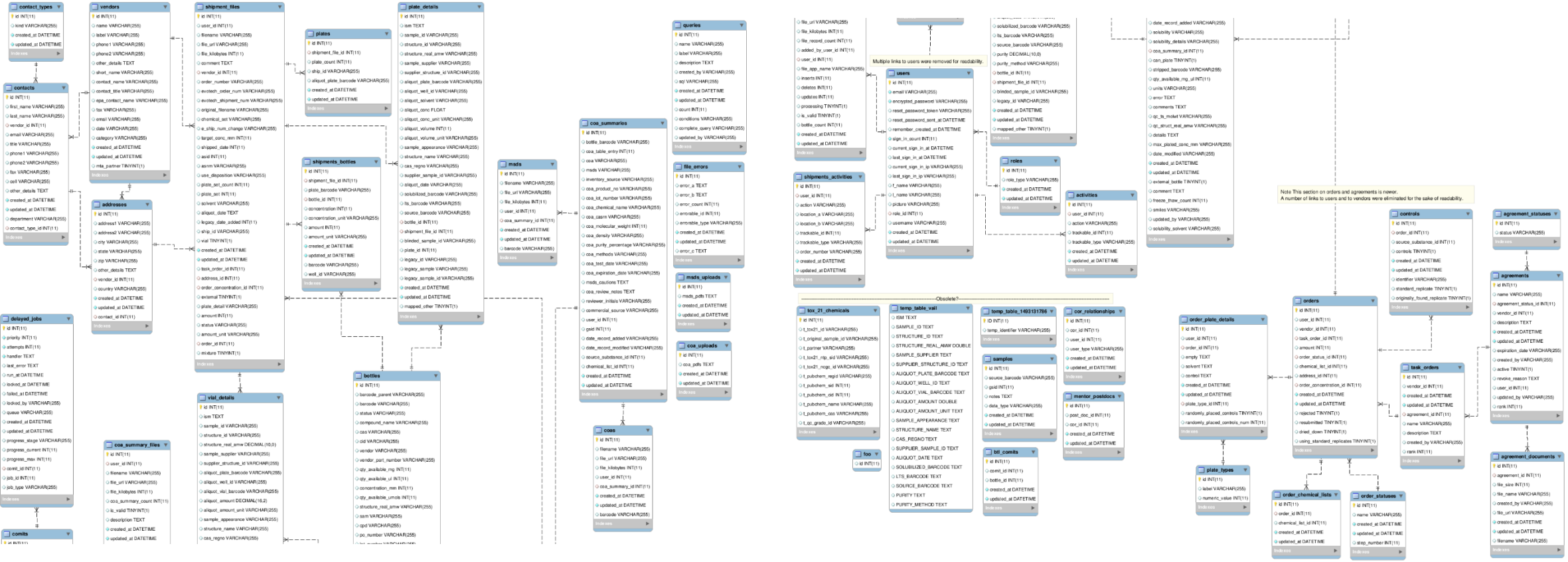


ChemTrack Shipments



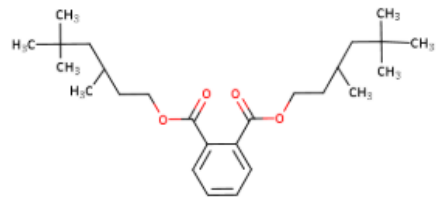
ChemTrack Schema

57 Tables

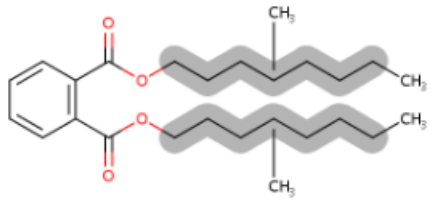


Bottles and Samples Need Chemistry

- Bottle Information
  - Barcode: TX013642
  - CAS-RN: 28553-12-0
  - Name: DIISONONYL PHTHALATE
- CoA Information
  - CAS-RN: 68515-48-0
  - Name: Bis(3,5,5-trimethylhexyl) phthalate
- Which Chemical?????



Bis(3,5,5-trimethylhexyl) phthalate
DTXSID: DTXSID0057889
CASRN: 14103-61-8
TOXCAST: 0



Diisononyl phthalate
DTXSID: DTXSID4022521
CASRN: 28553-12-0
TOXCAST: 10/450

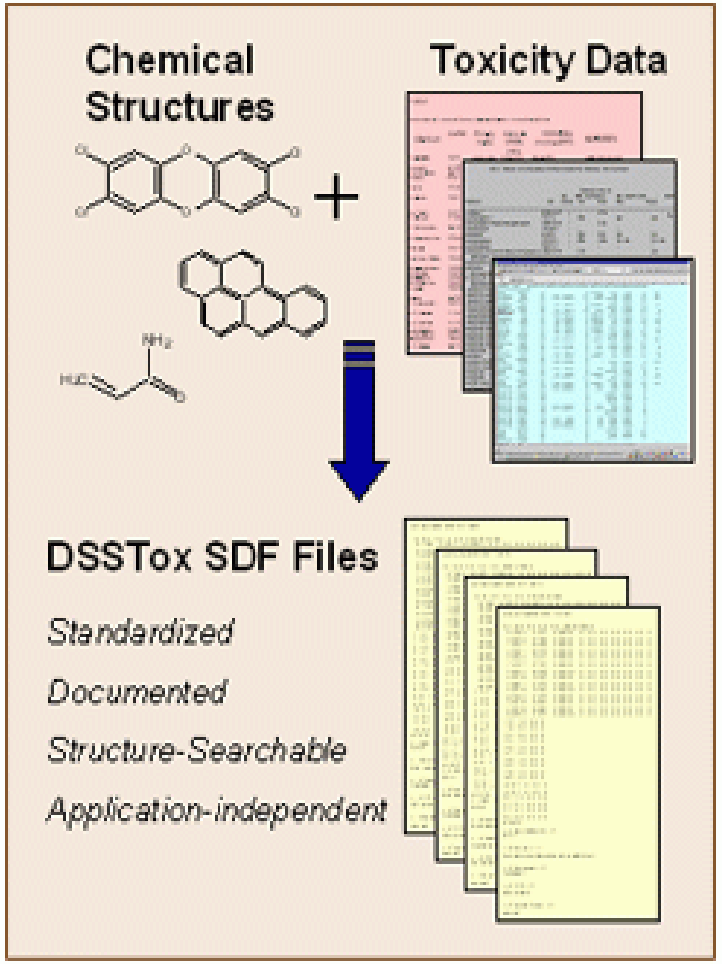
1 related chemical structure with this substance

DINP branched
DTXSID: DTXSID5028665
CASRN: 68515-48-0
TOXCAST: 5/296

DSSTox Ancient History

Goal: Linking chemical structures to data enabling SAR

- First release of data files in 2004
- Focused on high impact sets of data
  - Carcinogenic Potency Database
  - Drinking water disinfection by-products
  - EPA's Integrated Risk Information System
  - FDA's Maximum Daily Dose dataset
  - EPA's Fat Head Minnow Toxicity dataset
  - etc...
- Managed all chemical registration for ToxCast and Tox21 chemicals
- By 2014, roughly 20K manually curated substance records

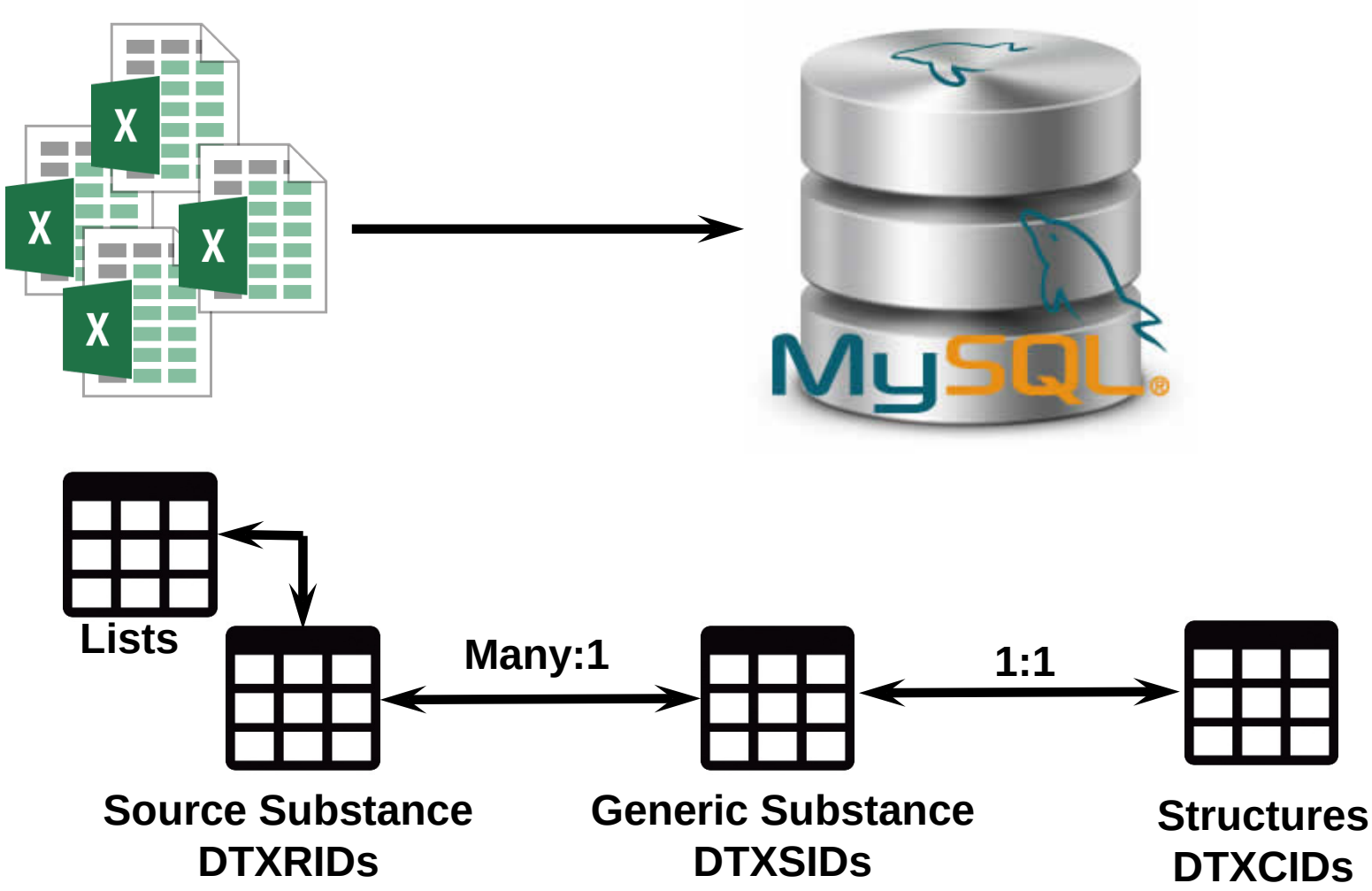


DSSTox Current History

- 762K substance records (28.5K manually curated)
- Central database for the Comptox Chemical Dashboard
- More Goals:
  - Become a hub for all chemical data relevant to an environmental scientist
  - Provide batch extraction of chemical data for our user community
  - Offer chemical list based views of our data
  - Provide list specific search capabilities

- Check out: https://comptox.epa.gov/dashboard

Generalized DSSTox Storage Architecture



Chemical Registration

United States Environmental Protection Agency

ACToR-DSSTox Chemical Registration

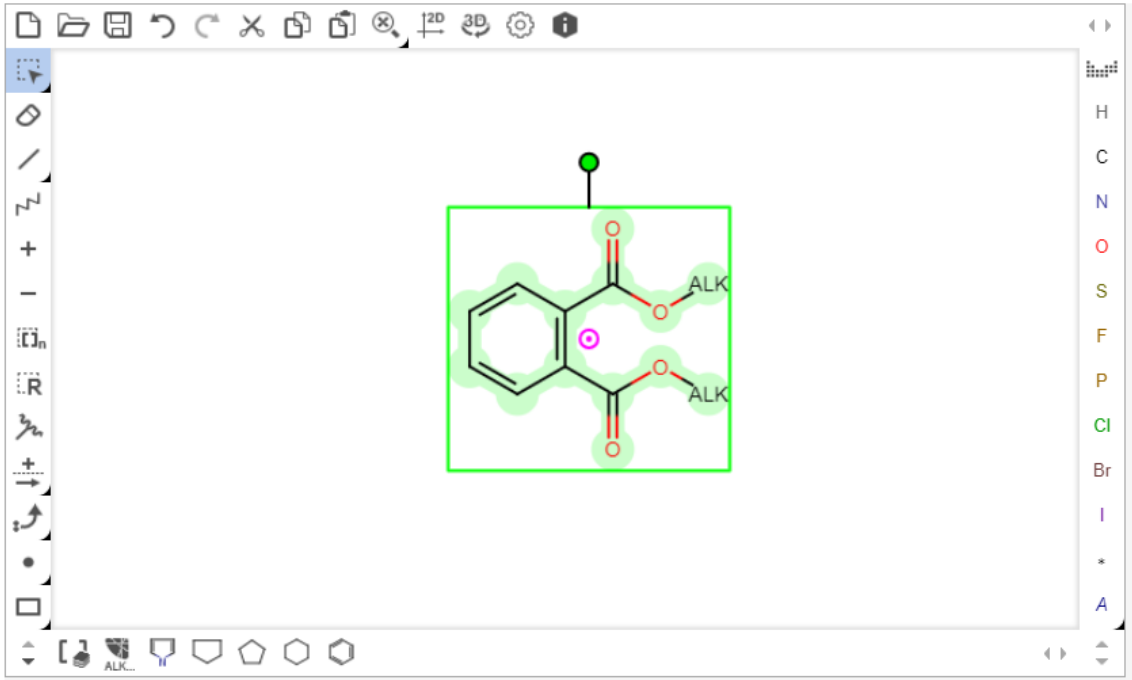
View/Edit a Single Record | Structure Search | Browse/Curate Records | Export DSSTox | Chemotypes | Manage Chemical Lists | Manage Property Data | Add Deleted Casrns

CAS-RN matched null

You are viewing the record associated with DTXSID5028665

CASRN: 68515-48-0

68515-48-0



Calculate from Structure

Substance_ID: DTXSID5028665

CAS: 68515-48-0

Name: DINP branched

Substance Type: Mixture/Formulation

QC Level: DSSTox_High

Data Source: STN(DSSTox)

QC Notes: mixture of dinonyl phthalates

Compound_ID:

Chemical Shown: Markush Query

Private Notes:

Source of CAS-Compound: Public

Double Stereo: None

Chiral Stereo: Unspecified

Chemical Form: Organic

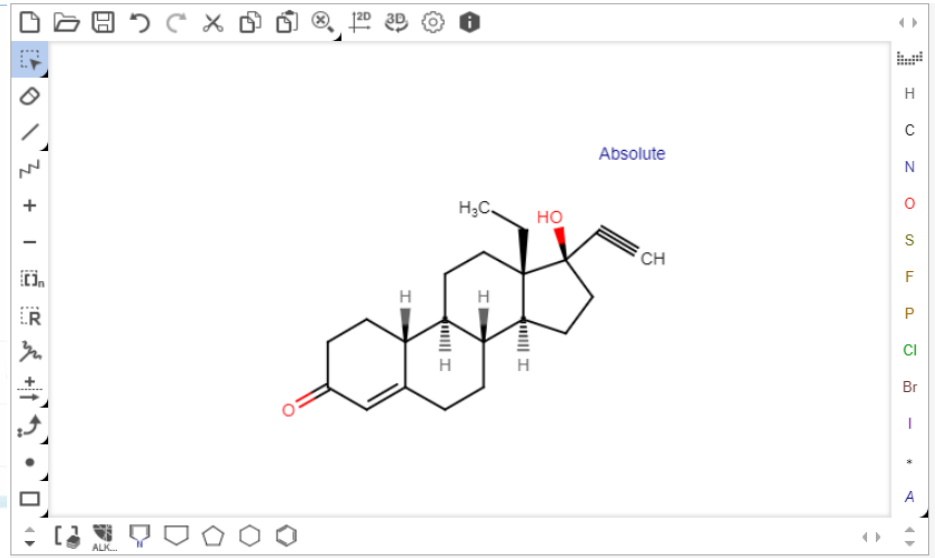
Chemical List Registration

Hits

	ssCAS-RN	ssName	Hit Desc	Hit Substance_ID	Hit Casrn	Hit Name
●		Norgestrel	Structure matched **SMILES**	DTXSID10859541	NOCAS_859541	13-Ethyl-17-ethynyl-17-hydroxy-1,2,6,7,8,9,10,11,12,13,14,15,16,1 tetradecahydro-3H-cyclopenta[a]phenanthren-3-one (non-preferred name)
●		Norgestrel	Mapped Identifier matched **NAME1**	DTXSID3036496	797-63-7	Levonorgestrel
●		Norgestrel	Mapped Identifier matched **NAME1**	DTXSID3047477	6533-00-2	dl-Norgestrel

Map hit | Cancel

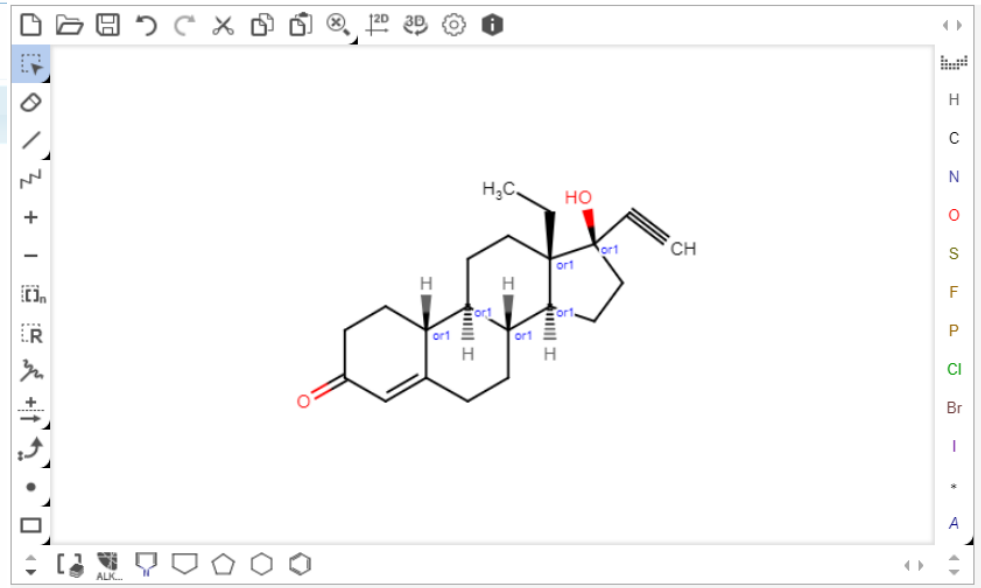
SMILES
Valid Synonym matched **NAME2**
Preferred Name matched **NAME1**
Valid Synonym matched other record: **NAME1**
Unique Synonym matched other record: **NAME2**
Unique Synonym matched other re
Mapped Identifier matched **NAME1**
Mapped Identifier matched **NAME2**
Name2Structure
Export All



Calculate from Structure

Substance_ID: DTXSID3036496
CAS: 797-63-7
Name: Levonorgestrel
Substance Type: Single Compound
QC Level: DSSTox_High
Data Source: STN(DSSTox)

Compound_ID:
Chemical Shown:
Private Notes:
Source of CAS-Compound:



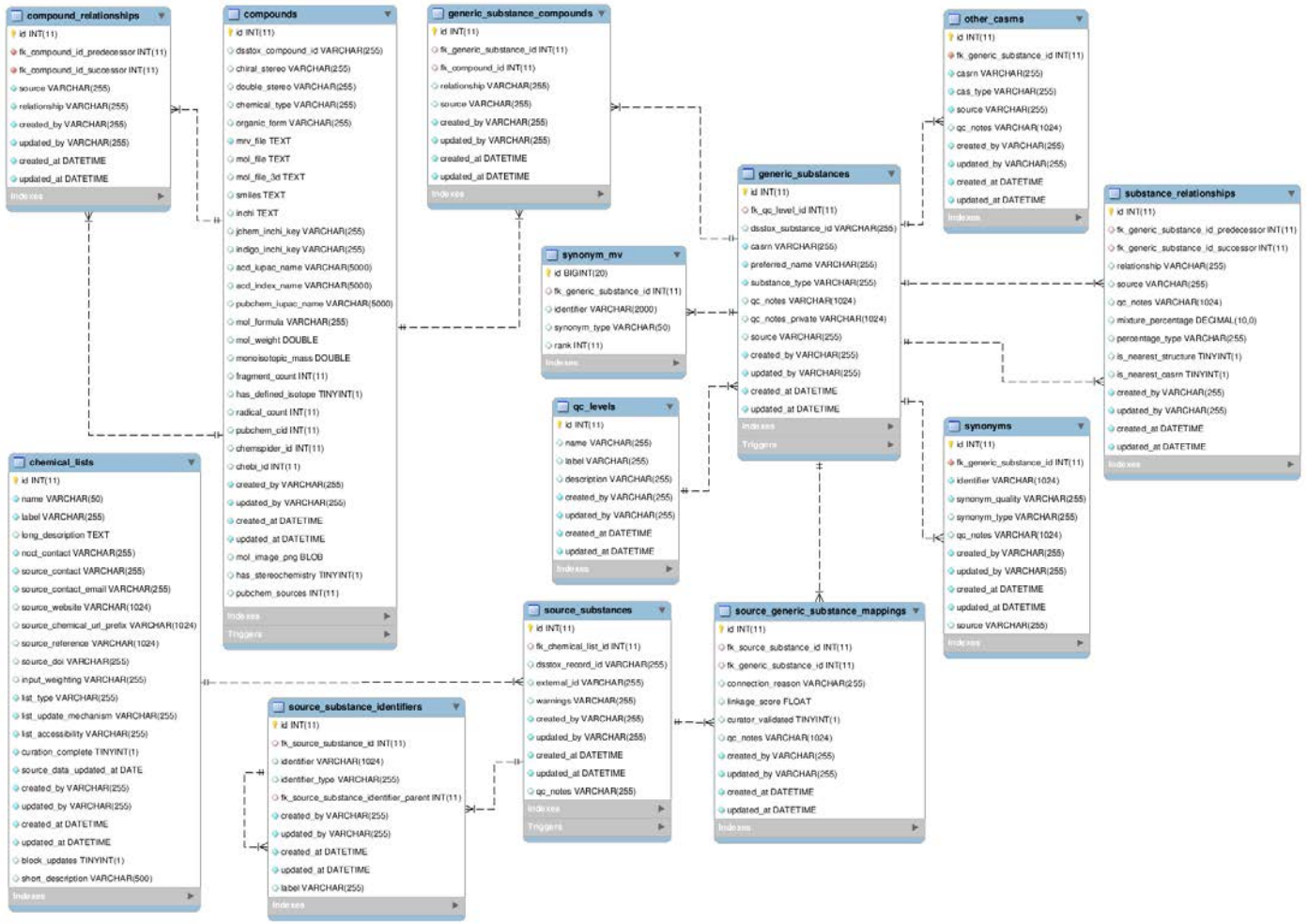
Calculate from Structure

Substance_ID: DTXSID3047477
CAS: 6533-00-2
Name: dl-Norgestrel
Substance Type: Mixture of Stereoisomers
QC Level: DSSTox_High

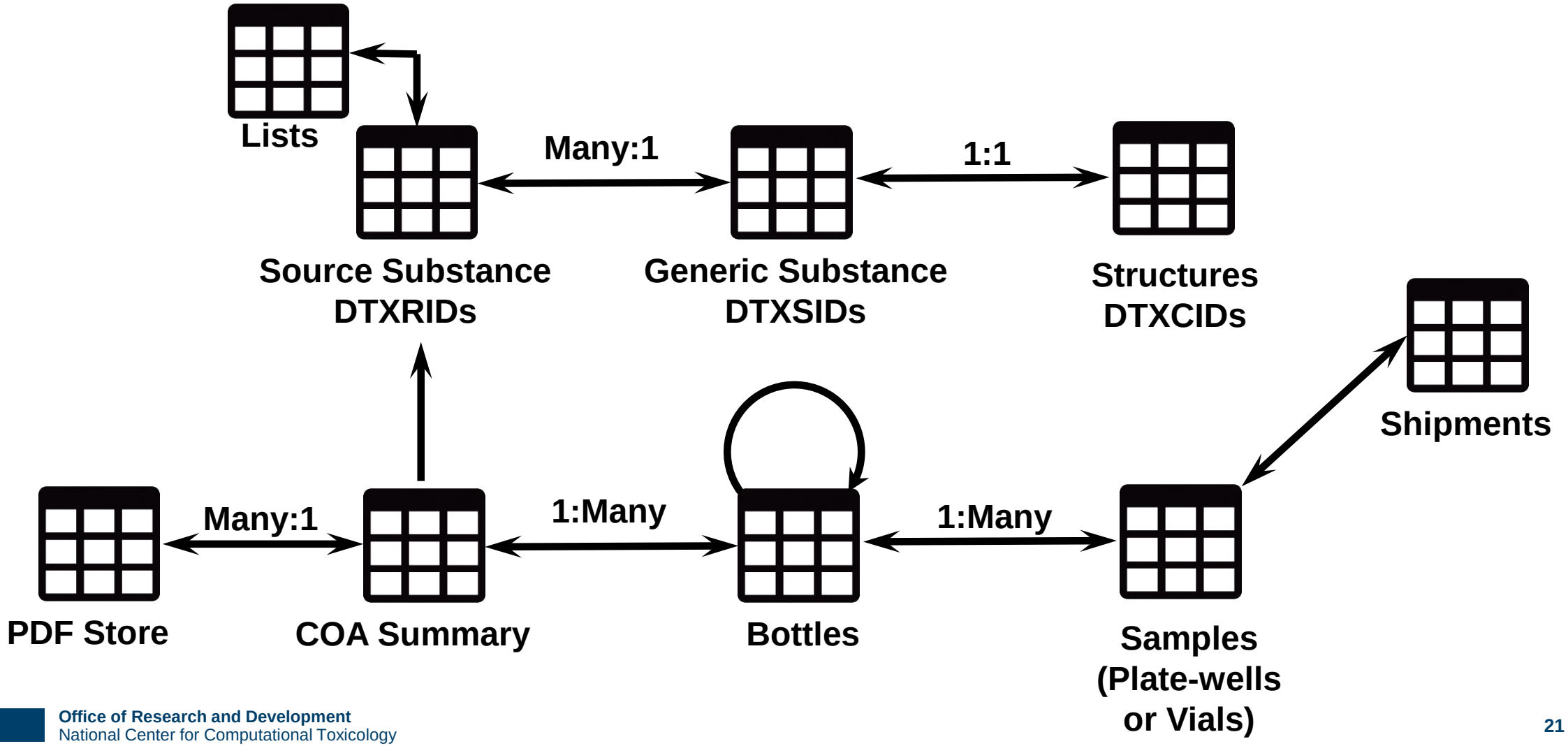
Compound_ID:
Chemical Shown:
Private Notes:

DSSTox Chemistry Schema

19 Tables



Link ChemTrack CoA Summaries to DSSTox



Wait, weren't we making mixtures…
"EVIL MIXTURES"

Question(s):

- **What is the relationship between NTA identification (methods) and chemical space detected?**
- Are there chemicals that cannot be detected
- If mixtures are bigger, is detection frequency less?
- If I put the same chemical in a different mixture, can they find it?
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- If I put the same chemical in a mixture with an isobaric chemical, can they find it?
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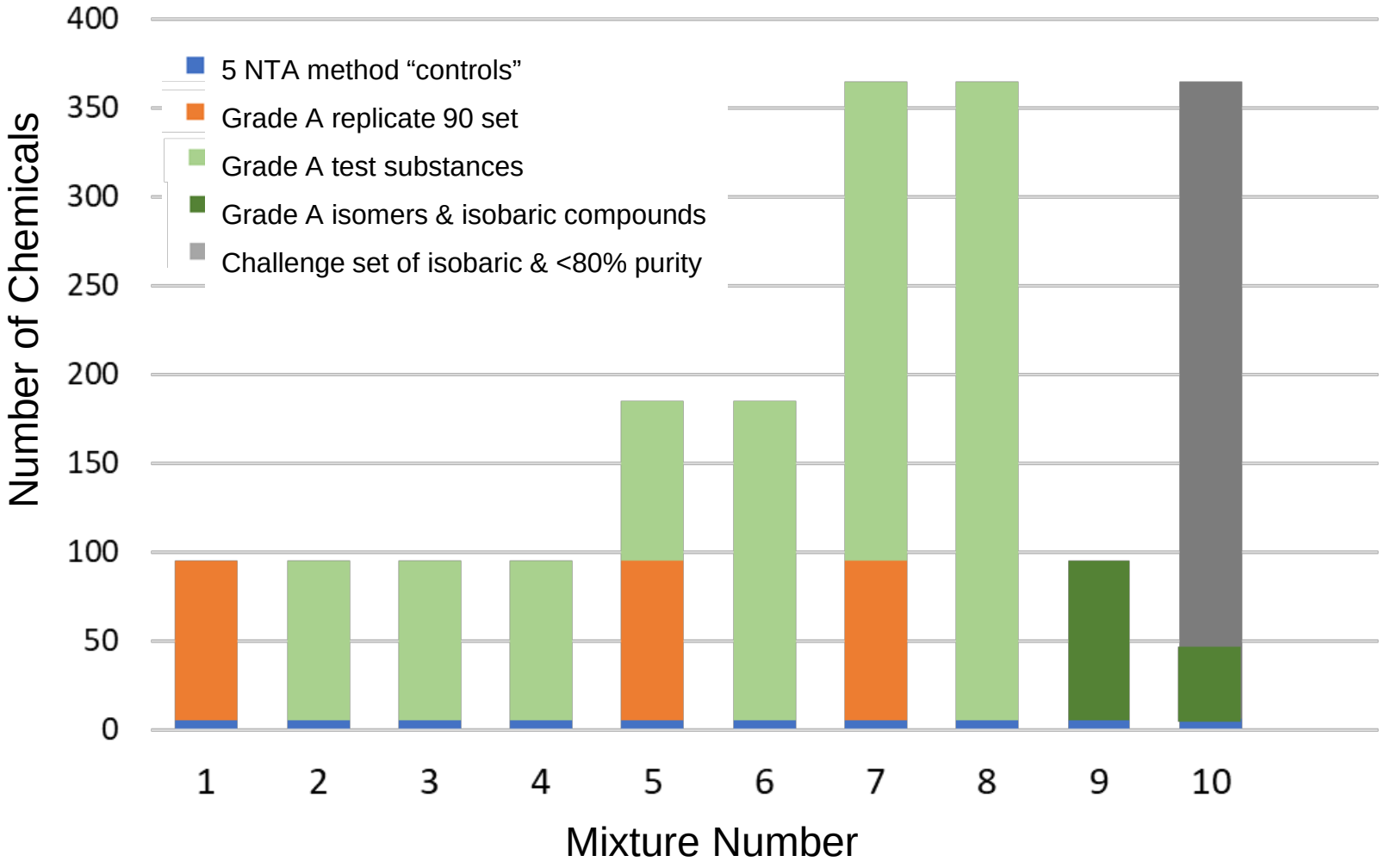
- What if I toss an ill-defined chemical in the mixture?
- Hmmm, polymers are fun…
- Maybe I should vary concentration…

General Mixture Plan…



<u>10 Prepared Mixtures</u>:

1,939 total spiked substances

1,269 unique substances:

1 → spiked 11 times

4 → spiked 10 times

57 → spiked 4 times

33 → spiked 3 times

388 → spiked 2 times

786 → spiked 1 time

Limiting My “Evil”

Comments from Confluence Page on Mixture Creation September 2015

- *Jon Sobus*: How loose do you want to get with respect to QC levels for the "messy mixtures"? I'm a little worried that a messy mixture with 384 might be too difficult.

- *Chris Grulke*: I think it might be difficult, but not more difficult than dealing with a real media sample…. **Muhuhahahahaha!**

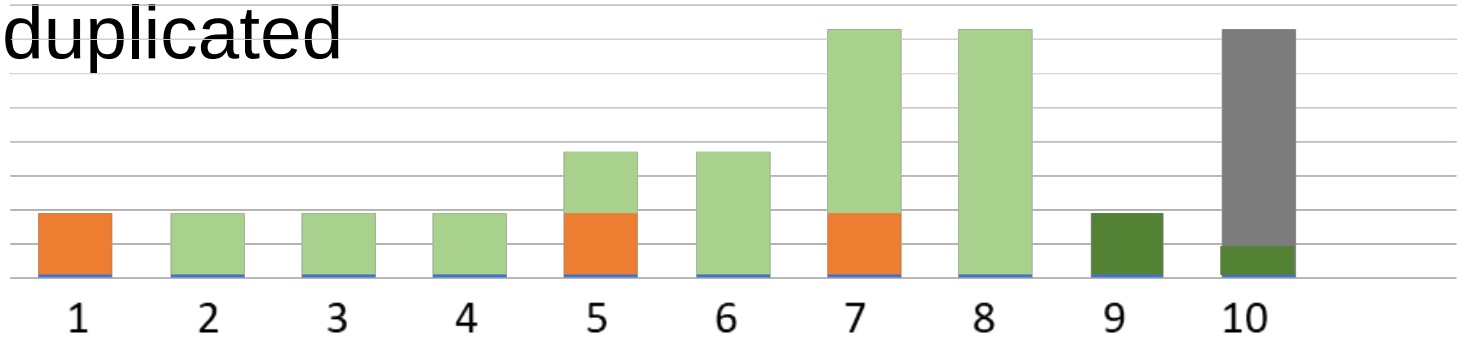
“Easy” Mixtures

General Easy Mixtures (2,3,4,6,8)

1. Sample available in the ToxCast Library
2. Samples Passed Analytical QC
3. No isobaric conflicts (based on 5 ppm resolution)
4. Span the logP and monoisotopic mass range
5. Only controls duplicated

Embedded Set Mixtures (1,5,7)

1. Obey rule 1-4 of General Easy Mixtures
2. Mixtures of 95,185,365 all embedding a common 95 chemicals



Selecting the "Control" Chemicals - Mixture Pilot Successes

- 947 chemicals identifier in dust
- 100 selected and placed in a blinded mixture
- 58 were identified when performing NTA on the mixture
- Jon picked 13
- I picked 5

Rank priority	CAS	DSSTox_name	LC_and_GC	QC_Score	LC_mode	Both concentrations
1	1085-12-7	Heptylparaben	yes	A	neg and pos	yes
2	120-32-1	Clorophene	yes	A	neg and pos	yes
3	13674-87-8	TDCPP	yes	A	neg and pos	yes
4	84-61-7	Dicyclohexyl phthalate	yes	A	neg and pos	yes
5	94-13-3	Propylparaben	yes	A	neg	yes
6	105-99-7	Dibutyl hexanedioate	yes	A	pos	yes
7	63-05-8	4-Androstene-3,17-dione	yes	A	pos	yes
8	63-25-2	Carbaryl	yes	A	pos	yes
9	77-93-0	Triethyl citrate	yes	A	pos	yes
10	78-42-2	Tris(2-ethylhexyl) phosphate	yes	A	pos	yes
11	84-66-2	Diethyl phthalate	yes	A	pos	yes
12	125-33-7	Primidone	yes	A	neg and pos	yes
13	4559-86-8	1,1,3,3-Tetrabutylurea	yes	A	pos	yes

Rager, J.E., et al., 2016. Environ. Int. 88, 269–280

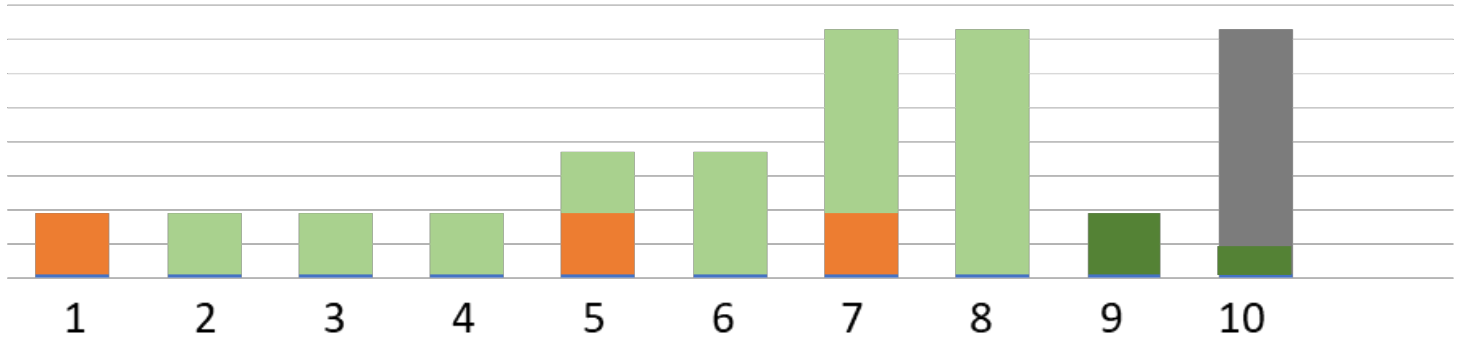
Making Hard Mixtures

Isobar Mixture (9)

1. Sample available in the ToxCast Library
2. Samples Passed Analytical QC
3. All isobaric conflicts (based on 5 ppm resolution) with conflicted chemicals run individually in Easy Mixtures

Isobar and QC Fail Mixture (10)

1. Dump in the rest of the isobars from the library
2. Add some things which we detected during QC, but with concentration issues.



Mixture Sample Documentation

Calculate from Structure

Substance_ID:	DTXSID30892536	Compound_ID:	
CAS:	NOCAS_892536	Chemical Shown:	No Structure
Name:	NTSMIX_Mix1	Private Notes:	Substance registered to enable loading of EVOTEC shipment files for daughter platings. Additional mapping of successor substances (mixture components) is needed
Substance Type:	Mixture/Formulation		
QC Level:	Incomplete		
Data Source:	Public		
QC Notes:	A mixture of chemicals sent to collaborators as part of a study to evaluate the capabilities and limitations of various NTA methods in identify chemicals	Source of CAS-Compound:	
		Double Stereo:	
		Chiral Stereo:	
		Chemical Form:	

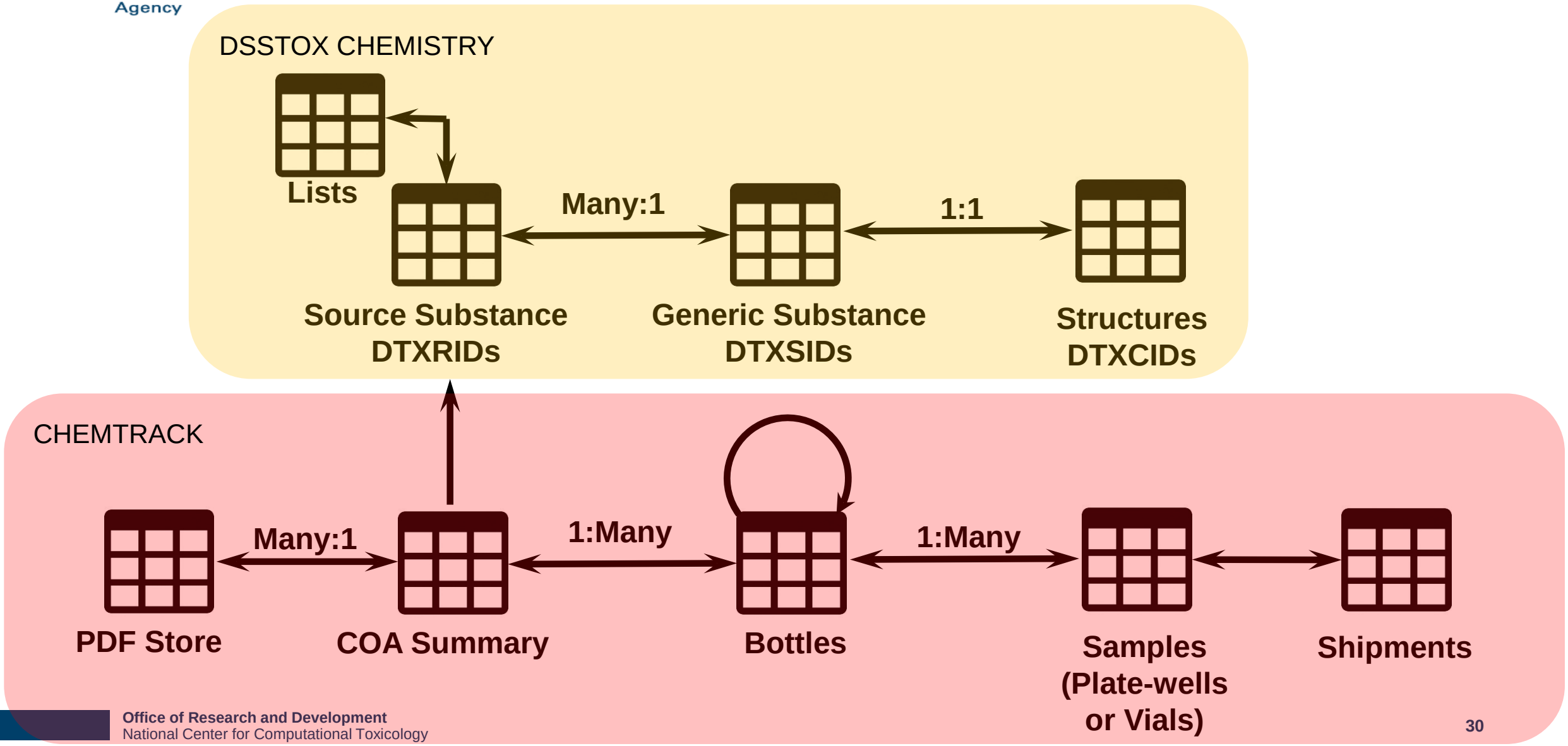
Lets Start the “Evil”

- ~~Evil Act I (completed 2 years ago)~~
  - ~~Yes, I designed the mixtures~~
  - ~~Yes, there were some mistakes in the mixtures~~
  - ~~Yes, I wanted to make them even more complicated~~
  - ~~Yes, you can blame me for everything~~

- Evil Act II (starting now)
  - Yes, I am going to talk about databases
  - Yes, It may get a bit boring
  - Yes, I will have all of the data
  - No, You can’t take a nap

- Evil Act III (only if I can convince Elin and Jon)
  - Yes, I want to make new mixtures to really cause problems

Covered Generalized Data Model



The “Evil” Dashboard Taskmaster

I Need
QSAR Predictions

I Need
ToxCast Results

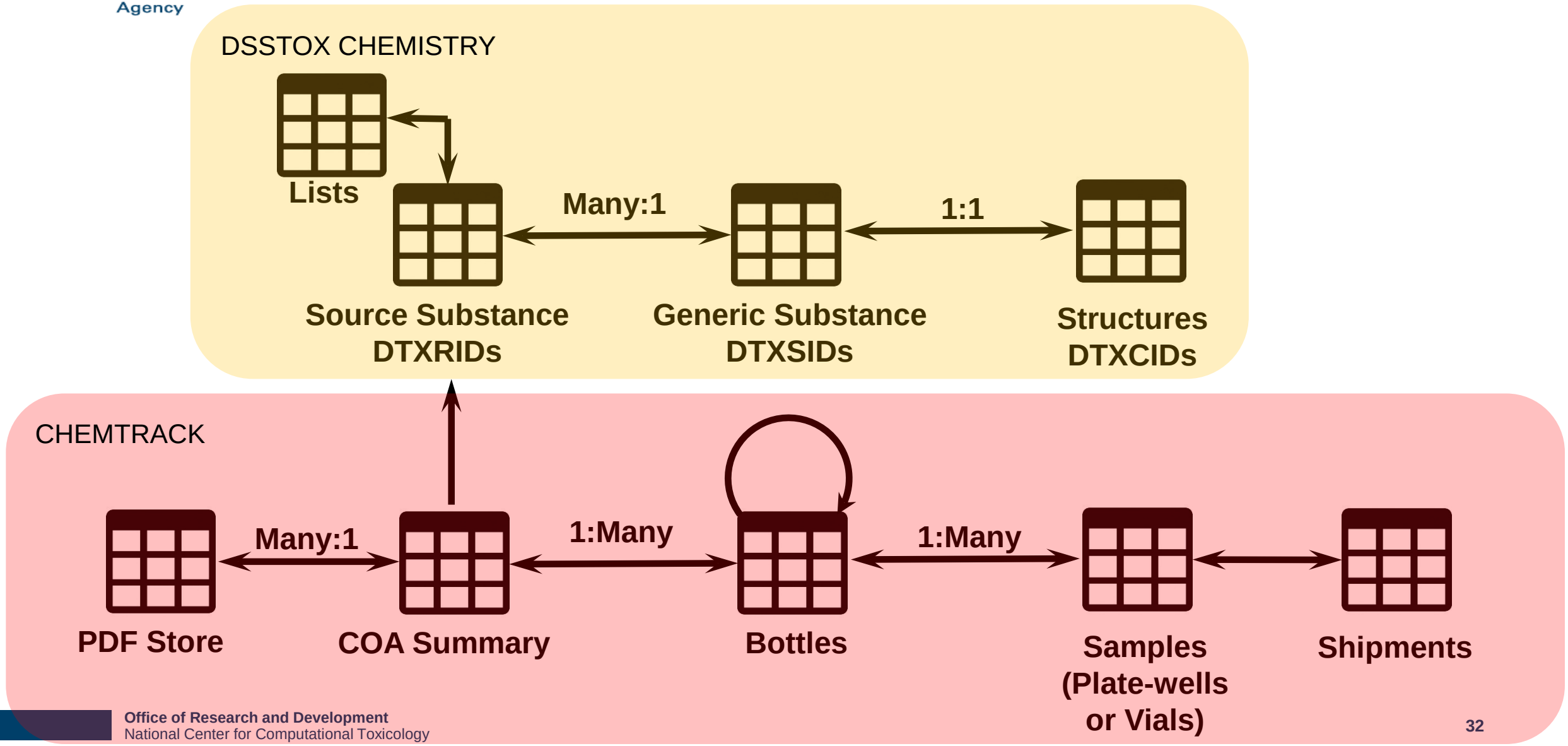
I Need
Analytical QC Data

I Need
PhysChem Data

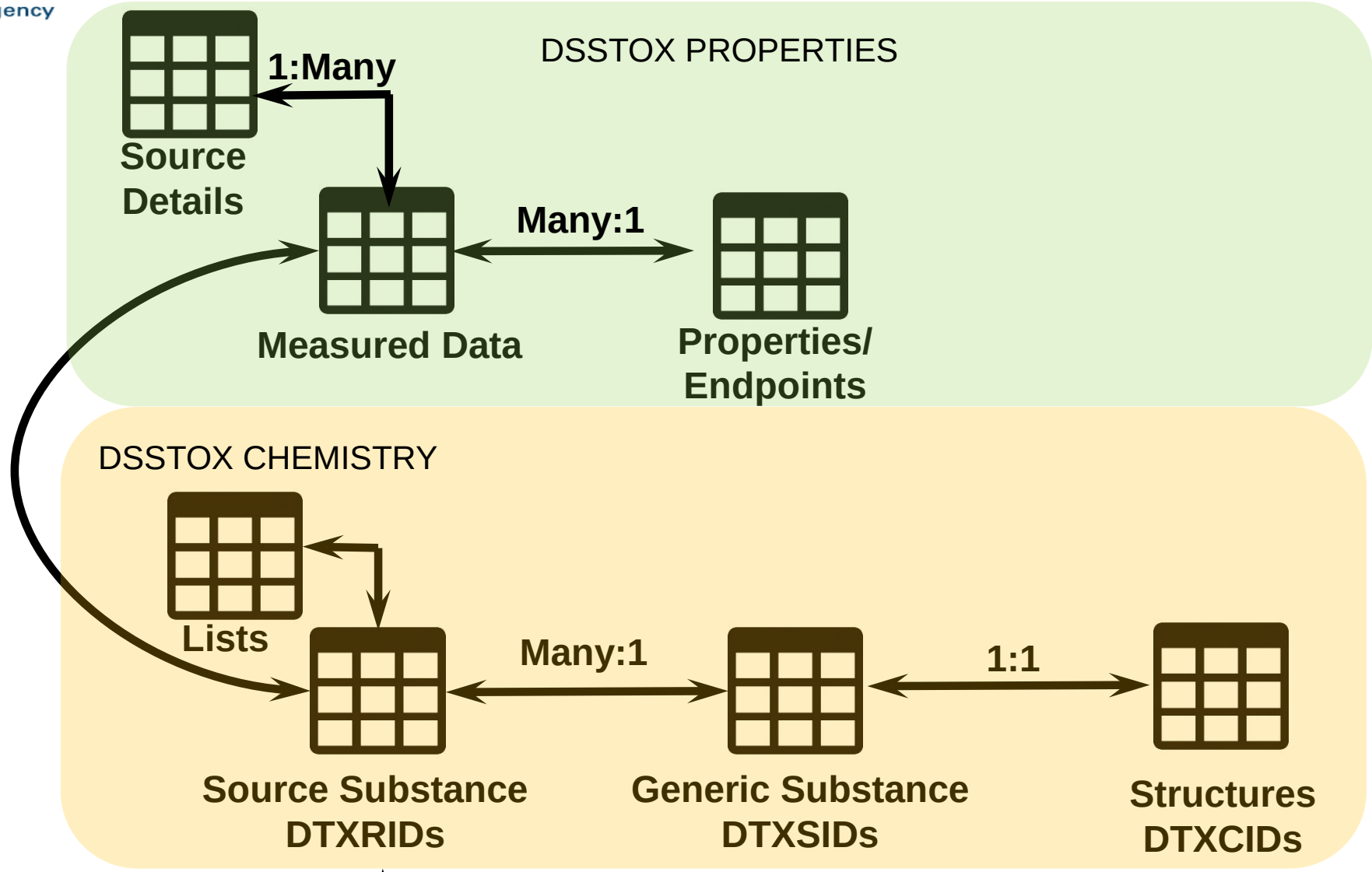
I Need
In Vivo Toxicity
Data

I Need
CPDat

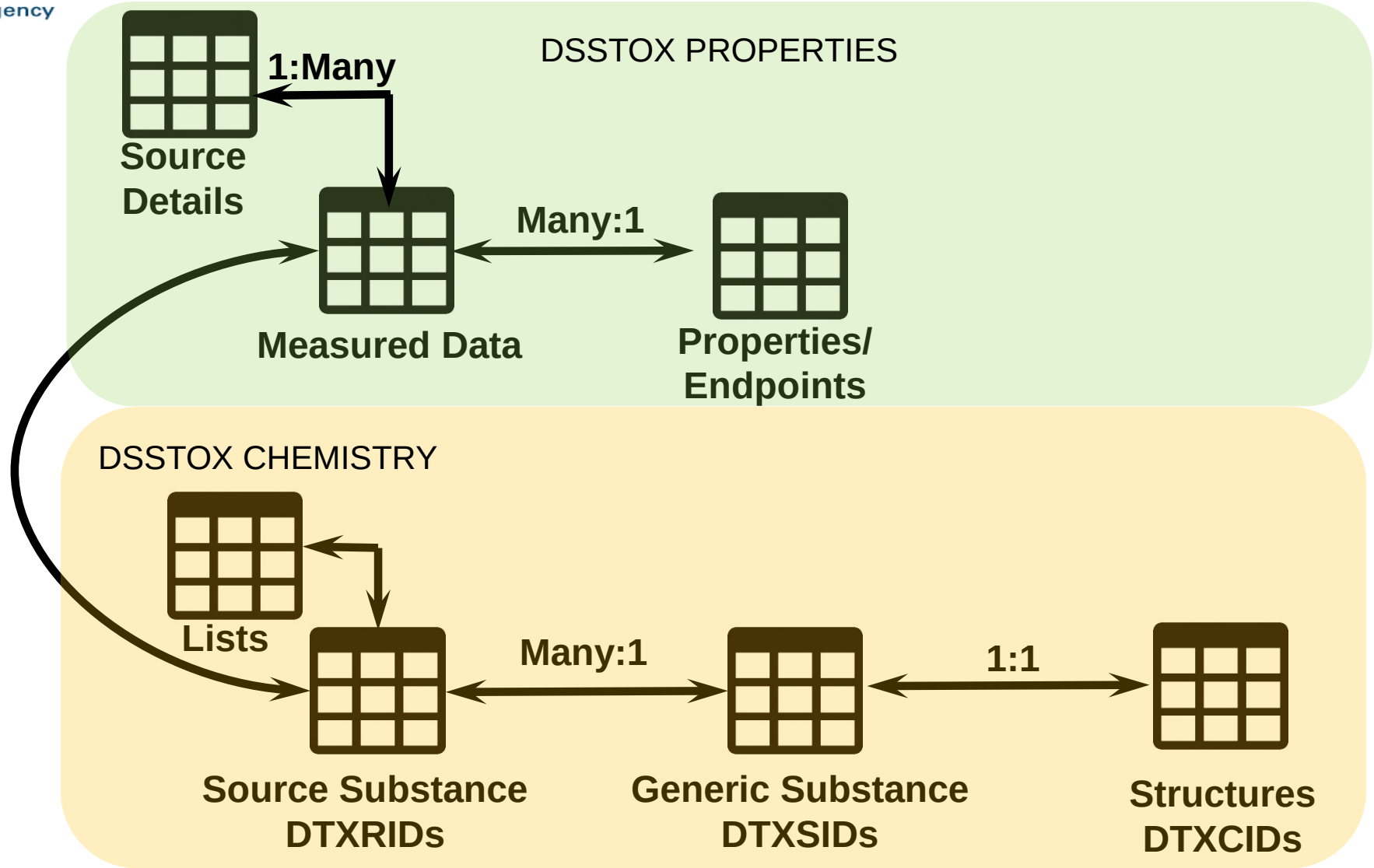
I Need PhysChem Data…



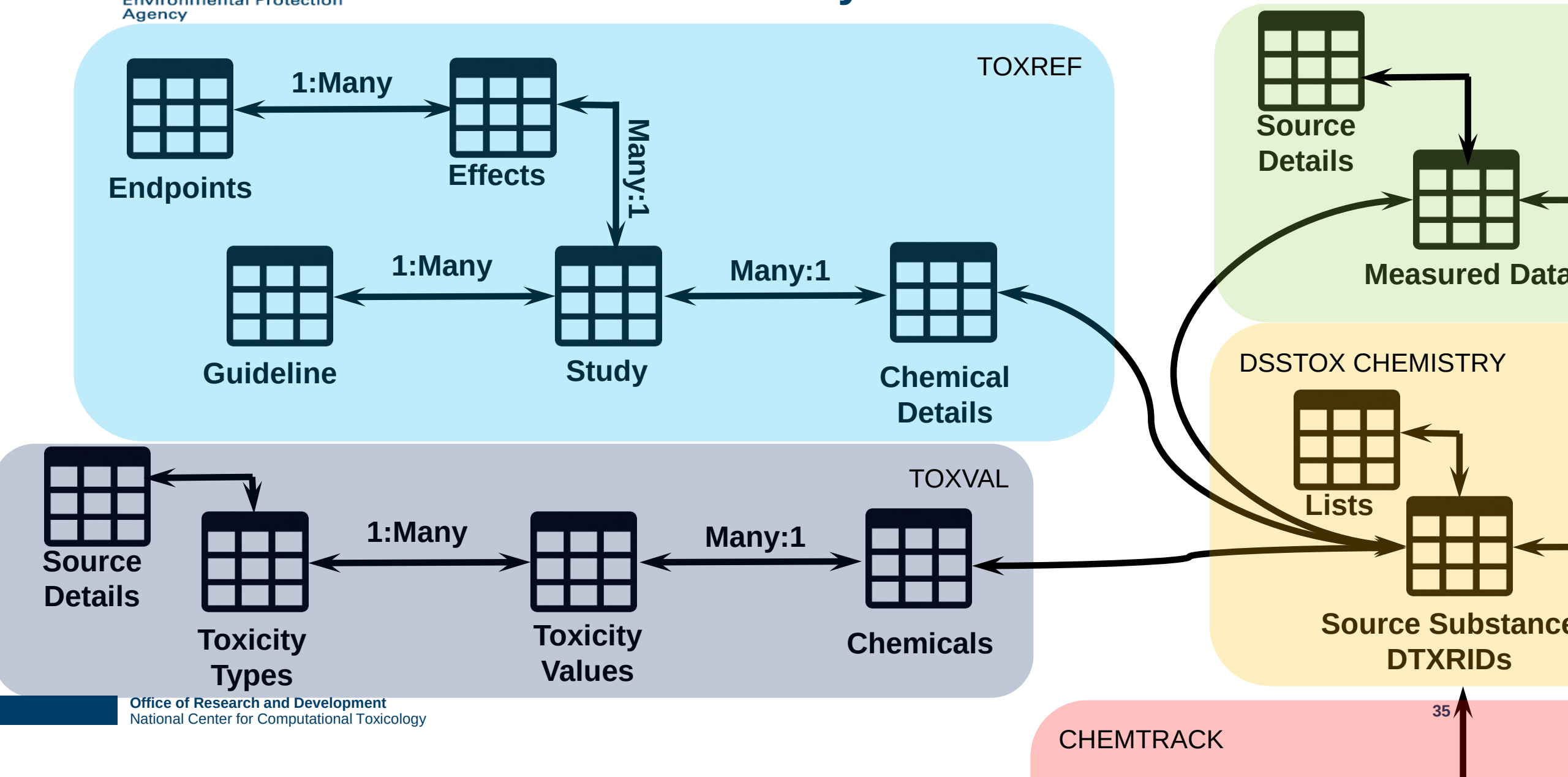
I Need PhysChem Data…



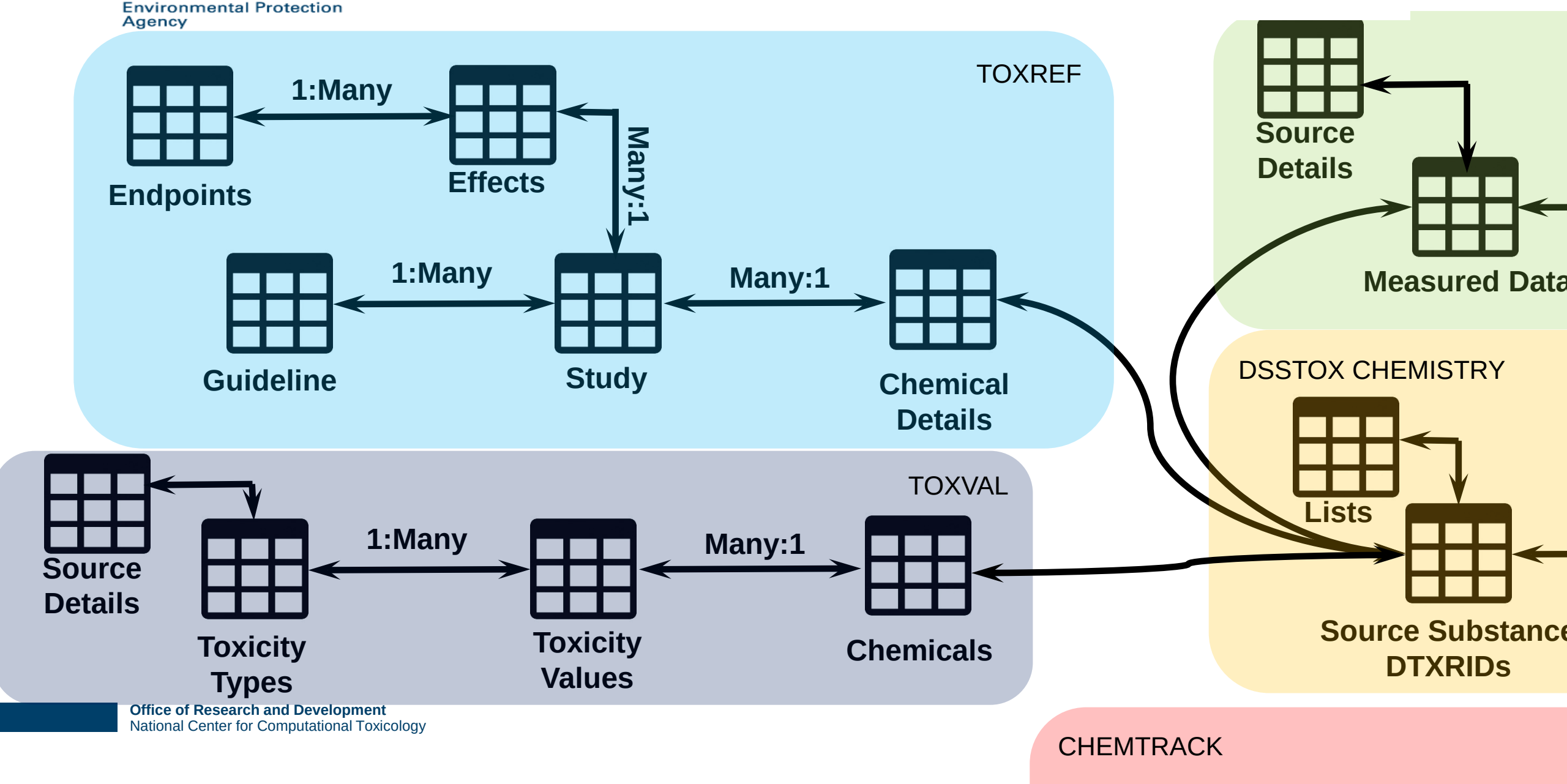
I Need *In Vivo* Toxicity Data…

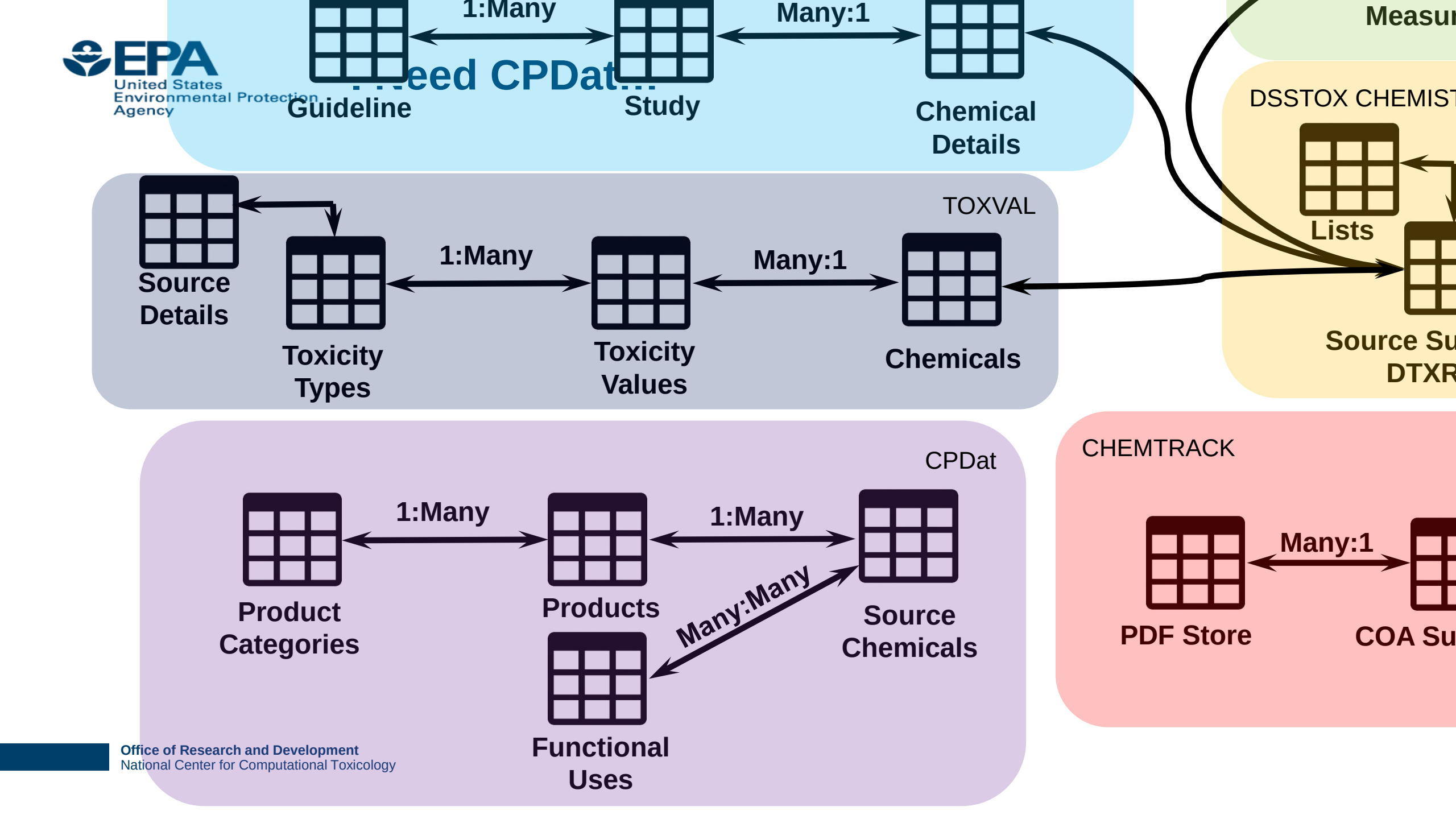


I Need *In Vivo* Toxicity Data…



I Need CPDat…


TOXREF
1:Many
Endpoints
Effects
Many:1
1:Many
Guideline
Study
Many:1
Chemical Details
Source Details
Measured Data
DSSTOX CHEMISTRY
Lists
Source Substance DTXRIDs
TOXVAL
Source Details
1:Many
Toxicity Types
Toxicity Values
Many:1
Chemicals
CHEMTRACK


EPA
United States
Environmental Protection
Agency
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Guideline
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Chemical
Details
DSSTOX CHEMIST
Lists
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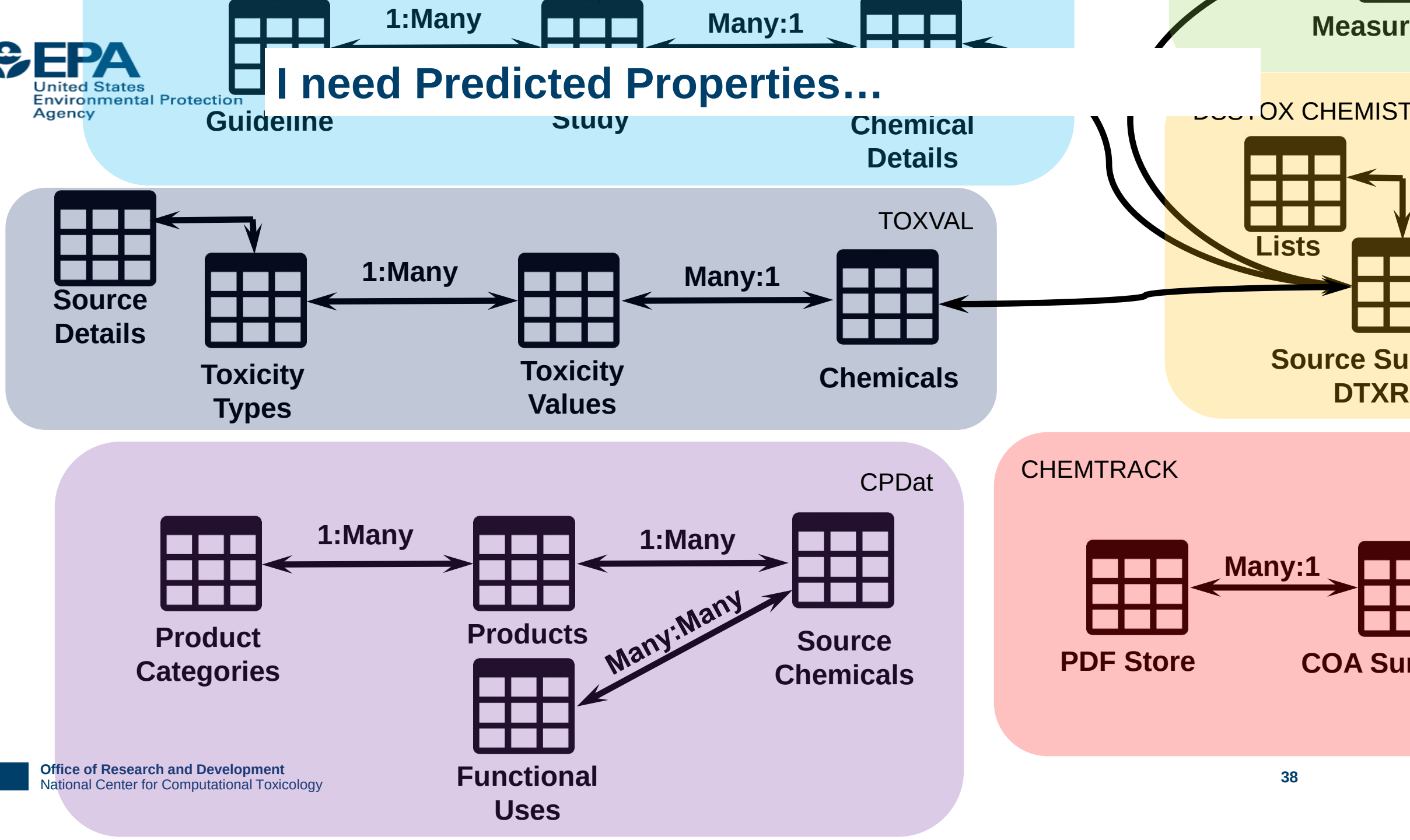
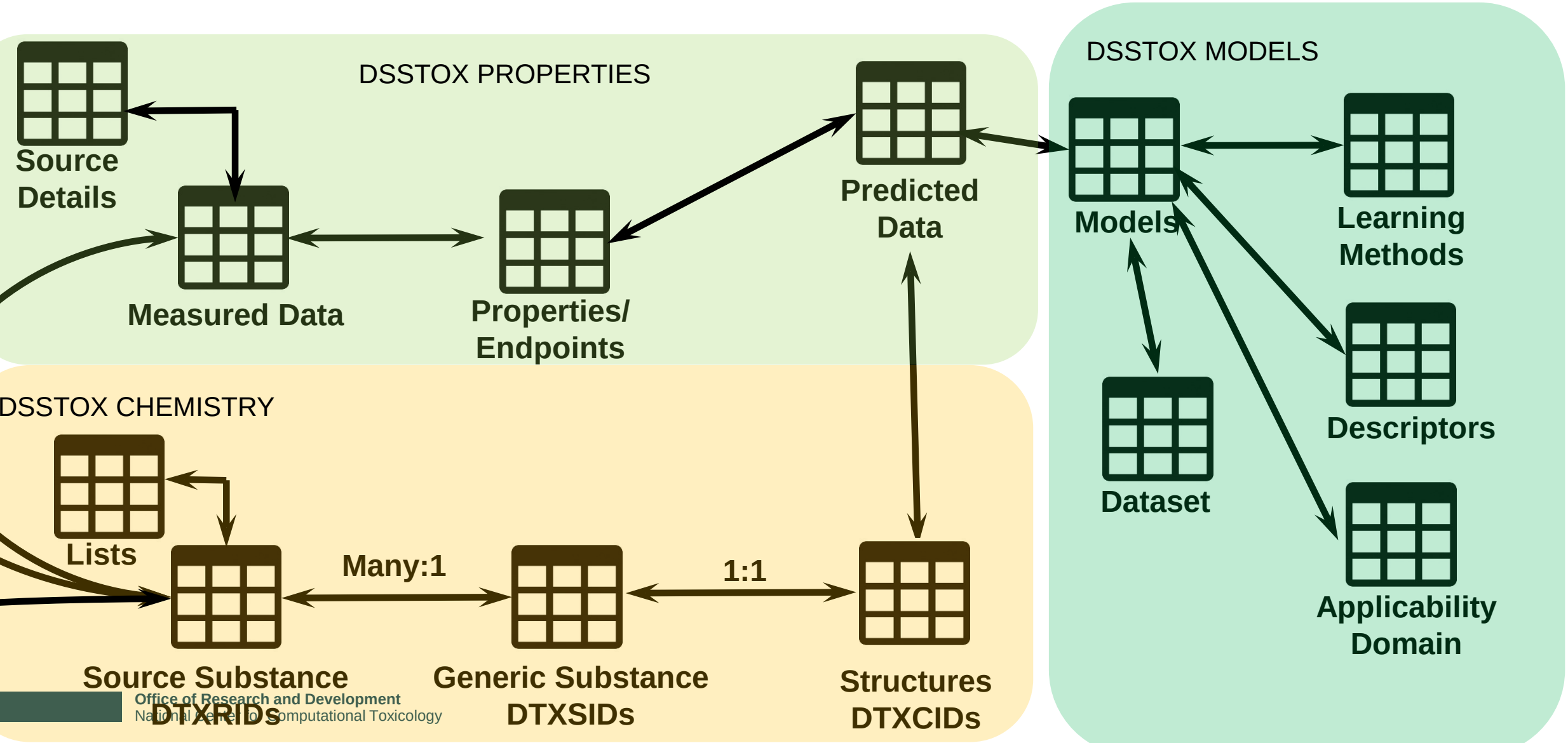
DTXR
TOXVAL
Source
Details
Toxicity
Types
1:Many
Toxicity
Values
Many:1
Chemicals
CPDat
Product
Categories
1:Many
Products
1:Many
Source
Chemicals
Many:Many
Functional
Uses
CHEMTRACK
PDF Store
Many:1
COA Su
Office of Research and Development
National Center for Computational Toxicology

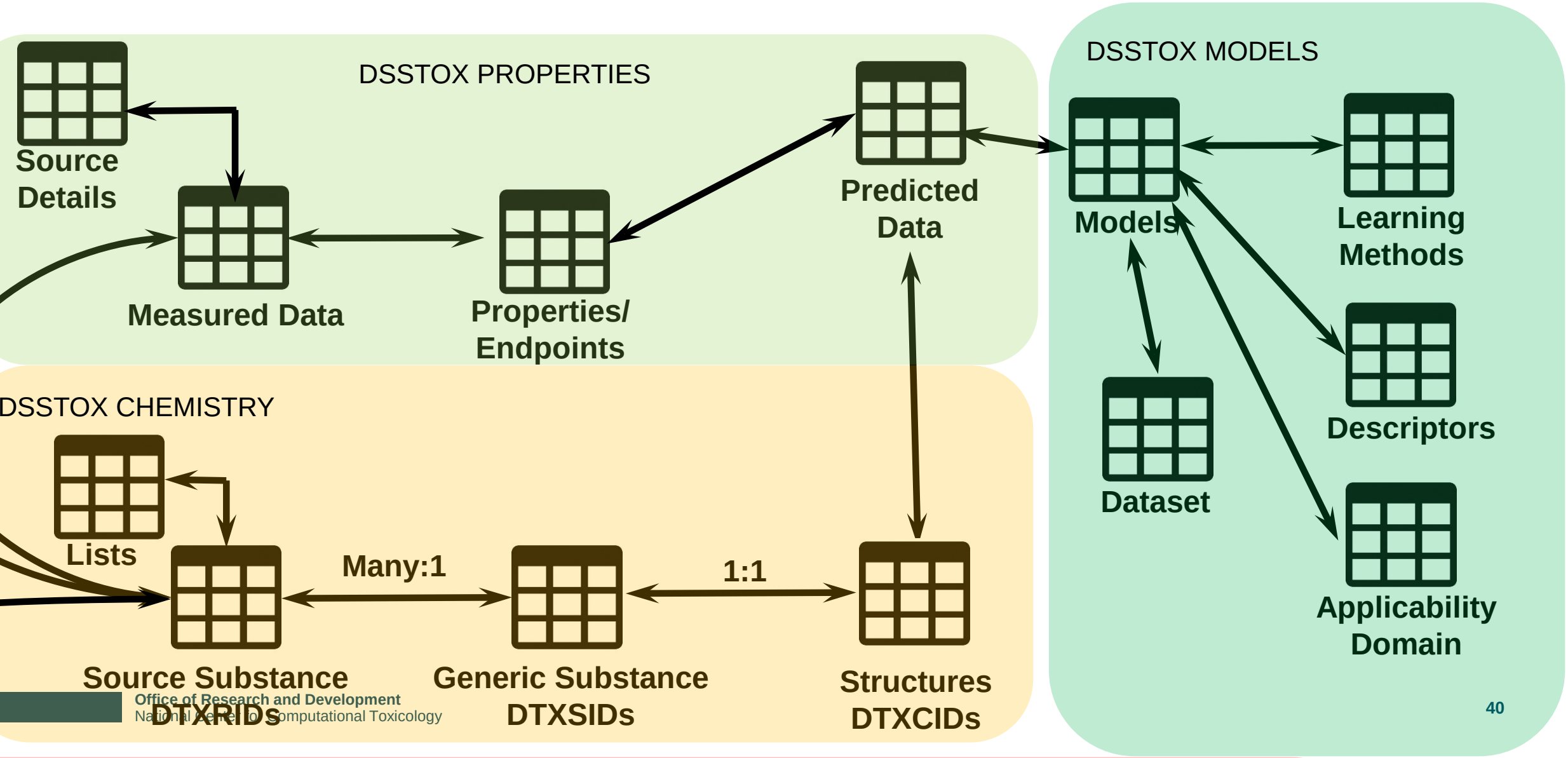
I need Predicted Properties…



I need Predicted Properties…



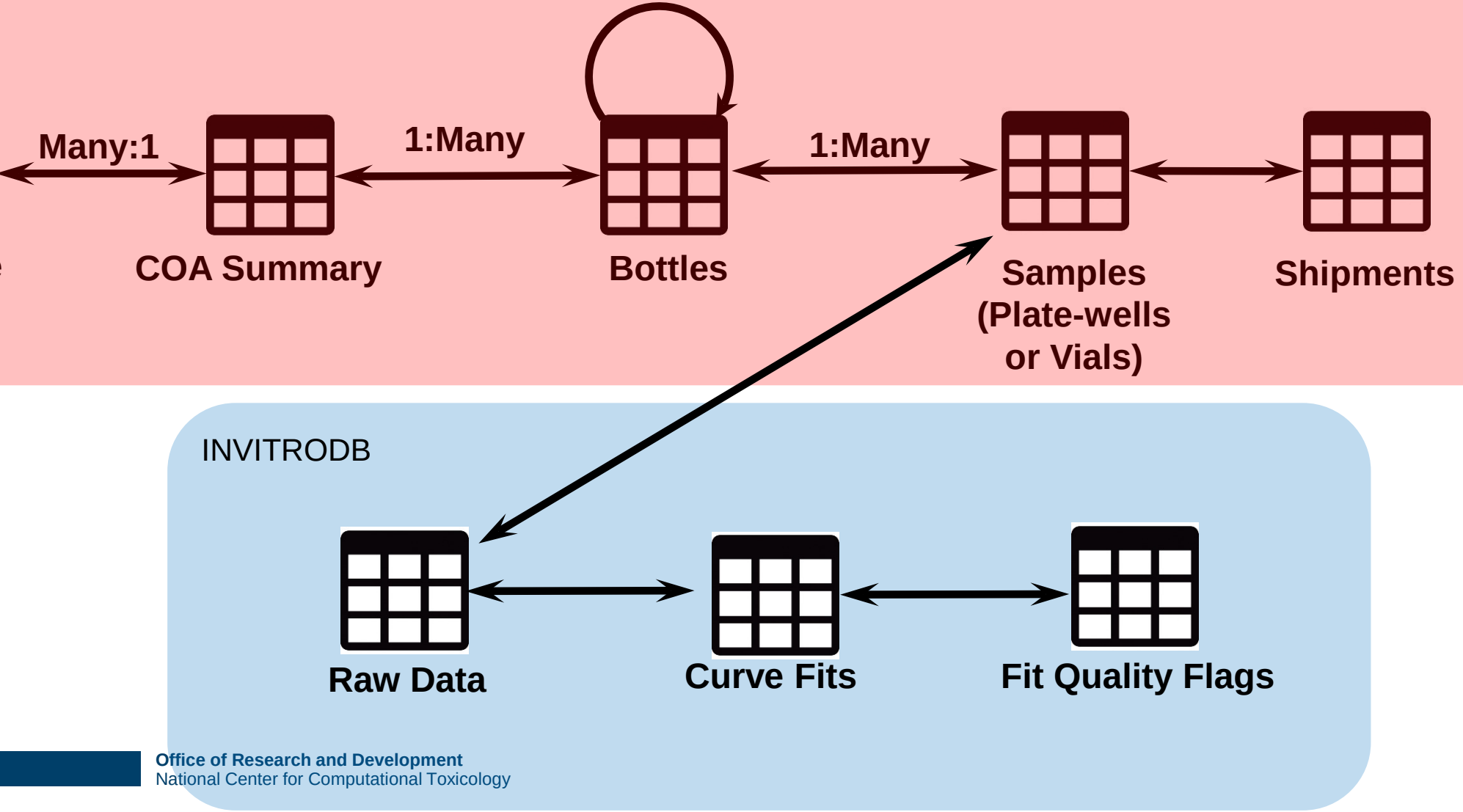
I need ToxCast Results…



Applicability

Source Substance
DTXRIDs

I need ToxCast Results…

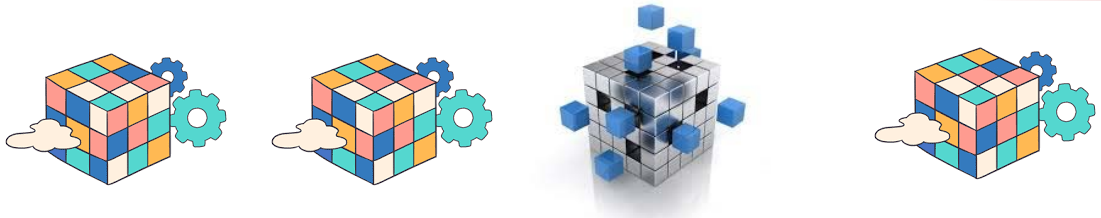


Its all too much! A path forward…

Fit-for-purpose technologies

Application/Analytics Layer

Virtual Databases (VDB's) – using Data Virtualization technology and some may be physical data especially high volume



Data Object Layer (Fit-for-Purpose)

Chemistry BioAssays Chemical Exposure Risk GenRA LitDb

Fit-for-purpose technologies (technology ecosystem)

Persistent Layer

Data orchestration using Pentaho (PDI) / or other technologies

ChemTrack ChemReg ChemProp Unstructured/ structured Pubmed . . . .

Data Source Layer

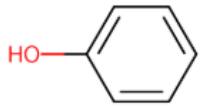
Raw data processing and data curation, quality tools

Contribution: Jeff Edwards and Amar Singh

Supporting Chemical Relationships

- HAZARD
- ADME
- EXPOSURE
- BIOACTIVITY
- SIMILAR COMPOUNDS
- GENRA (BETA)
- **RELATED SUBSTANCES**
- SYNONYMS
- LITERATURE
- LINKS
- COMMENTS

Searched Chemical



Phenol
DTXSID: DTXSID5021124
CASRN: 108-95-2
TOXCAST: 3/539

Predecessor: Component

3 related chemical structures with this substance

Carbonic dichloride polymer with 4,4'-(1...
DTXSID: DTXSID50872810
CASRN: 73990-30-4
TOXCAST: 0

Predecessor: Component

3 related chemical structures with this substance

Mixed esters of phosphoric acid with [1,...
DTXSID: DTXSID60872765
CASRN: 1003300-73-9
TOXCAST: 0

Predecessor: Component

4 related chemical structures with this substance

1(or2)-Phenoxypropanol
DTXSID: DTXSID6029759
CASRN: 41593-38-8
TOXCAST: 0

Predecessor: Component

2 related chemical structures with this substance

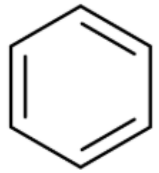
Phenol-formaldehyde resin
DTXSID: DTXSID2049713
CASRN: 9003-35-4
TOXCAST: 0

Predecessor: Component

3 related chemical structures with this substance

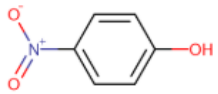
Phenol-formaldehyde-ammonia polymer
DTXSID: DTXSID8049624
CASRN: 35297-54-2
TOXCAST: 0

Transformation Parent



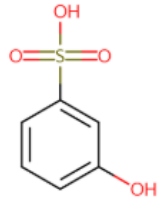
Benzene
DTXSID: DTXSID3039242
CASRN: 71-43-2
TOXCAST: 0

Transformation Product



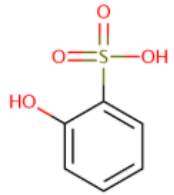
4-Nitrophenol
DTXSID: DTXSID0021834
CASRN: 100-02-7
TOXCAST: 13/571

Transformation Product



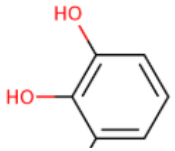
m-Phenolsulfonic acid
DTXSID: DTXSID8060406
CASRN: 585-38-6
TOXCAST: 0

Transformation Product



o-Phenolsulfonic acid
DTXSID: DTXSID90274036
CASRN: 609-46-1
TOXCAST: 0

Transformation Product



UVCB Chemicals

- UVCB chemical examples
  - Surfactants with undefined composition
  - Petroleum Distillates
  - Gelatins, hydrozylates
  - Formaldehyde, reaction products with diethanolamine
  - Fatty acids, linseed-oil, compds. with triethylamine

Chemical Families (e.g. PCBs)

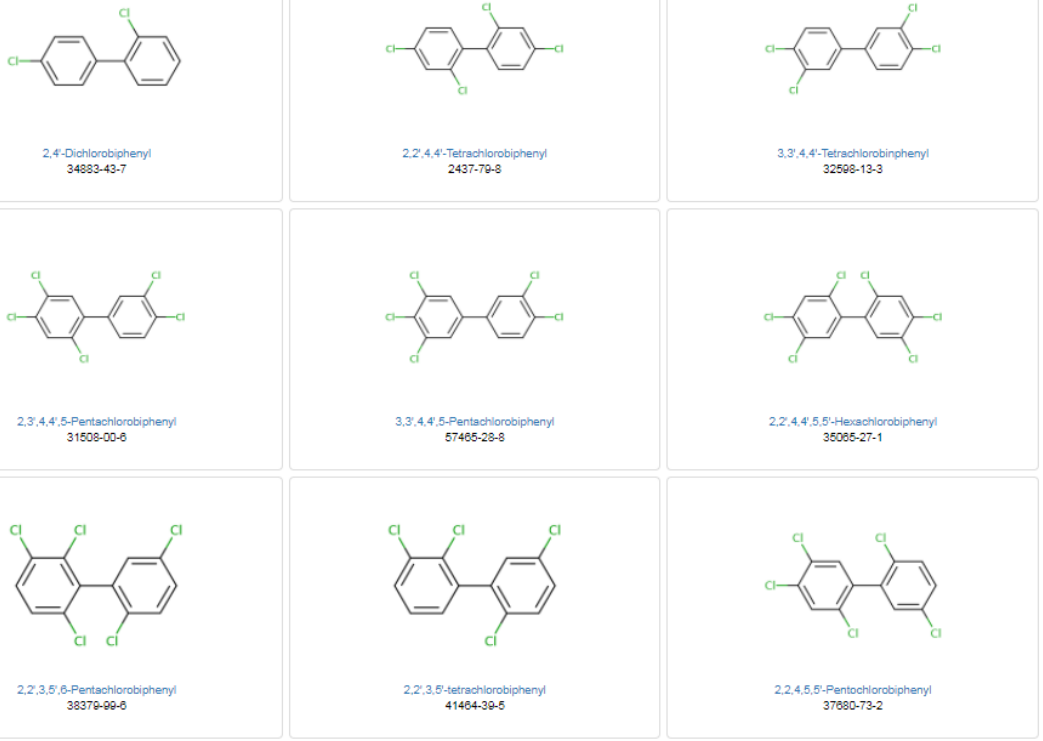
Successor Substances (209)

	CAS-RN	Relationship	
	32774-16-6	is a Representative Isomer of this	
	2051-60-7	is a Representative Isomer of this	
	2051-61-8	is a Representative Isomer of this	
	2051-62-9	is a Representative Isomer of this	
	13029-08-8	is a Representative Isomer of this	
	16605-91-7	is a Representative Isomer of this	
	25569-80-6	is a Representative Isomer of this	
	33284-50-3	is a Representative Isomer of this	
	34883-43-7	is a Representative Isomer of this	
	34883-39-1	is a Representative Isomer of this	
	33146-45-1	is a Representative Isomer of this	
	2050-67-1	is a Representative Isomer of this	
	2974-92-7	is a Representative Isomer of this	
	2974-90-5	is a Representative Isomer of this	Public
	34883-41-5	is a Representative Isomer of this	Public
	2050-68-2	is a Representative Isomer of this	Public

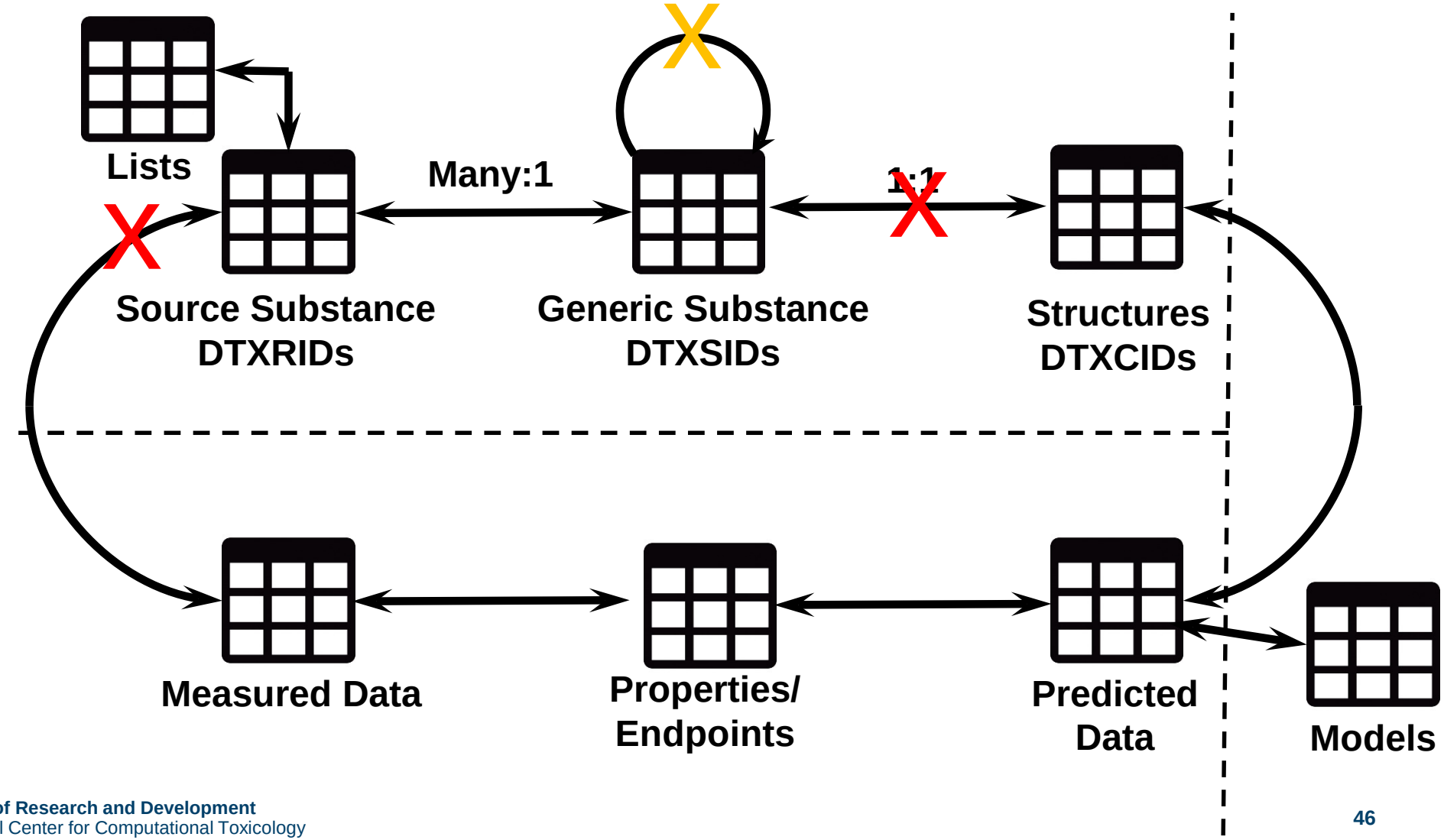
Related Chemicals

Found 209 chemicals

Download as: TSV Excel SDF



Data linkage breakdown



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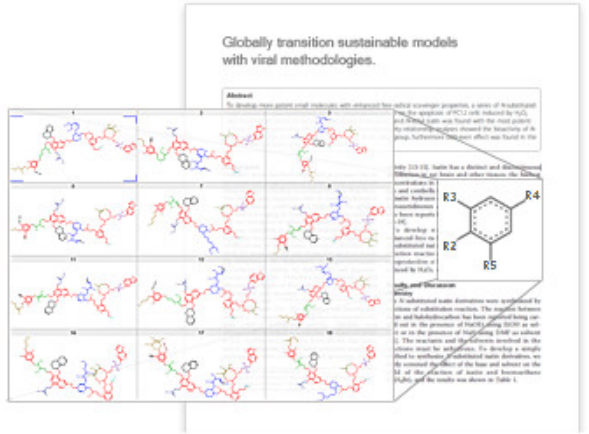
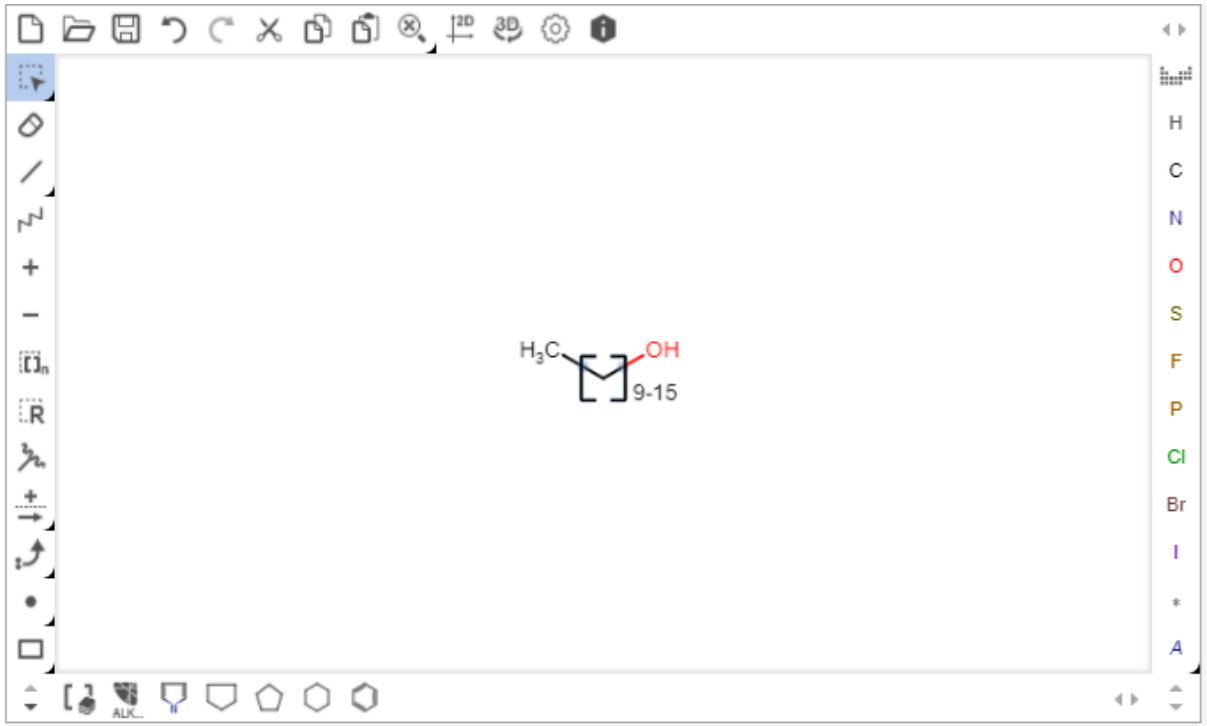
TOOLKIT FOR THE ANALYSIS OF VIRTUAL COMBINATORIAL LIBRARY AND PATENT MARKUSH STRUCTURES

Markush structures, or generic structures, are widely used in combinatorial libraries and chemical patents to define large chemical spaces. ChemAxon provides the most advanced Markush technology, including rapid structure search in Markush space, enumeration, overlap analyses, and automatic Markush composition. All Markush analysis features are available as an add-on for ChemAxon's JChem technology (JChem Base, JChem Cartridge and Instant JChem).



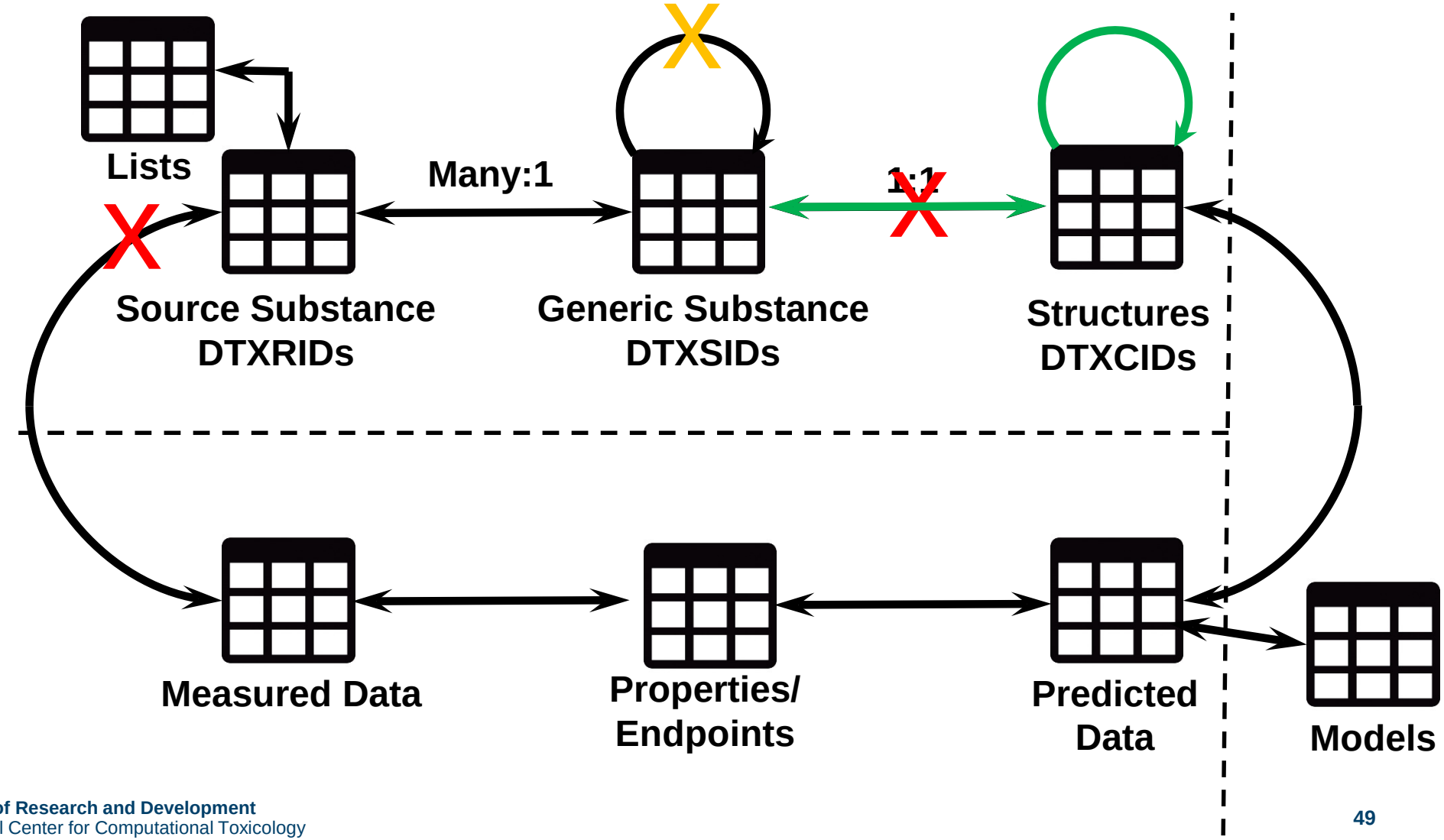
Update Record



Calculate from Structure

Substance_ID: DTXSID4028331
CAS: 67762-41-8
Name: C10-16 Alcohols
Substance Type: Mixture/Formulation
QC Level: DSSTox_High
Data Source: STN(DSSTox)
QC Notes: SDA (Soap and Detergent Association) Reporting Number: 15-060-00. SDA Substance Name: C10-C16 alkyl alcohol

Compound_ID:
Chemical Shown: Markush Enumerable
Private Notes:
Source of CAS-Compound: Public
Double Stereo: None
Chiral Stereo: None
Chemical Form: Organic
Organic Form: Parent


Lists
Many:1
1:1
Source Substance
DTXRIDs
Generic Substance
DTXSIDs
Structures
DTXCIDs
Measured Data
Properties/
Endpoints
Predicted
Data
Models

Collecting Property Distributions for Markush Members

- Melting Point
- Boiling Point
- Surface Tension
- **Vapor Pressure**
- LogKoa: Octanol-Air
- Henry's Law
- Index of Refraction
- Molar Refractivity
- Molar Volume
- Polarizability

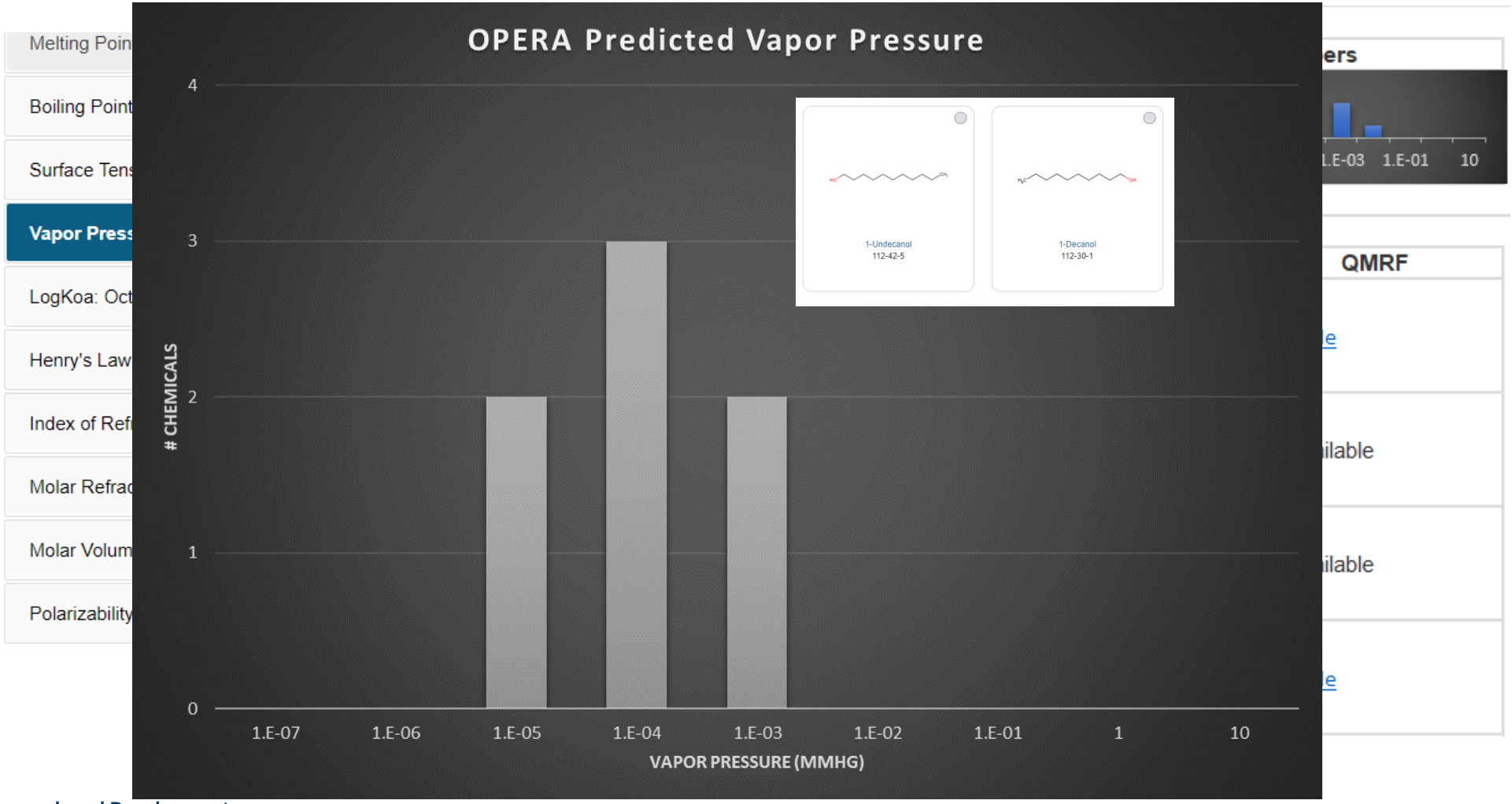
Experimental

Source	Result	
PhysPropNCCT	2.52e-05 mmHg	

Predicted

Source	Result	Calcu
NICEATM	5.23e-05 mmHg	Not Available
ACD/Labs	1.24e-04 mmHg	Not Available
TEST	1.24e-05 mmHg	TEST Report
OPERA	1.33e-05 mmHg	OPERA Model Report

Collecting Property Distributions for Markush Members



Conclusions

- There is a lot of data
- We want to connect it all
- Please, share your priorities through the Comptox Dashboard! https://comptox.epa.gov/dashboard

“Evil” Status

- ~~Evil Act I (completed 2 years ago)~~
  - ~~Yes, I designed the mixtures~~
  - ~~Yes, there were some mistakes in the mixtures~~
  - ~~Yes, I wanted to make them even more complicated~~
  - ~~Yes, you can blame me for everything~~
- ~~Evil Act II (continuing)~~
  - ~~Yes, I am going to talk about databases~~
  - ~~Yes, we want all your data~~
  - ~~Yes, you are going to probably want to take a nap~~
- Evil Act III (only if I can convince Elin and Jon)
  - Yes, I want to make new mixtures to really cause problems

Acknowledgements

EPA NCCT IT
Jeff Edwards
Jeremy Dunne
Amar Singh

EPA NCCT Registration
David McKee
Inthirany Thillainadarajah
Sakuntala Sivasupramaniam

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Katie Paul-Friedman
Richard Judson
Duncan McPherson

EPA NERL CPDat
Kathie Dionisio
Katherine Phillips
Kristin Isaacs
Brian Meyer

EPA NCCT ChemTrack
Chris Higgins
Jon Gardner
Kathy Coutros

EPA United States Environmental Protection Agency

Questions?