An Online Prediction Platform to Support the Environmental Sciences

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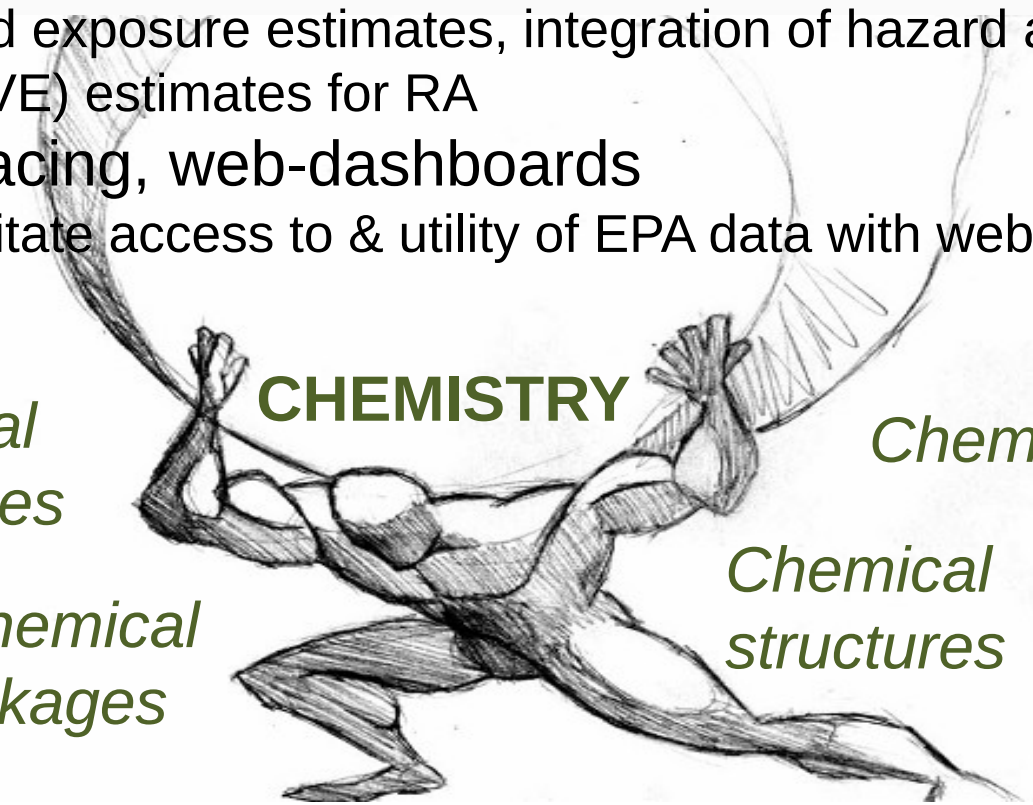
This work was reviewed by the U.S. EPA and approved for presentation but does not necessarily reflect official Agency policy.

March, 13-17, 2016
ACS Spring Meeting, San Diego, CA

EPA's National Center for Computational Toxicology (NCCT)

- ToxCast (EPA) & Tox21 (Multi-Agency)
  - screening >3800 (ToxCast) to >10K (Tox21) environmentally relevant chemicals across 10's to 100's of HTS assays
- ToxRef DB – guideline animal toxicity study reference DB
- ExpoCast (DBs, models), Rapid Toxicity Assessments
  - rapid exposure estimates, integration of hazard and exposure (IVIVE) estimates for RA
- Public-facing, web-dashboards
  - facilitate access to & utility of EPA data with web tools



NCCT (iCSS) Chemistry Dashboard

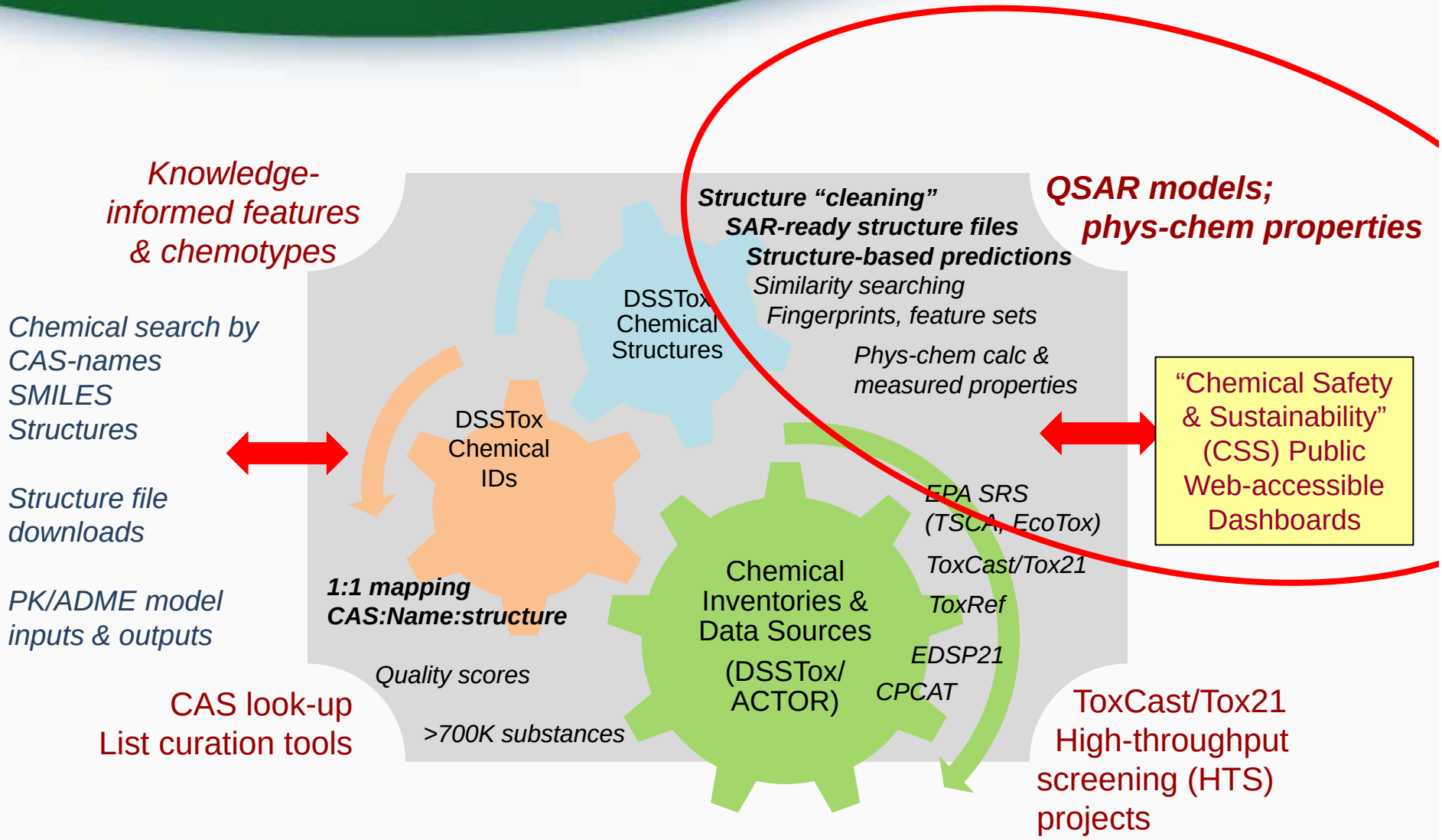
- Why build yet another public chemistry tool?
- Who is it being built for?
- How is it being built?
- What functionality & data will be included?

Using Chemistry to improve linkages across EPA Resources

- NCCT ToxCast/EDSP Dashboards
- NCCT ExpoCast, CPCat, ACToR
- EPA Chemical Safety & Sustainability (CSS) research
- EPA Substance Registry System (SRS)
- EPA Integrated Risk Information System (IRIS)
- EPA Office of Pesticides (Inerts, Active Ingredients)
- EPA Endocrine Disruption Screening Program (EDSP)
- EPA Office of Water's Chemical Contaminants List
- EPA Office of Pollution Prevention & Toxics ChemView

Just lists (pdfs, tables, names, CAS, etc.)!!

Chemistry Foundation to Support Multiple NCCT & EPA Projects

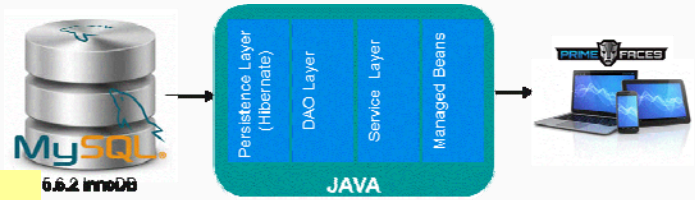


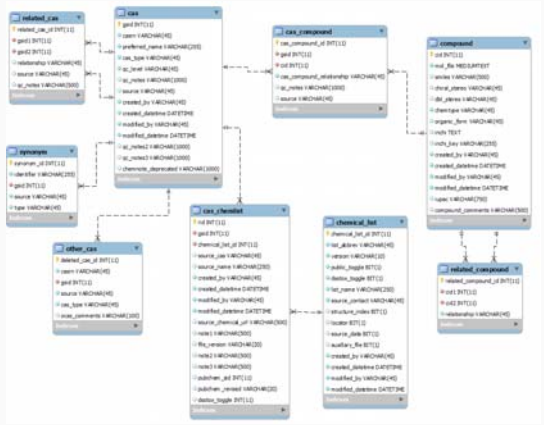
DSSTox Update

DSSTox_v1

DSSTox_v2

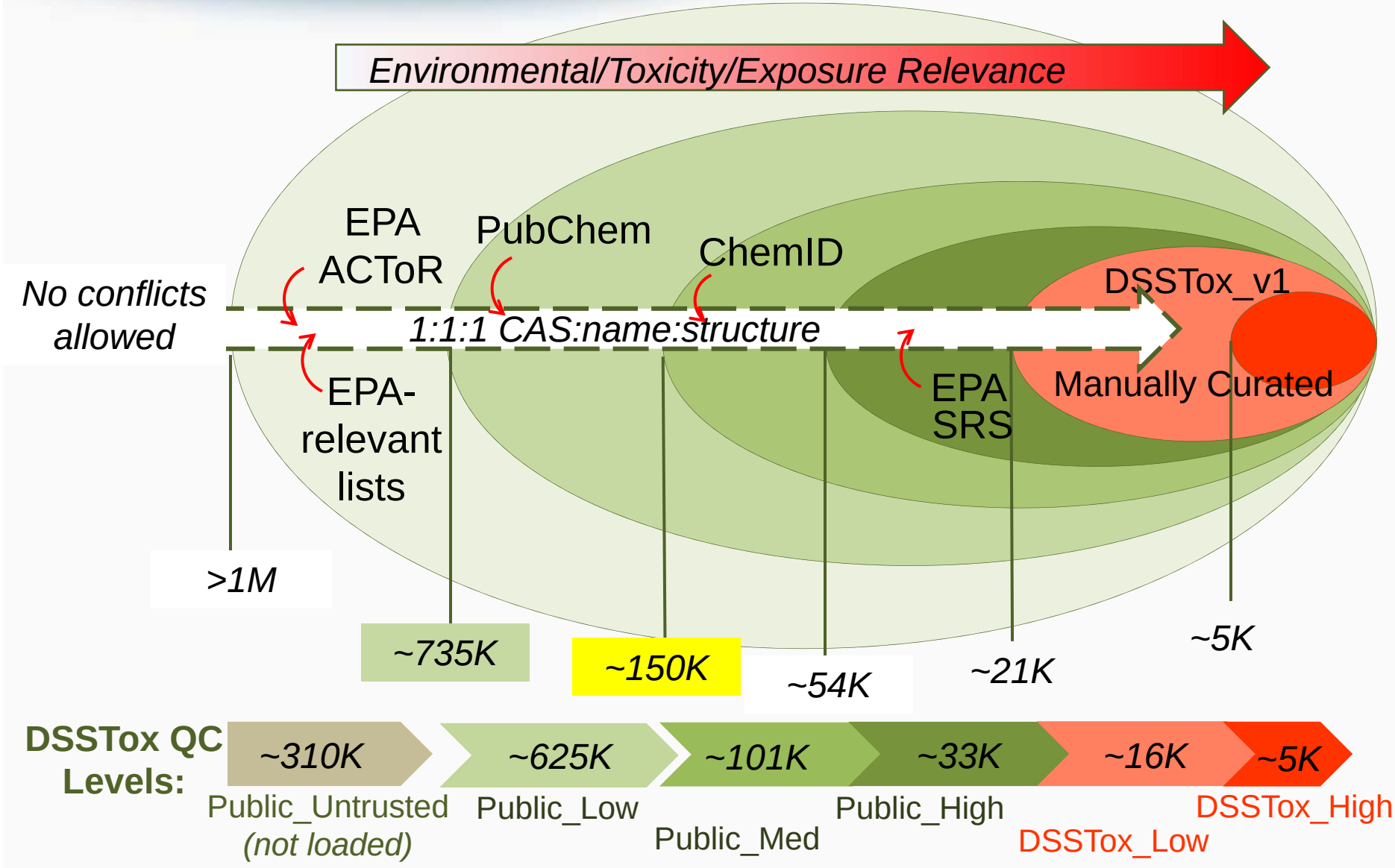
- Convert DSSTox tables to MySQL
- Develop curation interface
- Implement cheminformatics workflow
- Expand chemical content
- Expand data inventories
- Web-services & Dashboard access



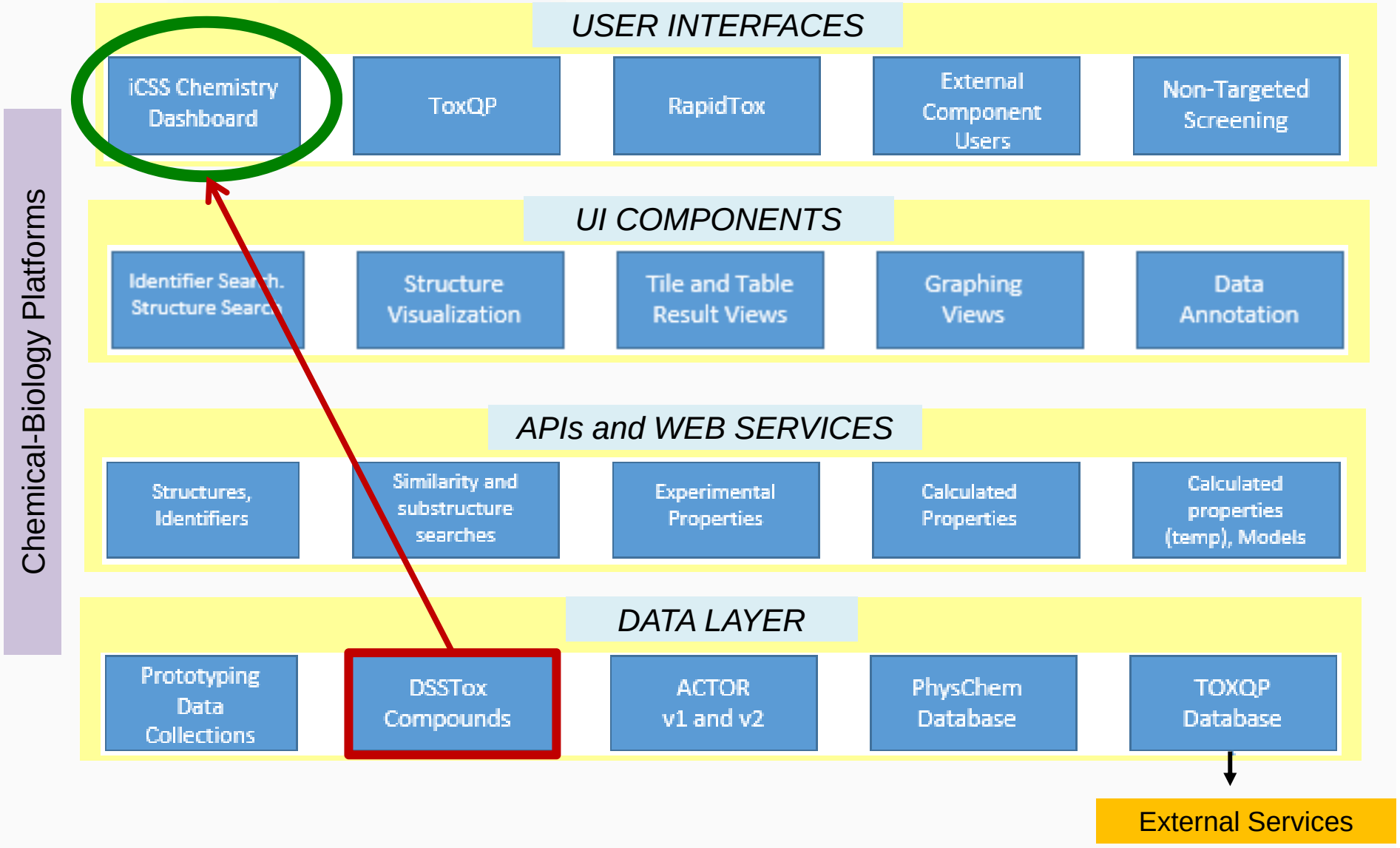


- manually curated 25K substance records
- EPA-focus, environmental tox datasets
- Emphasis on accurate CAS-name-structure annotations
- Public resource for high-quality structure-data files (SDF)

EPA's Distributed Structure-Searchable Toxicity Database (DSSTox)

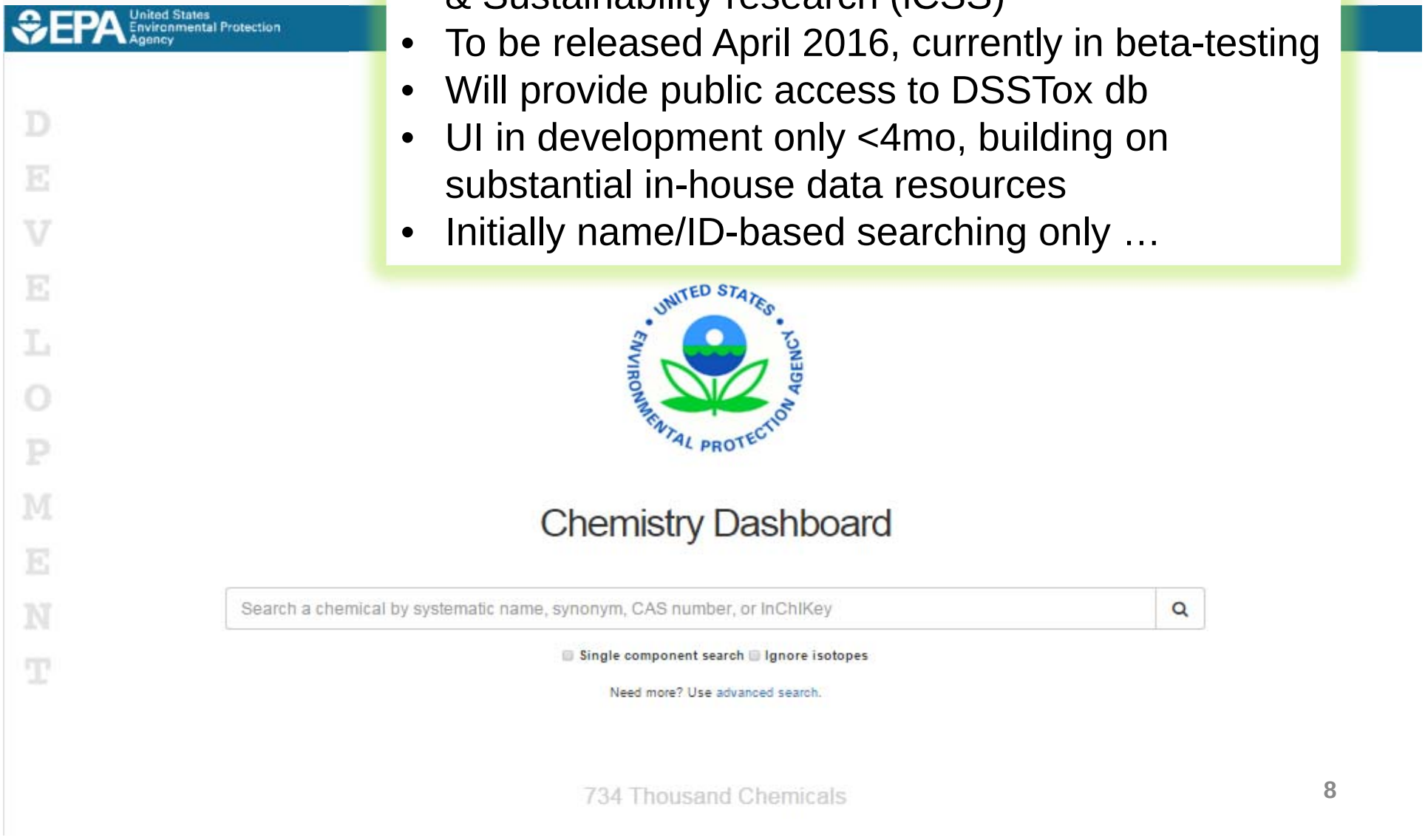


Building the Chemistry Software Architecture

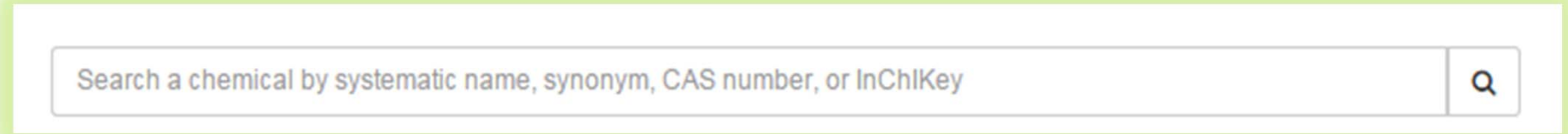


iCSS Chemistry Dashboard

- Web interface supporting EPA's Chemical Safety & Sustainability research (iCSS)
- To be released April 2016, currently in beta-testing
- Will provide public access to DSSTox db
- UI in development only <4mo, building on substantial in-house data resources
- Initially name/ID-based searching only …



Componentizing API for Resolving Chemical Names



- Look familiar?
  - *ChemSpider, PubChem, ChEMBL, NCI Resolver …*
- ONE reusable EPA component API that searches for Names and CAS Registry Numbers…
- … and SMILES, and InChIKeys, and recognizes invalid CAS Numbers, and converts SMILES when they aren't in DB, etc. etc.

iCSS Chemistry Dashboard Releasing in April 2016

EPA United States Environmental Protection Agency

Search Chemical

DEVELOPMENT

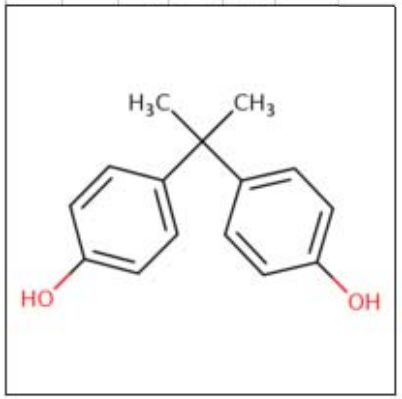
Bisphenol A

80-05-7 DTXSID7020182

Formerly DSSTox GSID, new unique public substance ID, essential for RDF/semantic web applications

Searched by Synonym: Found 1 result for 'bisphenol A'.

2D 3D



Intrinsic Properties

Molecular Formula: C15H16O2 Search in DSSTox

Average Mass: 228.291 g/mol

Monoisotopic Mass: 228.11503 g/mol

Structural Identifiers

Citation

Chemical Properties | External Links | Synonyms | PubChem Biological Activities | PubChem Articles | PubChem Patents | Comments

CSV Excel

Property	Average (Exp.)	Range (Exp.)	Average (Pred.)	Range (Pred.)
Solubility	0.001 (1)	0.0005257 to 0.0005257	0.38 (2)	0.003675 to 0.7565
Melting Point	154.929 (7)	153.0 to 158.0	144.033 (3)	131.8 to 158.0
Boiling Point	200.0 (1)	200.0 to 200.0	348.95 (2)	334.4 to 363.5
LogP	3.357 (3)	3.32 to 3.431	3.524 (3)	3.205 to 3.727
Atmospheric Hydroxylation Rate	N/A	N/A	0.0 (1)	4.237e-11 to 4.237e-11

About Contact ACToR DSSTox Privacy Accessibility Help

iCSS Chemistry Dashboard Releasing in April 2016

- Original raw source result view
- Users can submit comments
- Source details provided
- Range of results possible for single chemical

Chemical Properties: Melting Point

	Average	Range
Experimental	154.929 (7)	153.0 to 158.0
Predicted	144.033 (3)	131.8 to 158.0

CSV Excel

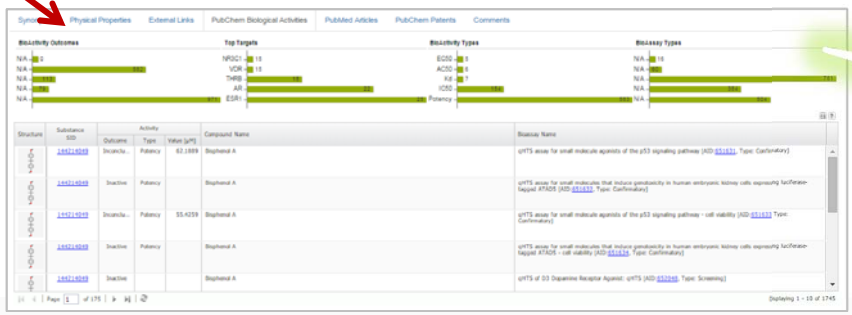
Property	Raw Result	Mean Result	Minimum Result	Maximum Result	Result Unit	Result Type	Source
Estimated MP (oC)	131.76	131.8	131.8	131.8	°C	predicted	EPI SUITE
Melting Point	153-158 °C	155.5	153.0	158.0	°C	experimental	Alfa Aesar
Melting Point	154-157 °C	155.5	154.0	157.0	°C	experimental	Merck Millipore
Melting Point	153-158 °C	155.5	153.0	158.0	°C	experimental	Alfa Aesar
Melting Point	155-158 °C	156.5	155.0	158.0	°C	predicted	J and K Scientifi
Melting Point	156 °C	156.0	156.0	156.0	°C	experimental	TCI
Melting	153 °C	153.0	153.0	153.0	°C	experimental	Jean-Claude Br

iCSS Chemistry Dashboard Releasing in April 2016

- Links external resources: EPA, NIH, property predictors

Chemical Properties | External Links | Synonyms | PubChem Biological Activities | PubChem Articles | PubChem Patents

General	Toxicology	Publications	Biochemistry	Prediction
ToxCast Dashboard 2	ACTOR	Toxline	CCRIS	Chemicalize
EPA Substance Registry Service	DrugPortal	Environmental Health Perspectives		
NIST Chemistry Webbook		NIEHS		
eChemPortal		National Toxicology Program		
Household Products Database		Google Books		
HSDB				
PubChem				
Chemspider				
EDSP Dashboard				
CPCat				
DrugBank				
HMDB				



e.g., ChemAxon's "Chemicalize" web-service

e.g., PubChem's bioactivity summary

Linkage to External Predictor, e.g. Chemicalize

Chemicalize.org (powered by ChemAxon)

www.chemicalize.org/structure/#!m

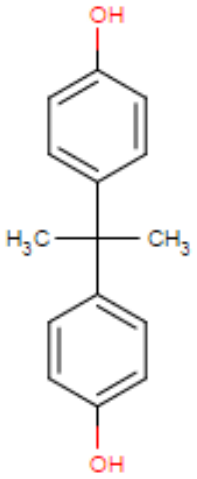
chemicalize.org beta
by ChemAxon

Properties Viewer Webpage Viewer Chem Search Web Search Doc

CC(C)(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1

Molecule

Molecule



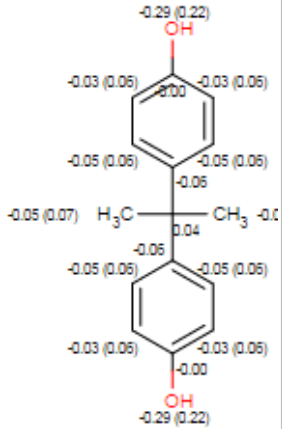
Names and identifiers

Common names: 4,4'-bisphenol A, 4,4'-bisphenol A, diphenylolprop
bisphenol A, bisphenol-A, bisphenol A, 4,4' isopropylidinediphenol,
IUPAC: 4-[2-(4-hydroxyphenyl)propan-2-yl]phenol

Smiles: CC(C)(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1
InChI: 1S/C15H16O2/c1-15(2,11-3-7-13(16)8-4-11)12-5-9-14(17)10-
InChI key: IISBACLAFKSPIT-UHFFFAOYSA-N
CAS: 27100-33-0, 80-05-7, 137885-53-1, 27360-89-0, 28106-82-3,

Charge

Atomic Charges



Elemental Analysis

Formula: $C_{15}H_{16}O_2$
Isotope formula: C15H16O2
Composition: C (78.92%), H (7.06%), O (14.02%)
Isotope composition: C (78.92%), H (7.06%), O (14.02%)
Mass: 228.2863
Exact mass: 228.115029756

Webpages

Sulfone
29 Apr 2015 - original page
wn.com/Sulfone

Microsoft Word - NLPFIN New.doc
27 Mar 2014 - original page
reach-clp-helpdesk.de/de/Downloads/NLP-Liste.pdf?__blob=pul

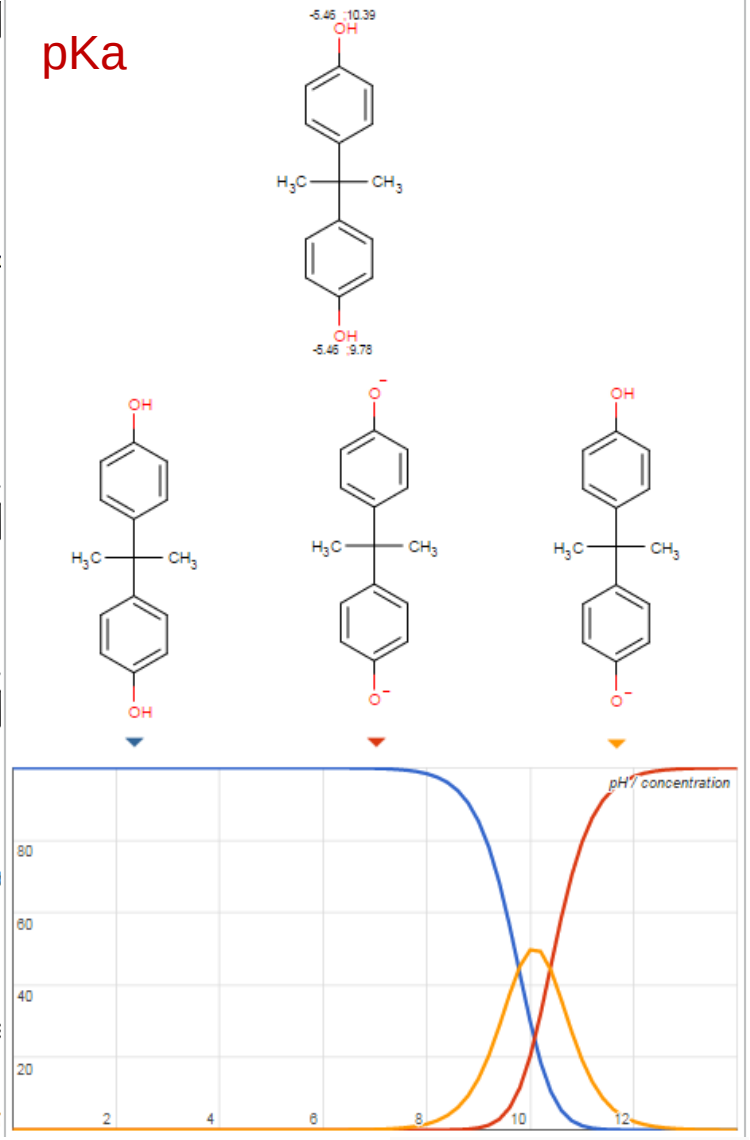
No title
17 May 2014

No title
17 Oct 2012 - original page
patbase.com/getimg/prt_text.asp?id=1551799&pn=EP1248760E

Breast Neoplasms - Genes | CTD
20 Nov 2015 - original page
ctdbase.org/detail.go;jsessionid=E301927D5D648246D5BAA72

pKa

pKa



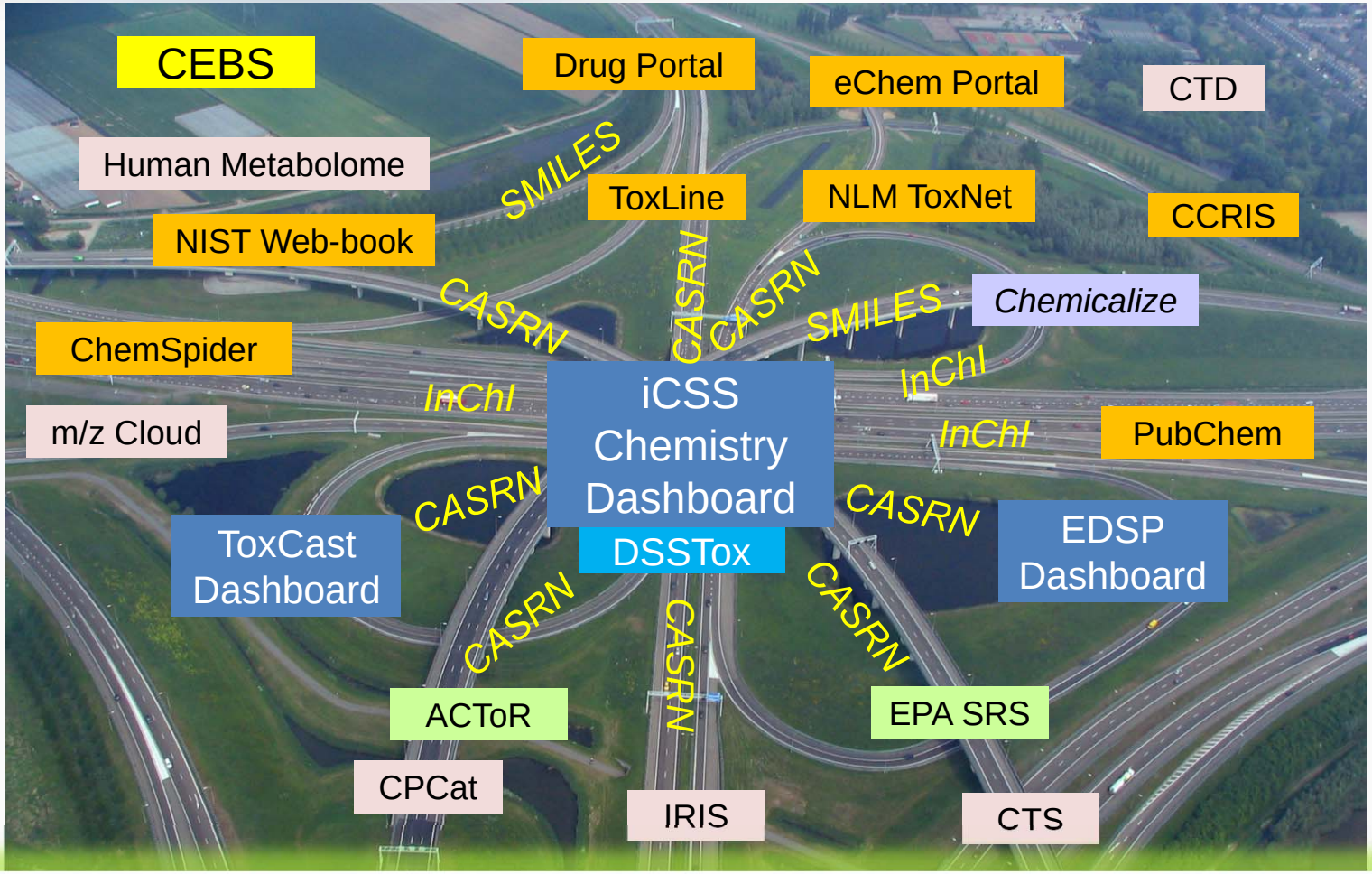
How are linkages created? e.g., CASRN

- ACTOR http://actor.epa.gov/actor/GenericChemical?casrn=80-05-7
- Toxcast Dashboard http://actor.epa.gov/dashboard2/#chemical/80-05-7
- NIST Webbook http://webbook.nist.gov/cgi/cbook.cgi?ID=80-05-7
- TOXNET http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+toxline:@term+@rn+80-05-7
- EPA SRS http://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/advancedsearch/externalSearch.do?p_type=CASNO&p_value=80-05-7

- Some links pass InChIKeys for searching
- Some links pass SMILES for searching/prediction
- Some links pass a list of rank-ordered identifiers for searching (think Google Books, Pubmed, Google Scholar)

Requires linked website be “chemically indexed”

Creating Linkages to Data Sources …



Creating linkages to indexed content is the easy part,
… creating accurate chemical-data listings is hard!

Diverse quality in databases

- Challenges in assembling a database
  - Sourcing high quality data – sorting wheat from chaff
  - How to mesh data together – based on structure? On name? On CAS number? Other identifier?
  - Checking self-consistency of data?
  - Structure validation versus property value validation – very different challenges

Existing Online Property Prediction Platforms

- ACD/Interactive Laboratory (Ilab)
- Igor Tetko's OCHEM
- The OECD Toolbox
- etc…

Learn from others' examples,
… make open, transparent, reusable,
… tailor to EPA's needs!

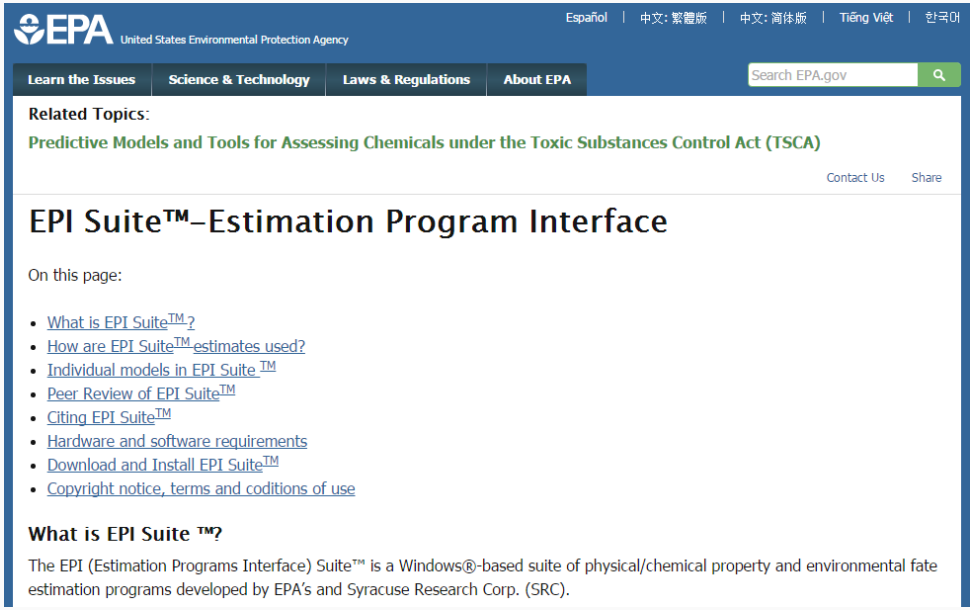
iCSS Chemistry Dashboard

- Deliver web-based platform hosting chemical property data of interest to “environmental toxicology & exposure” scientists (powered by DSSTox)
- Provide access to experimental data sets
  - e.g. EPISuite’s PHYSPROP: logP, BP, MP, WSol, etc.

but…

“data quality” is a major concern & challenge

a LOT of time was spent cleaning & curating data!

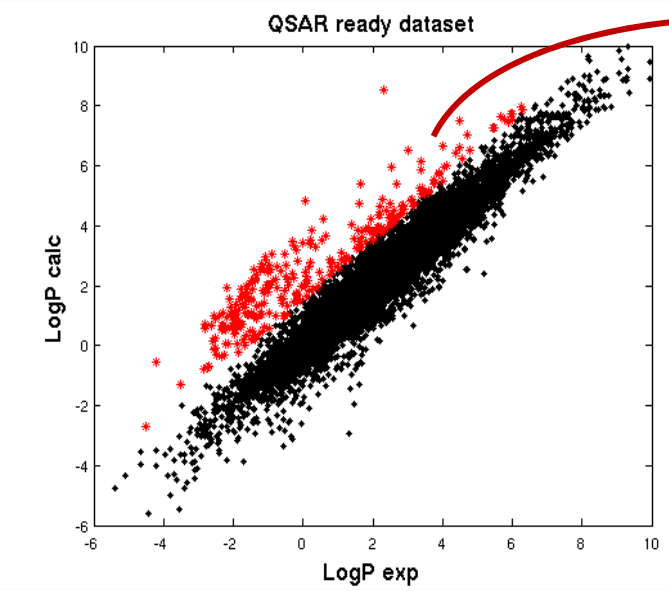


Global vs Local Models

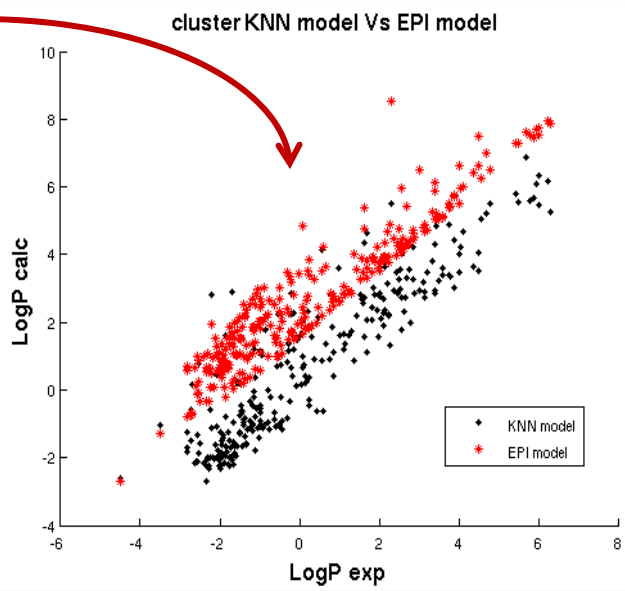
Applicability Domain (AD) of original EPI Suite LogP Model

(accuracy of the global model is an issue)

EPISuite Predicted vs. Experimental



EPISuite vs kNN Comparison of Cluster



** 280 cmpd cluster outside AD of EPI Suite → Compared to new model predictions*

Building “NCCT Models”

- Collect “Open Data” for various endpoints of interest to EPA, from e.g.
  - *PubChem*
  - *eChemPortal*
  - *Open Data Sources*

- & Build QSAR prediction models
  - ✓ Using modern machine-learning approaches
  - ✓ Ensuring high quality data as inputs
  - ✓ Populating database with measured & predicted values
  - ✓ Making experimental data training sets available
  - ✓ Allowing real-time predictions *(in the future)*

Open Data Set - example

- 200,000 melting points and 13,000 pyrolysis data points

Research article

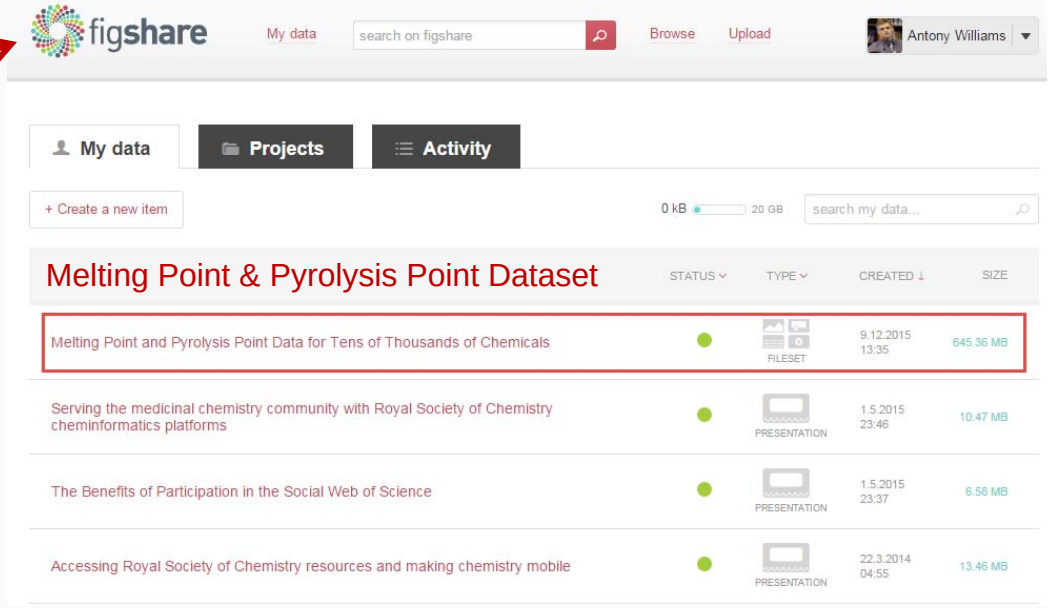
Open Access

The development of models to predict melting and pyrolysis point data associated with several hundred thousand compounds mined from PATENTS

Igor V. Tetko[1,2*], Daniel M. Lowe[3] and Antony J. Williams[4]

Journal of Cheminformatics
December 2016, 8:2

- Modeling this much data is a challenge!
- Accessibility to data?
  - Figshare.com
  - DataDryad.com
  - Institutional Repositories
  - Publishers?

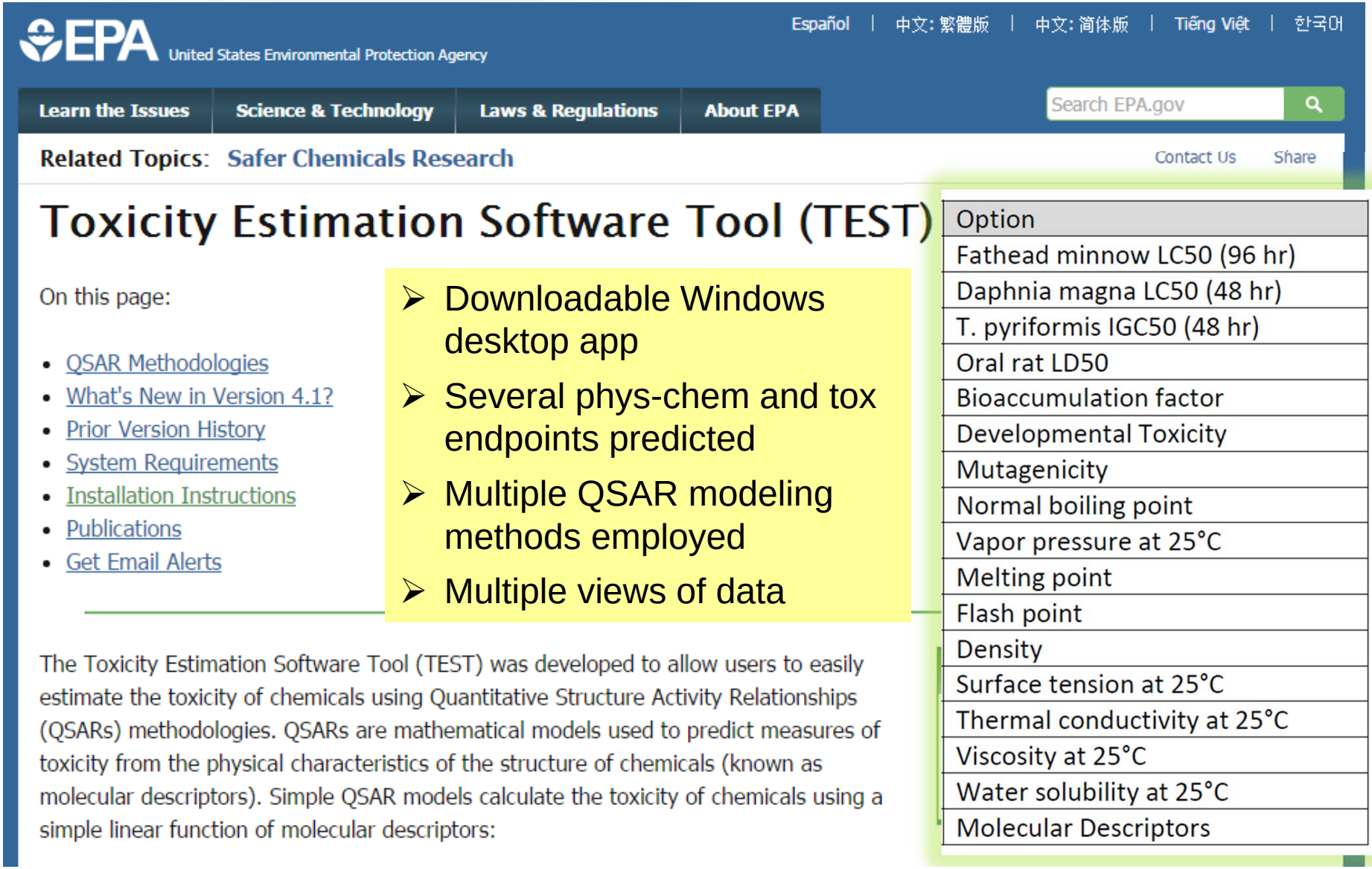


Integrating other EPA predictors

- ExpoCast
  - ➢ near & far-field exposure models
- Environmental Fate Simulator (EFS)
  - ➢ air/soil/water distribution, biotransformation
- CERAPP
  - ➢ estrogen receptor activity QSAR model
- T.E.S.T *(in progress)*
  - ➢ phys-chem properties & toxicity endpoints

e.g., T.E.S.T.

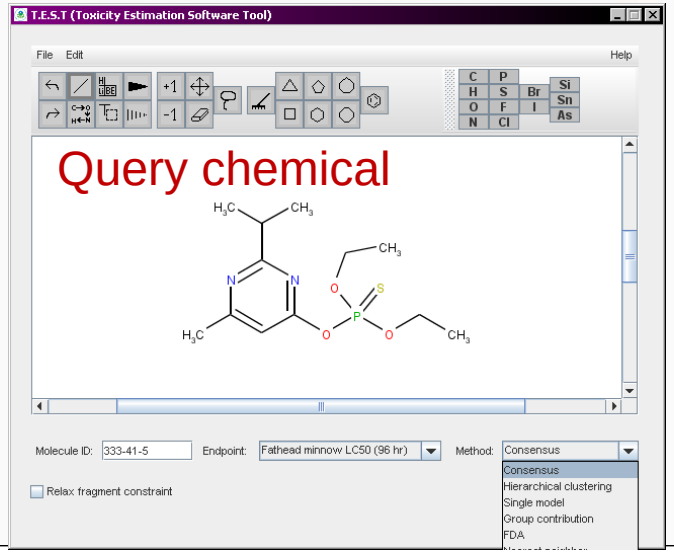
http://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test



- Downloadable Windows desktop app
- Several phys-chem and tox endpoints predicted
- Multiple QSAR modeling methods employed
- Multiple views of data

Option
Fathead minnow LC50 (96 hr)
Daphnia magna LC50 (48 hr)
T. pyriformis IGC50 (48 hr)
Oral rat LD50
Bioaccumulation factor
Developmental Toxicity
Mutagenicity
Normal boiling point
Vapor pressure at 25°C
Melting point
Flash point
Density
Surface tension at 25°C
Thermal conductivity at 25°C
Viscosity at 25°C
Water solubility at 25°C
Molecular Descriptors

T.E.S.T. QSAR Model Prediction Views



Model # 1296

Toxicity prediction results for 333-41-5 for Hierarchical clustering method

Prediction results

Endpoint	Experimental value CAS: 333-41-5 Source: ECOTOX	Predicted value[a]	Prediction interval
Fathead minnow LC_{50} (96 hr) -Log(mol/L)	4.81	5.39	4.54 ≤ Tox ≤ 6.24
Fathead minnow LC_{50} (96 hr) mg/L	4.70	1.23	0.17 ≤ Tox ≤ 8.71

[a]Note: the test chemical was present in the external test set.

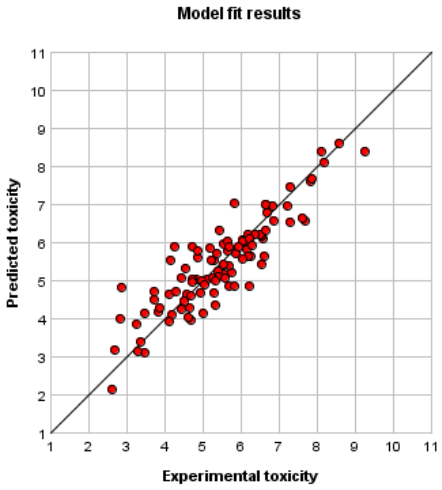
Prediction results

Cluster model predictions and statistics

Cluster model	Test chemical descriptor values	Prediction interval -Log(mol/L)	r^2	q^2	#chemicals
1296	Descriptors	6.010 ± 1.136	0.793	0.733	101
1300	Descriptors	5.458 ± 1.312	0.729	0.645	111
1301	Descriptors	5.136 ± 1.169	0.747	0.718	294
1302	Descriptors	4.922 ± 1.182	0.774	0.751	641

Model statistics

Parameter	Value
Endpoint	Fathead minnow LC_{50} (96 hr)
r^2	0.793
q^2	0.733
#chemicals	101
Model	Model # 1296



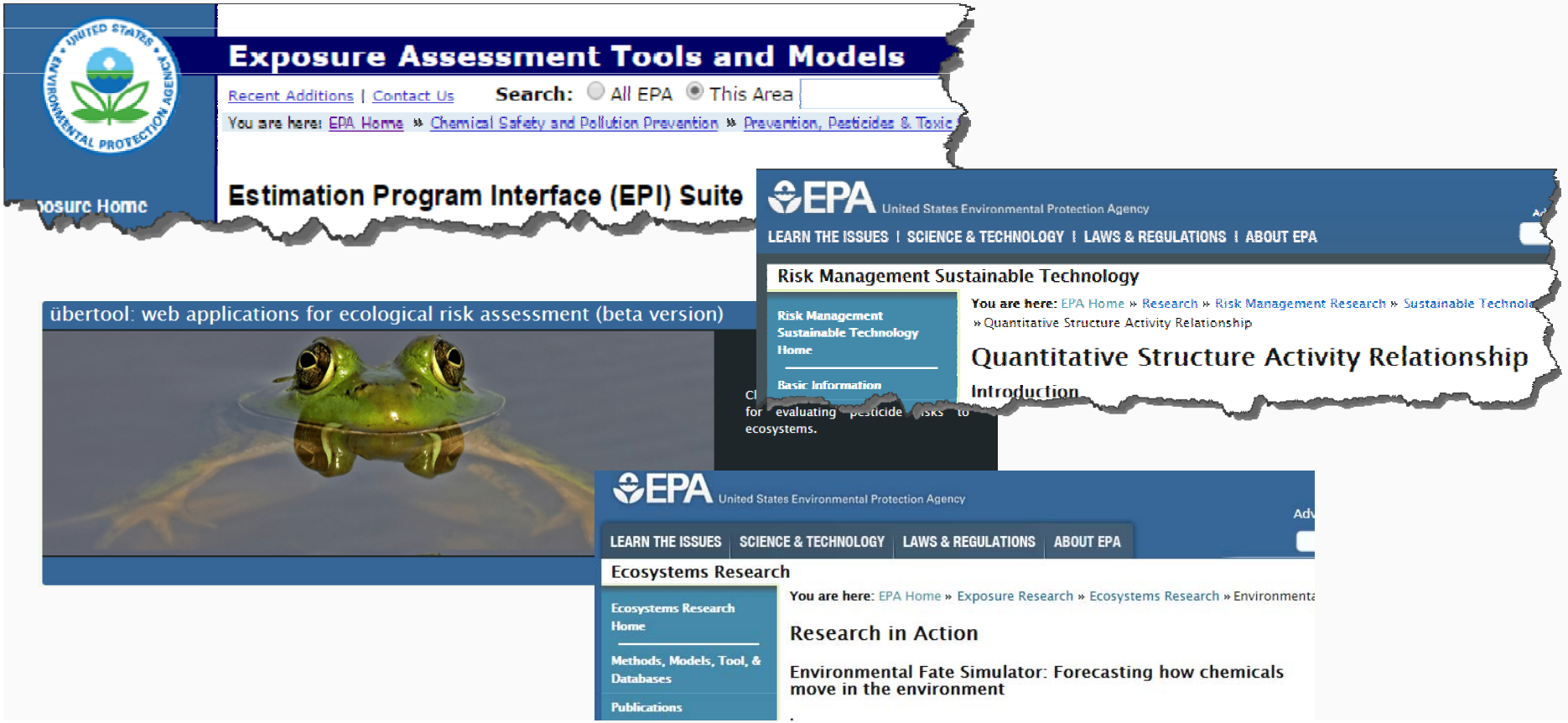
Cluster models with violated constraints

Cluster Model	r^2	q^2	# chemicals	Message
1121	0.810	0.576	10	Rmax constraint not met
1209	0.799	0.574	11	Fragment constraint not met
1247	0.919	0.647	20	Fragment constraint not met
1264	0.869	0.781	22	Fragment constraint not met
1268	0.675	0.553	24	Fragment constraint not met

Descriptor values for test chemical

A Platform for Predictions

- Developing a platform for hosting prediction models
- Coordinating efforts with other EPA prediction platforms and programs



Conclusions

- iCSS Chemistry Dashboard will provide public access to data & services focused on chemicals of interest to EPA & environmental tox communities
- Initially serve up results for measured & pre-predicted data*, on-the-fly predictions in the future*
- Data quality impacts models *- public domain chemical-data linkages require curation/validation*
- All data and models will be available as OPEN DATA and OPEN CODE

Stay tuned!!

Acknowledgements

NCCT Contributors to the iCSS Chemistry Dashboard

- Jeff Edwards
- Jeremy Fitzpatrick
- Jordan Foster
- Jason Harris
- Dave Lyons
- Kamel Mansouri
- Aria Smith
- Jennifer Smith
- Indira Thillainadarajah
- Chris Grulke
- Antony Williams

Want to learn more?

1. Expansion of DSSTox: Leveraging public data to create a semantic cheminformatics resource with quality annotations for support of U.S. EPA applications (CINF 130)

Division of Chemical Information PAPER ID: 2385741

SESSION: Chemistry, Data & the Semantic Web: An Important Triple to Advance Science, 8:15 AM - 11:55 AM

Wednesday, March, 16, 2016 from 10:40 AM - 11:05 AM

Room 25B - San Diego Convention Center

2. Influence of data curation on QSAR Modeling – examining issues of quality versus quantity of data (MPPG 124)

Multidisciplinary Program Planning Group PAPER ID: 2394881

SESSION: Big Data Science, 1:30 PM - 4:30 PM

Thursday, March, 17, 2016 from 1:30 PM - 2:00 PM

ROOM & LOCATION: Room 3 - San Diego Convention Center