Application of Predictive Tools to Environmental Assessment and Remediation

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Disclaimer:

"This presentation is based on a report to be finalized under contract to Health Canada, Contaminated Sites Division; however, this report and presentation does not necessarily reflect the opinion of Health Canada nor is it Health Canada guidance."

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Overview

- Background on Risk Management of Contaminated Sites
- Remediation Exposure Checklist Tool
- Contaminated Site Remediation Measures
- Chemicals of interest
- Information Gathering

Predictive Toxicology Tools

- Searching for Data
- Modeling Hazard and Risk
- Using *in vitro* data
- Biokinetics
- Environmental Exposure
- Mode-of-Action and Pathways
- Toxicity Values

- Application to Risk Assessment and Management
- Conclusions

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Risk Management of Contaminated Sites

- Health Canada Contaminated Sites – Expert Support under Federal Contaminated Sites Action Plan (FCSAP)
- Site specific advice on human health risk assessment, risk management and remediation of contaminated sites
- Risk Assessment and Management of data poor chemicals (e.g., Perfluorinated chemical clusters which persist in the environment) and data rich chemicals (e.g., Petroleum Hydrocarbons, Chlorinated solvent clusters such as Tetrachloroethylene, Trichloroethylene, Vinyl Chloride, etc.)
- Co-occurrence of Contaminants, interact or competitively bind with each other (e.g., metals)
- Fate and transport issues in various environments and climates also pose complex temporal issues

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Remediation Exposure Checklist Tool

- The Remediation Check List tool developed by Health Canada Contaminated Sites Division lists 10 to 15 remediation technologies, each with a conceptual exposure model describing the main routes of exposure & mitigative measures for each exposure route
- Fact sheet format summarizing the process, materials, residuals, by-products, effects, discharges (both solid, liquid, and gaseous), limitations for Northern sites, time frame, and long-term considerations (post remediation)
- Tool uses a selection of technologies with flowcharts and a decision matrix for evaluating human health exposure concerns related to remediation technologies
- In an assessment matrix, an Expert Support reviewer can evaluate the potential exposure pathways related to Remediation Plans and contaminants and the general and unique conditions at the site.

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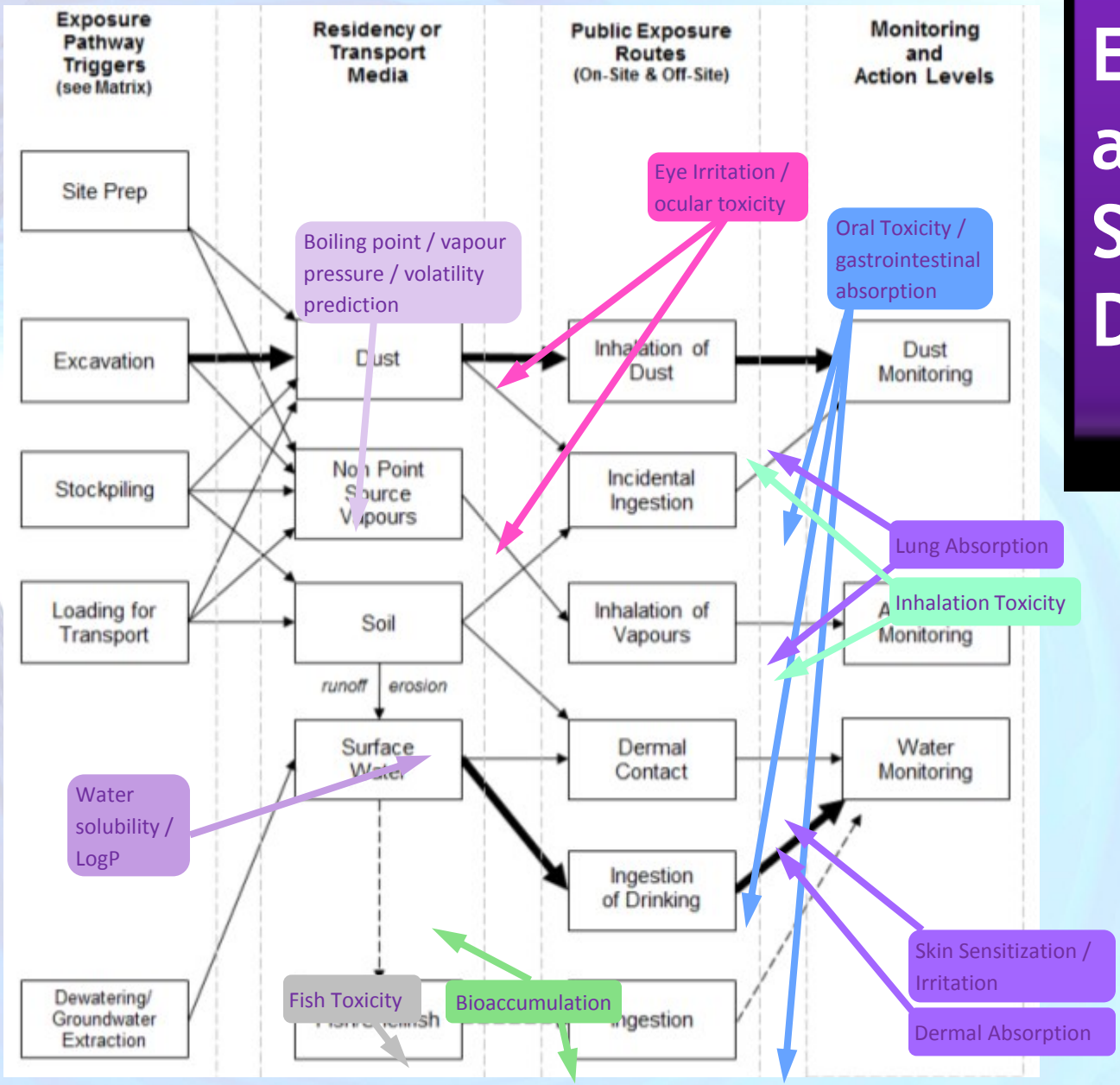
Remediation Exposure Checklist Tool

Technology	Primary Media	Secondary Media	Typical contaminant classes
Groundwater Extraction & Treatment (Pump and Treat)	Ground-water	NAPL (as part of multi-phase)	Soluble (All Types)
Permeable/Passive Reactive Barriers	Ground-water	-	Soluble VOCs and inorganics; cVOCs, possible for NAPL or PAHs
Monitored Natural Attenuation and/or Institutional Controls	Ground-water	Soil and Sediment	All (moderately for inorganics)
Excavation & Off-Site Disposal	Soil	Groundwater and NAPL for Source Area Removal	All (Shallow, < 8 to 10 m)
Excavation & On-Site Bio (Incl. Landfarming)	Soil	Groundwater for Source Area Removal	Shallow VOCs/SVOCs, Fuels
Soil Vapour Extraction & Bioventing	Soil	Occasionally for NAPL	VOCs/cVOCs, Fuels
In Situ (Active/Enhanced) Bioremediation	Soil and Ground-water	-	Aerobic - VOCs & Fuels; Anaerobic - cVOCs
In Situ Chemical Oxidation	Soil and Ground-water	Possible for NAPL and Sediment	VOCs/cVOCs; cSVOCs, Fuels
Sediment Dredging and Off-Site Disposal	Sediment	NAPL at manufactured gas plants and creosote sites	All
Dual or Multi-Phase Extraction	NAPL	Soil and Groundwater at NAPL sites	Free-Phase Hydrocarbon (LNAPL), VOCs, cVOCs, Fuels

Contaminated Site Remediation Measures

- In Situ Chemical Oxidation (e.g., Chlorinated Chemicals)
- In Situ Bioremediation (Petroleum Hydrocarbons- see Predictive Toxicology Tool Application in Bioremediation (Price and Chowdhury, 2011))
- Incineration (for Persistent Chemicals like PFOA, PFOS and PFAS)
- Excavation and off-site disposal
- Groundwater extraction and treatment
- Excavation & on-site Bioremediation
- Sediment dredging and off-site disposal
- Dual or Multi-phase extraction
- Soil Vapour Extraction & Bioventing
- Permeable/Passive reactive barriers
- Monitored Natural Attenuation

Excavation and Off-Site Disposal



Exposure pathway for Excavation and Off-Site Disposal. The colored boxes map potentially useful predictive toxicology models to the flowchart

Using Predictive Models on Exposure Pathway Analysis

OpenTox's "IST FDA v3b Maximum Recommended Daily Dose" model, http://lazar-services.in-silico.ch/model/116)

Water solubility:
OpenTox model for XLogP (http://apps.ideaconsult.net:8080/ambit2/model/9)
Many other LogP models available…

Fish Toxicity:
OpenTox model "IST EPA v4b Fathead Minnow Acute Toxicity (LC50_mmol)" (http://lazar-services.in-silico.ch/model/259)
OpenTox ECOSAR LC50 fish model (http://apps.ideaconsult.net:8080/ambit2/model/238008)
TOPKAT's daphnid fish toxicity model
OECD QSAR Toolbox model on acute aquatic toxicity (2 models: EcoSAR classification and Verhaar classification)

Bioaccumulation
Bioconcentration factor model from CAESAR
BCFBAF bioaccumulation model from US EAP's EPISuite

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Chemicals of Interest

- **Petroleum Hydrocarbons (PHCs):** n-hexane, Benzene, Toluene, Xylenes, F1-F4 fractions
- **Poly Aromatic Hydrocarbons (PAHs):** Naphthalene, Fluorene, Pyrene, Chrysene, Benzo [a]pyrene, Anthracene
- **Chlorinated Solvents:** Tetrachloroethyelene (Perchloroethylene - PERC), Trichloroethylene (TCE); Dichloroethylene (DCE); Vinyl Chloride (VC)
- **Perfluorinated chemical clusters** (PFCs - PFOA, PFOS, PFHxS)
- **Binary Metal/Metalloid Cluster** (Arsenic, Antimony, Lead, Zinc, Mercury, Selenium etc.)

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Polycyclic Aromatic Hydrocarbons (PAHs)

- Many PAHs have been identified as carcinogenic, mutagenic and teratogenic

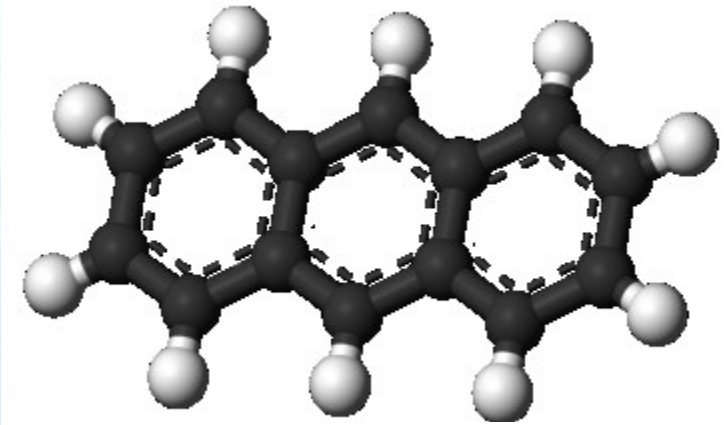
- Naphthalene, Pyrene, Fluorene, Chrysene, Benzo[a]pyrene, Anthracene

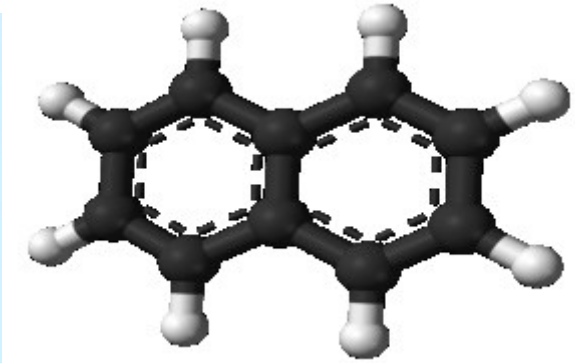
Anthracene:

- Oxidises to Anthraquinone
- Photodimerises reversibly with UV
- not classified as carcinogenic

Naphthalene

- (IARC) classifies naphthalene as possibly carcinogenic to humans and animals (Group 2B)
- Naphthalene and chlorine can react to form 1-chloronaphthalene even without a catalyst
- Naphthalene can be alkylated by reaction with alkenes or alcohols, with sulfuric or phosphoric acid as the catalyst

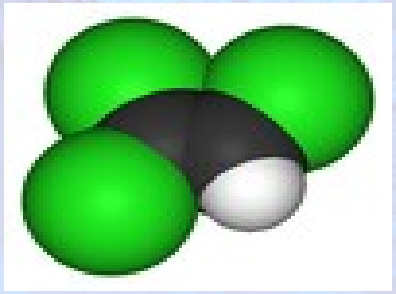




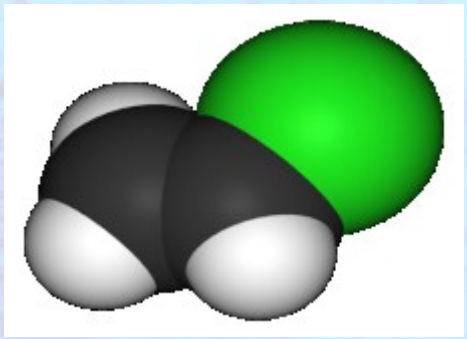
Chlorinated Solvents - Trichloroethylene (TCE)

- Exposure may be ingestion, inhalation and dermal
- Distributes readily across membranes and thus affects all organs
- Can also accumulate in adipose tissue
- Metabolites of TCE: trichloroethanol (TCOH), trichloroethanol glucuronide (TCOG), trichloroacetic acid (TCA), and dichloroacetic acid (DCA)
- Degradation product of high toxic concern - Vinyl Chloride (VC)

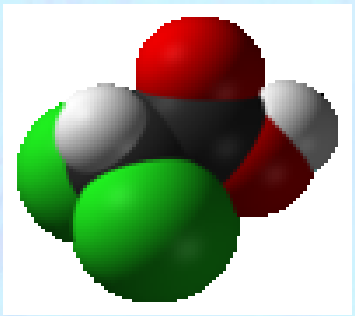
- Unstable in the presence of metal over prolonged exposure
- Neurotoxic, Cardiotoxic, Hepatotoxic



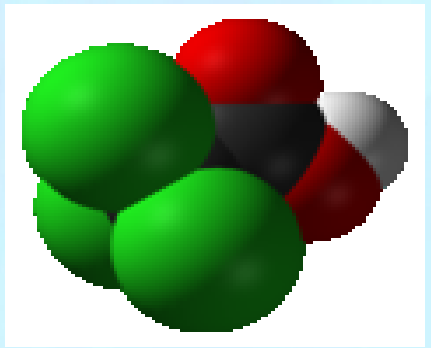
TCE



VC



DCA



TCA

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Perfluorooctanoic Acid (PFOA)

- Persistent organic pollutant not degraded by any natural process due to the strength of the carbon-fluorine bond
- Carcinogenic potential of PFOA is suspected
- Exposure though inhalation, ingestion, dermal contact
- Distributed to blood and liver, where it covalently binds to proteins (mainly serum albumin)
- PFOA is not metabolized but excreted through urine.
- Resorption in kidneys is very strong, leading to serum half-life of PFOA of 2.3 years
- Persistence leads to chronic exposure of a majority of the population
- indications of sub-chronic/chronic reproductive toxicity, but not with much evidence
- PFOA has been shown to be hepatotoxic in rodents (it activates PPARα), leading to hypertrophy and changes in lipid metabolism

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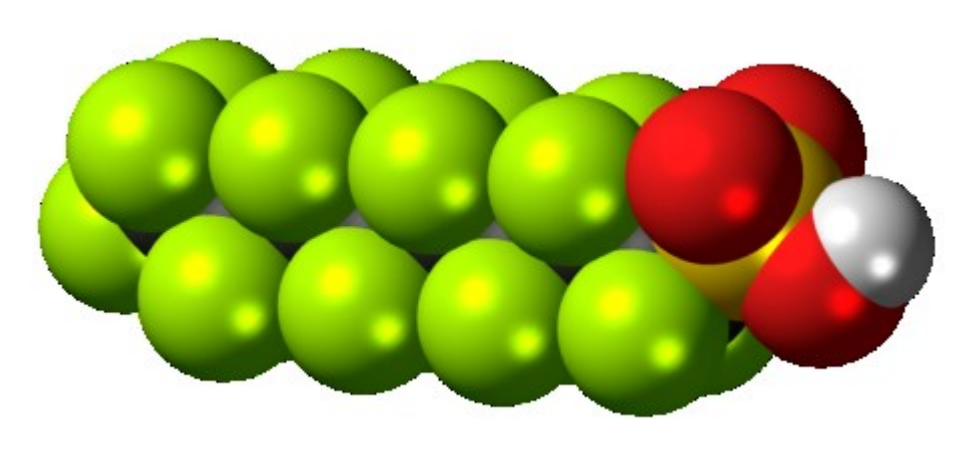
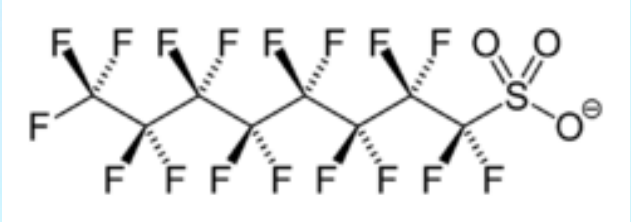
Perfluorooctane Sulfonate (PFOS)

- Persistent organic pollutant
- Excreted within days in rodents, but only within months in non-human primates and within years in humans
- Tested negative in mutation assays in *S. typhimurium*, *E.coli*, and other mutagenicity assays
- Believed to be a sub-chronic developmental toxin





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Contaminated Sites (Human Health issues)

- Available data on chemical concentrations (spatial and temporal extent) at sites
- Prediction of future intake by human and ecological receptors
- Compare predicted intake of fish and terrestrial organisms (plants and animals) with Lowest or No Observable Adverse Effect Levels (NOAELs/LOAELs)
- Consider human intake through drinking water, soil, food chain
- Consider uncertainties and variability e.g., due to complex geochemical processes in different sites
- Mixture issues - there is evidence that the combined effect of PCBs and TCE is greater than the additive effect of their individual toxicities. However predictive models for mixtures are currently limited.

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Contaminated Sites

- Mines – metals / Metalloids and metallic oxides
- Dry Cleaning sites – Chlorinated solvents
- Hazardous Materials storage areas e.g., PHCs, PAHs, halogenated hydrocarbons
- Compare predicted intake of fish and terrestrial organisms (plants and animals) with Lowest Observable Adverse Effect Levels (LOAELs)
- Consider human intake through drinking water, soil, food chain
- Consider uncertainties e.g., due to complex geochemical processes

Predictive Toxicology Tools

- (Q)SARs and provide estimates to fill knowledge gaps
- Clustering of chemicals based on hazard or biological data
- Evaluate issues involving reactivity, metabolism
- Toxicokinetics and Toxicodynamics
- Fate and Exposure
  - Searching for Data
  - Modeling Hazard
  - Read Across
  - Using *in vitro* data
  - Biokinetics
  - Environmental Exposure
  - Mode-of-Action and Pathways
  - NOAELs
- Weight of Evidence Framework
- Validation Principles, Verification
- Incorporating Uncertainty

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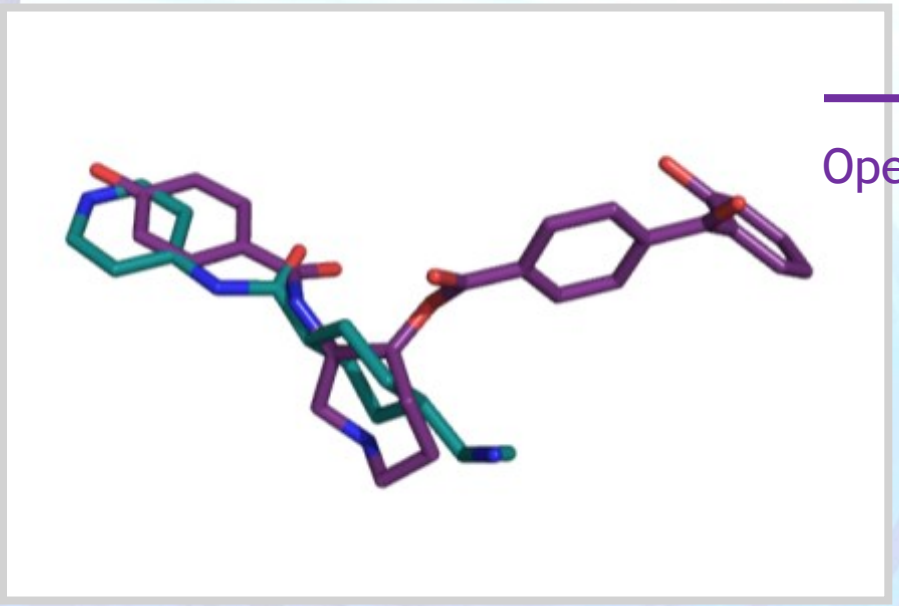
Predictive Toxicology Challenge & Use Case

Input Structure



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Out – Toxic or Not?

- LD50
- Liver Toxicity
- Secondary Metabolites
- Bioavailability
- Mutagenicity
- Carcogenicity
- ReproductiveToxicology
- Skin Irritation
- Aqua Toxicity
- Combined predictions for arrays of mutiple end points

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Metabolites & degradation products

Metabolites, Metabolic Enzymatic induction and the the creation of Reactive Intermediates may all lead to toxicity, e.g., in drug-drug interactions and hepatotoxic adverse events.

According to ECHA Guidance B, further investigation may be required for degradation products and metabolites if considered relevant for the chemical safety assessment, PBT assessment or classification and labeling.

OpenTox supports metabolite prediction and model building based on metabolites.

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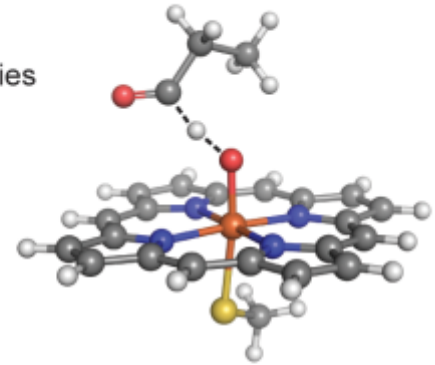
SMARTCyp Service for Predicting Metabolites

Atom Reactivity Library

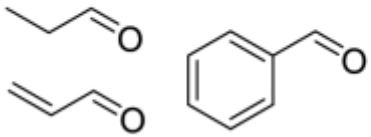
A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



B. Define SMARTS Rules

Group calculations by fragments and calculate average energies

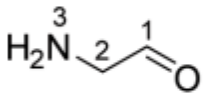


[CX3H1](=O)[#6]

40.2 kJ/mol

SMARTCyp

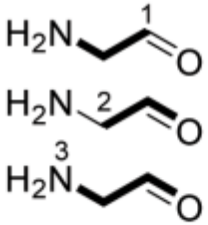
1. Assign Energies By SMARTS matching



Atom	SMARTS	Energy
1	[CX3H1](=O)[#6]	40.2
2	[CX4][N]	39.8
3	[N^3][H1,H2]	54.1

2. Compute Accessibility Descriptor

$A_i = Maxbonds_i / Maxbonds_{all}$



$A_1 = 2 / 3 = 0.67$

$A_2 = 2 / 3 = 0.67$

$A_3 = 3 / 3 = 1.00$

3. Compute Score and Rank Atoms

Score, S = E - 8A
Lowest score gets rank 1

$S_1 = 40.2 - 8*0.67 = 34.84$ → Atom 1 - Rank 2

$S_2 = 39.8 - 8*0.67 = 34.44$ → Atom 2 - Rank 1

$S_3 = 54.1 - 8*1.00 = 46.10$ → Atom 3 - Rank 3

SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

www.farma.ku.dk/index.php/SMARTCyp/7990/0/

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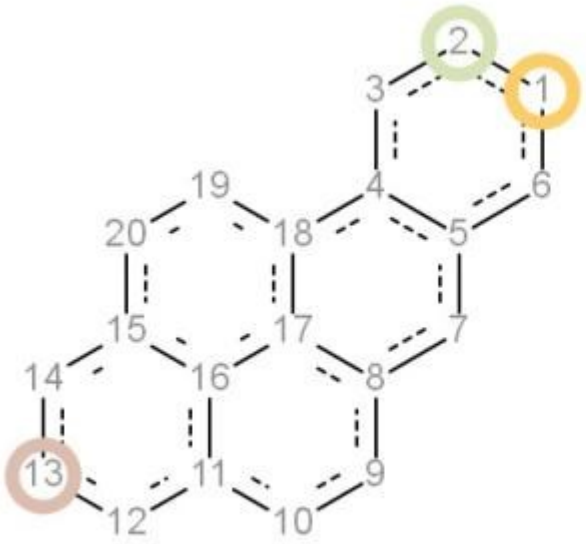
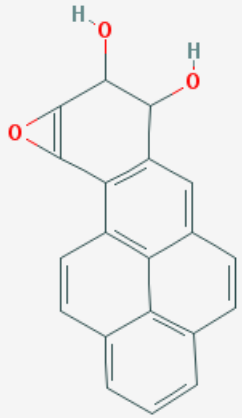
SMARTCyp Results - Benzoapyrene



Standard | CYP2C | CYP2D6

1: null

Rank	Atom	Score	Energy	Accessibility	2DSASA
1	**C.1**	**71.46**	**80.8**	**1**	**33.5**
2	**C.13**	**71.57**	**80.8**	**1**	**30.76**
3	**C.2**	**72.38**	**80.8**	**0.89**	**32.67**
4	C.6	72.57	80.8	0.89	27.97
4	C.12	72.57	80.8	0.89	27.97
4	C.14	72.57	80.8	0.89	27.97
7	C.3	73.54	80.8	0.78	26.05
8	C.10	73.57	80.8	0.78	25.23
9	C.9	74.49	80.8	0.67	24.4
9	C.20	74.49	80.8	0.67	24.4



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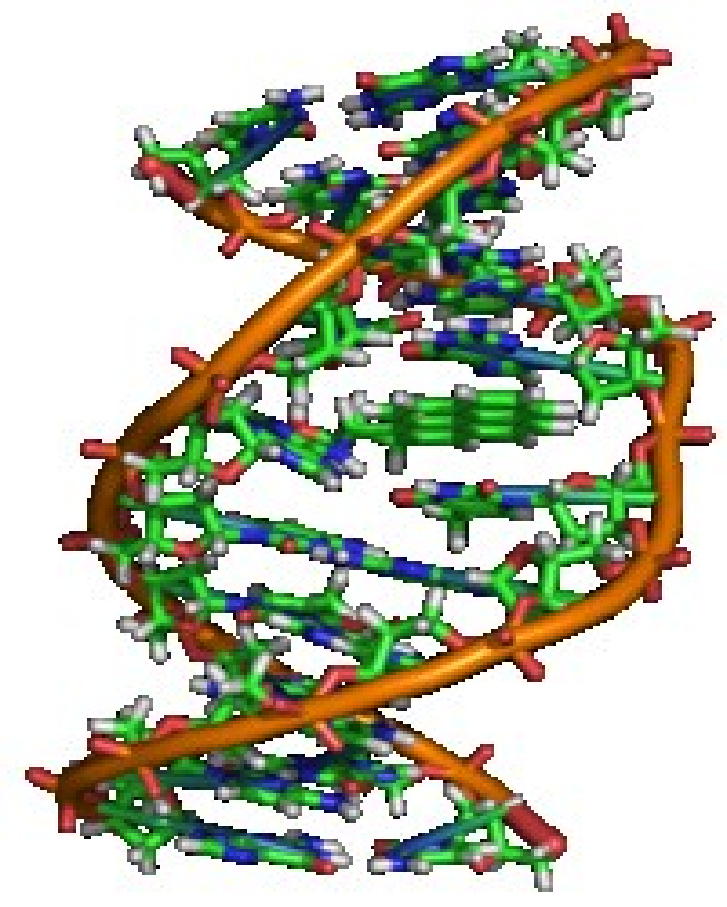
Benzo[a]pyrene Mechanism



- Benzo[a]pyrene – a carcinogen

- Enzymatic metabolism of benzo[a]pyrene to benzo[a]pyrene diol epoxide; intercalates in DNA, covalently bonding to the nucleophilic guanine nucleobases at the N2 position.

- X-ray crystallographic and NMR structure" binding distorts the DNA by perturbing the double-helical DNA structure.

- Disrupts the normal process of copying DNA and induces mutations - occurrence of cancer after exposure. (Volk et al 2003)

- This mechanism of action is similar to that of aflatoxin which binds to the N7 position of guanine (Eaton et al 1994)

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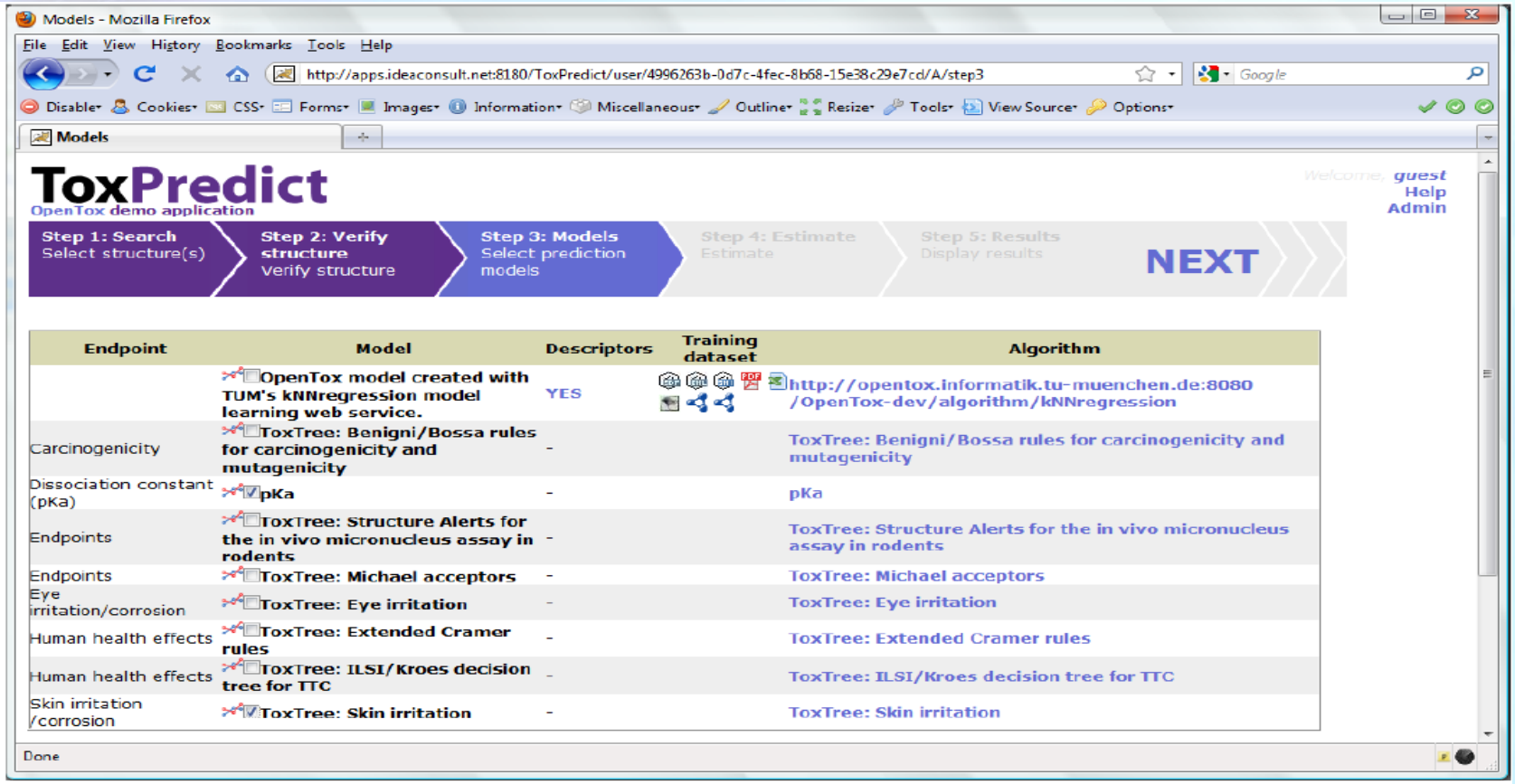
ToxPredict



Simple building of predictive toxicology applications based on well-established methods and databases compliant with OpenTox Standards

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ToxPredict Developed by Ideaconsult

ToxPredict Results - Benzo[a]pyrene

- ToxTree: Structure Alert for *in vivo* micronucleus assay in rodents
- IST DSSTox Carcinogenic Potency DBS Hamster non-carcinogen
- IST DSSTox Carcinogenic Potency DBS MultiCellCall carcinogen
- IST DSSTox Carcinogenic Potency DBS Mutagenicity mutagen
- IST Kazius-Bursi Salmonella mutagenicity mutagen
- pKa-SMARTS 9.8
- XLogP 5.96
- START Biodegradability Class 2 (Persistent chemical)
- F96h-LogLC50mmol/L (ECOSAR) 1.3
- Cramer rules High (Class III)
- Benigni/Bossa rules Structural Alert for genotoxic carcinogenicity
- EPAFM LC50 fish OpenTox model created with SCR regression model 5.81
- CADASTER Aquatic tox (fish) Lethal Concentration - log(mol/L) 7.9
- CADASTER HMGU Aqueous Solubility log(mol/L) 8.0

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ToxPredict Results - PFOS

- ToxTree: No Structure Alert for *in vivo* micronucleus assay in rodents
- IST FDA v3b Maximum Recommended Daily Dose 0.0495527 mmol
- IST DSSTox Carcinogenic Potency DBS MultiCellCall non-carcinogen
- IST DSSTox Carcinogenic Potency DBS Mutagenicity non-mutagen
- pKa-SMARTS 4.65
- XLogP 6.33
- START Biodegradability Class 2 (Persistent chemical)
- F96h-LogLC50mmol/L (ECOSAR) -2.83
- Cramer rules High (Class III)
- Benigni/Bossa rules Structural Alert for nongenotoxic carcinogenicity
- ToxTree Eye Irritation: Serious lesions to the eye
- CADASTER Aquatic tox (fish) Lethal Concentration -log(mol/L) 5.6
- CADASTER UI Aqueous Solubility log(mg/L) -0.2

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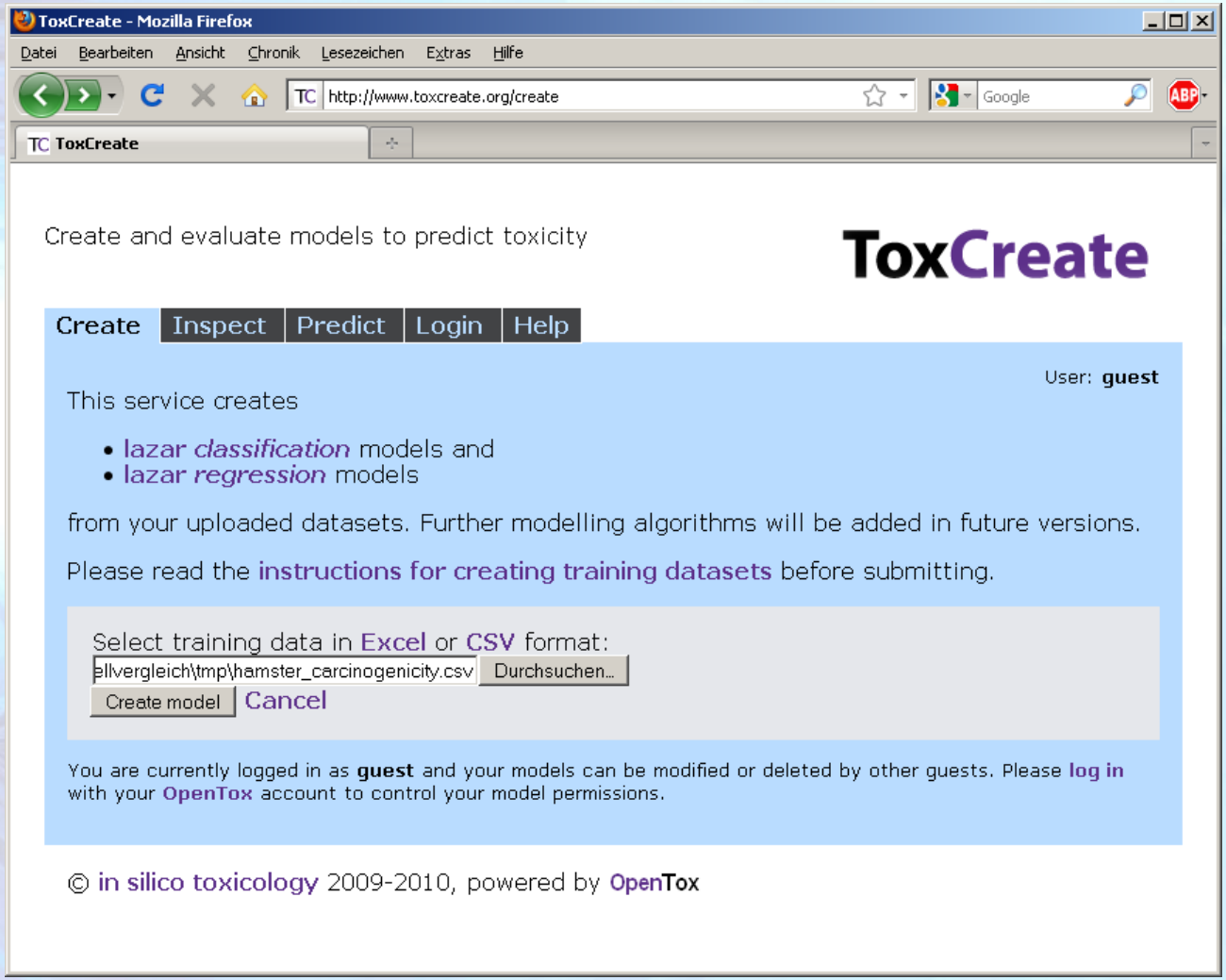
ToxCreate - (Q)SAR Model Building application



Developed by In Silico Toxicology

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	OECD Principle	OpenTox addresses Validation Principles by...
1	Defined Endpoint	providing a unified source of well defined and documented toxicity data with a common vocabulary
2	Unambiguous Algorithm	providing transparent access to well documented models and algorithms as well as to the source code
3	Defined Applicability Domain	integrating tools for the determination of applicability domains during the validation of prediction models
4	Goodness-of-fit, robustness and predictivity	providing scientifically sound validation routines for the determination of errors and confidences
5	Mechanistic interpretation (if possible)	integrating tools for the inference, correlation or prediction of toxicological mechanisms and the recording of opinions and analysis in reports

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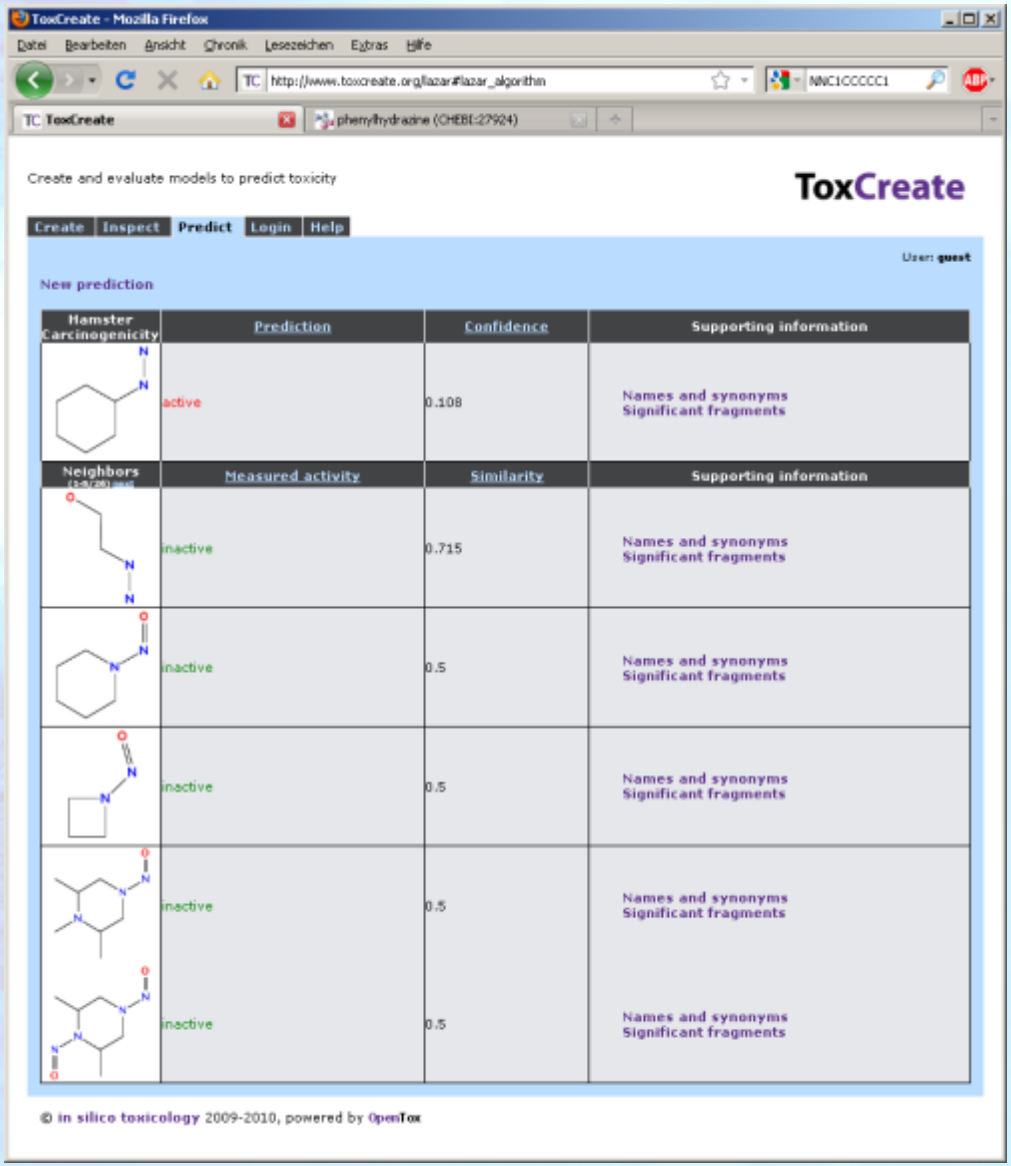
ToxCreate – Confidence, Supporting Information



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lazar results - Napthalene

c1ccc2ccccc2c1									
	**DSSTox Carcinogenic Potency DBS MultiCellCall:** carcinogen (Measured activity)	**DSSTox Carcinogenic Potency DBS Mutagenicity:** non-mutagenic (Measured activity)	**DSSTox Carcinogenic Potency DBS Rat:** carcinogen (Measured activity)	**Kazius-Bursi Salmonella mutagenicity:** mutagenic (Confidence : 0.207) Details	**DSSTox Carcinogenic Potency DBS SingleCellCall:** carcinogen (Measured activity)	**EPA v4b Fathead Minnow Acute Toxicity LC50_mmol:** -1.31966066045884 (Measured activity)	**DSSTox ISSCAN v3a Canc:** carcinogen (Measured activity)	**DSSTox Carcinogenic Potency DBS Hamster:** non-carcinogen (Confidence : 0.084) Details	**DSSTox Carcinogenic Potency DBS Mouse:** carcinogen (Measured activity)

lazar results - Napthalene: Validation results for Kazius-Bursi Salmonella mutagenicity

Kazius-Bursi Salmonella mutagenicity

Status:	Completed
Started:	08/26/2011 - 03:18:24PM GMT
Training compounds:	4067
Endpoint:	Mutagenicity
Warnings:	show
Algorithm:	lazar
Type:	classification
Descriptors:	Fminer backbone refinement classes
Training dataset:	Excel sheet , SDF , YAML *(experts)*
Feature dataset:	Excel sheet , SDF , YAML *(experts)*
Model:	QMRF Editor, YAML *(experts, models cannot be represented in Excel)*

Validation:

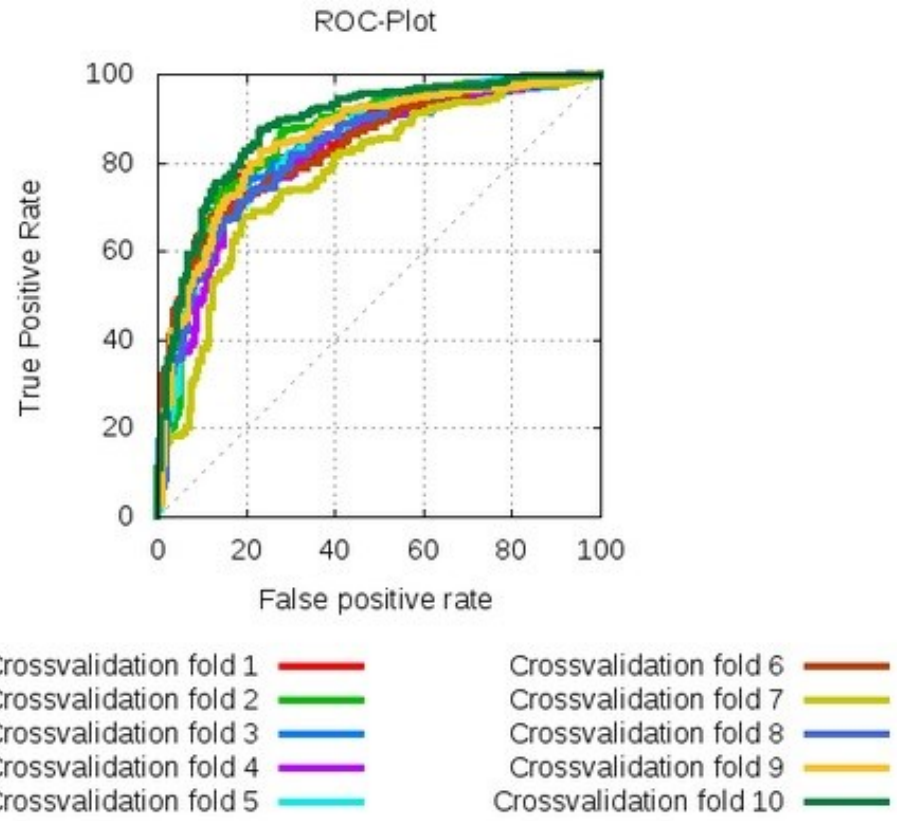
Detailed report:	show
Number of predictions:	4056
Correct predictions:	75.62 %
Average area under ROC:	0.835
Specificity:	0.707
Sensitivity:	0.794

Confusion Matrix:

		Measured	
		mutagenic	non-mutagenic
Predicted	mutagenic	1819	518
	non-mutagenic	471	1248

lazar results - Napthalene: Validation results for Kazius-Bursi Salmonella mutagenicity

Figure 7. ROC Plot (true class is 'mutagenic')



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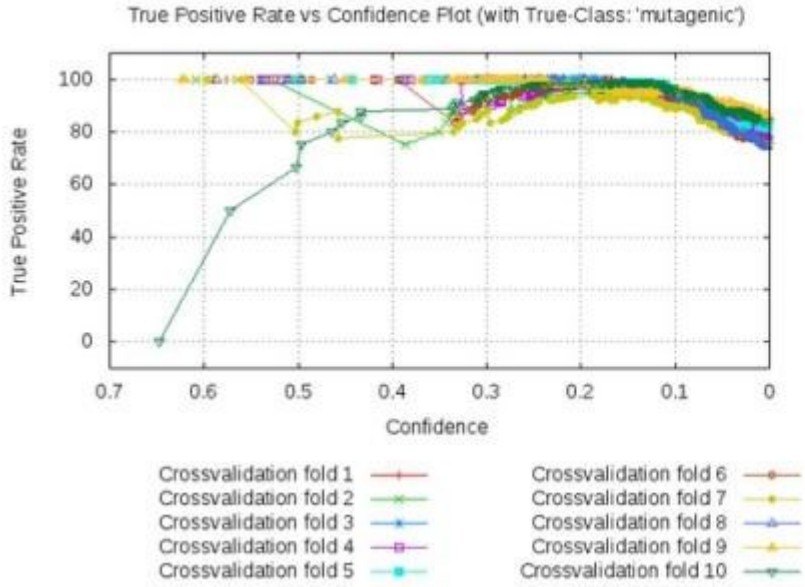
lazar results - Napthalene: Validation results for Kazius-Bursi Salmonella mutagenicity



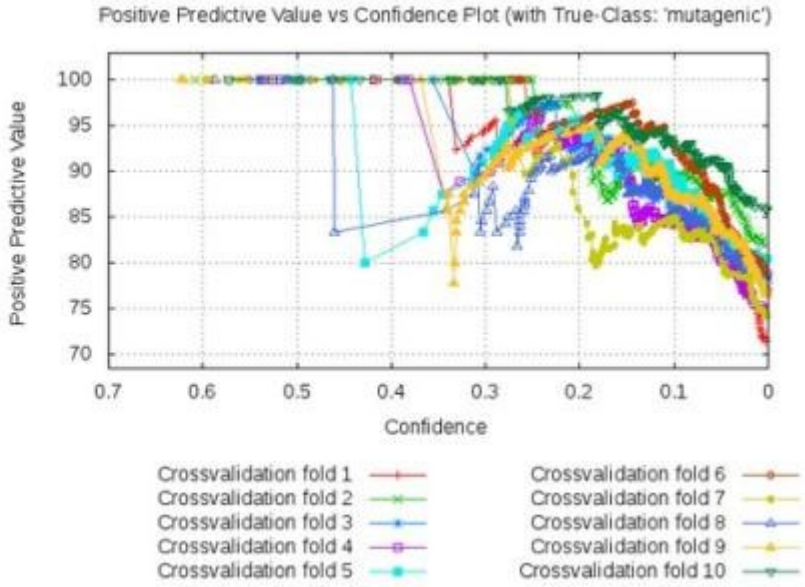


Table 6. Confidence Plots

Figure 11. Confidence Plot

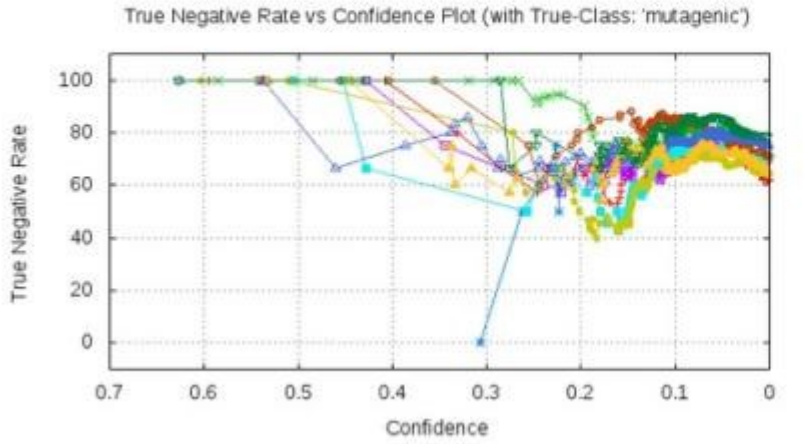
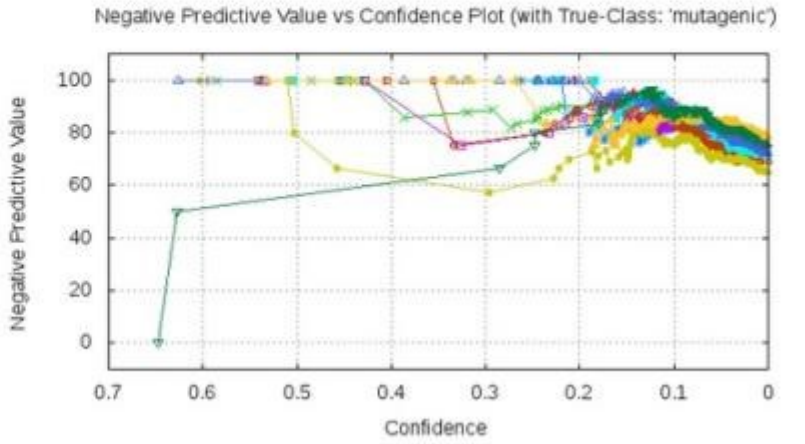
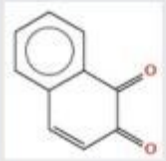


Figure 12. Confidence Plot



lazar results - 1,2-Naphthoquinone

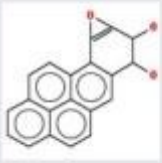
O=C1c2ccccc2\C=C/C1=O										
	**DSSTox Carcinogenic Potency DBS MultiCellCall:** non-carcinogen (**Confidence** : 0.0312) Details	**DSSTox Carcinogenic Potency DBS Mutagenicity:** non-mutagenic (**Confidence** : 0.109) Details	**DSSTox Carcinogenic Potency DBS Rat:** non-carcinogen (**Confidence** : 0.102) Details	**Kazius-Bursi Salmonella mutagenicity:** mutagenic (**Measured activity**)	**FDA v3b Maximum Recommended Daily Dose mmol:** 0.00807302232901515 (**Confidence** : 0.124) Details	**DSSTox Carcinogenic Potency DBS SingleCellCall:** non-carcinogen (**Confidence** : 0.0912) Details	**EPA v4b Fathead Minnow Acute Toxicity LC50_mmol:** 0.019332323229228 (**Confidence** : 0.337) Details	**DSSTox ISSCAN v3a Canc:** carcinogen (**Confidence** : 0.233) Details	**DSSTox Carcinogenic Potency DBS Hamster:** non-carcinogen (**Confidence** : 0.203) Details	**DSSTox Carcinogenic Potency DBS Mouse:** non-carcinogen (**Confidence** : 0.222) Details

lazar results - Benzoapyrene

c1ccc2c(c1)cc3ccc4cccc5c4c3c2cc5										
	**DSSTox Carcinogenic Potency DBS MultiCellCall:** carcinogen (**Measured activity**)	**DSSTox Carcinogenic Potency DBS Mutagenicity:** mutagenic (**Measured activity**)	**DSSTox Carcinogenic Potency DBS Rat:** carcinogen (**Measured activity**)	**Kazius-Bursi Salmonella mutagenicity:** mutagenic (**Measured activity**)	**FDA v3b Maximum Recommended Daily Dose mmol:** Not enough similar compounds in training dataset.	**DSSTox Carcinogenic Potency DBS SingleCellCall:** carcinogen (**Measured activity**)	**EPA v4b Fathead Minnow Acute Toxicity LC50_mmol:** Not enough similar compounds in training dataset.	**DSSTox ISSCAN v3a Canc:** carcinogen (**Measured activity**)	**DSSTox Carcinogenic Potency DBS Hamster:** non-carcinogen (**Confidence :** 0.084) Details	**DSSTox Carcinogenic Potency DBS Mouse:** carcinogen (**Measured activity**)

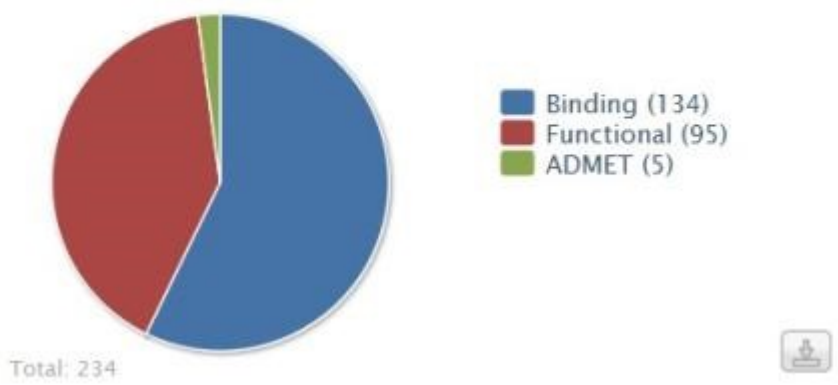
lazar results - benzo[a]pyren-7,8-dihydrodiol-9,10-epoxide

C1=CC2=C3C(=C1)C=CC4=C3C(=CC5=C4C6=C(O6)C(C5O)O)C=C2

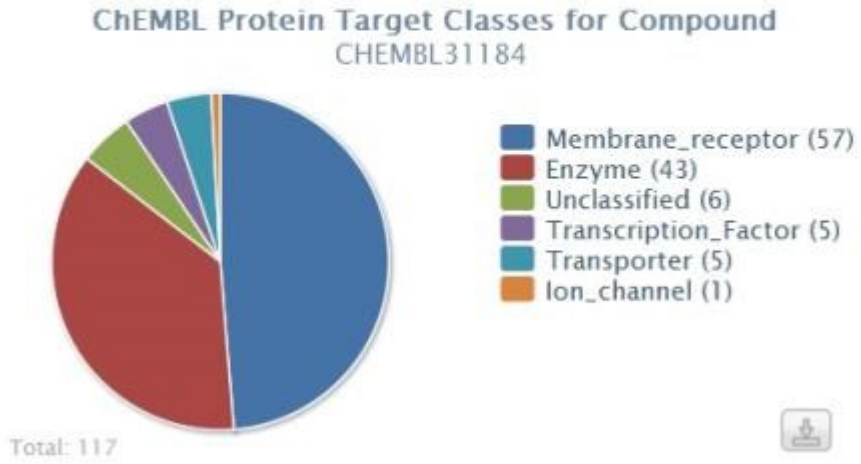
	DSSTox Carcinogenic Potency DBS MultiCellCall: non-carcinogen (Confidence : 0.0207) Details	DSSTox Carcinogenic Potency DBS Mutagenicity: non-mutagenic (Confidence : 0.0682) Details	DSSTox Carcinogenic Potency DBS Rat: non-carcinogen (Confidence : 0.0108) Details	Kazius-Bursi Salmonella mutagenicity: mutagenic (Confidence : 0.33) Details	FDA v3b Maximum Recommended Daily Dose mmol: 0.00741008606306342 (Confidence : 0.0715) Details	DSSTox Carcinogenic Potency DBS SingleCellCall: non-carcinogen (Confidence : 0.0358) Details	EPA v4b Fathead Minnow Acute Toxicity LC50_mmol: 0.00187790343913157 (Confidence : 0.0856) Details	DSSTox ISSCAN v3a Canc: noncarcinogen (Confidence : 0.131) Details	DSSTox Carcinogenic Potency DBS Hamster: non-carcinogen (Confidence : 0.246) Details	DSSTox Carcinogenic Potency DBS Mouse: carcinogen (Confidence : 0.0843) Details
										

ChEMBL (Assays) - benzo[a]pyrene

Compound Assay Summary



Compound Target Summary



OpenTox

ToxCast Assays

Compound	ToxCast Phase
Naphthalene	2a
Pyrene	2b
Fluorene	2b
Chrysene	Tox21
Benzo[a]pyrene	Tox21
Anthracene	2a
Anthraquinone	Tox21
TCE	Tox21
TCOH	n/a
TCOG	n/a
TCA	2a
DCA	2b
VC	n/a
PFOA	1 (v2)
PFOS	1 (v1 and v2)

OpenTox

ToxCast (Actor) - PFOA

Source	Assay	Assay Name	Species	Gene	Value	Units
Attagene	ATG_ERa_TRANS	Attagene Factorial trans Era	Homo sapiens	ESR1	52.0	uM
Attagene	ATG_ERE_CIS	Attagene Factorial cis ERE	Homo sapiens	ESR1	48.0	uM
Attagene	ATG_NRF2_ARE_CIS	Attagene Factorial cis NRF2/ARE	Homo sapiens	NFE2L2	51.0	uM
Attagene	ATG_PPARa_TRANS	Attagene Factorial trans PPARa	Homo sapiens	PPARA	42.0	uM
Attagene	ATG_PPARg_TRANS	Attagene Factorial trans PPARg	Homo sapiens	PPARG	53.0	uM
Attagene	ATG_PPRE_CIS	Attagene Factorial cis PPRE	Homo sapiens	PPARA PPARD PPARG	40.0	uM
Attagene	ATG_PXRE_CIS	Attagene Factorial cis PXRE	Homo sapiens	NR1I2	43.0	uM
BioSeek	BSK_KF3CT_ICAM1_down	HEK_HDFn_IL_1b_TNF_a_IFN_g_TGF_b_24_CD54_ICAM_1_down	Homo sapiens	ICAM1	40.0	uM
BioSeek	BSK_3C_uPAR_down	HUVEC_IL_1b_TNF_a_IFN_g_24_CD87_uPAR_down	Homo sapiens	PLAUR	4.44	uM
BioSeek	BSK_BE3C_uPAR_up	BrEPI_IL_1b_TNF_a_IFN_g_24_CD87_uPAR_up	Homo sapiens	PLAUR	1.48	uM
BioSeek	BSK_BE3C_MMP1_up	BrEPI_IL_1b_TNF_a_IFN_g_24_MMP_1_up	Homo sapiens	MMP1	40.0	uM
BioSeek	BSK_LPS_Eselectin_up	HUVEC_PBMC_LPS_24_CD62E_E_Selectin_up	Homo sapiens	SELE	40.0	uM
BioSeek	BSK_3C_IL8_up	HUVEC_IL_1b_TNF_a_IFN_g_24_CXCL8_IL_8_up	Homo sapiens	IL8	40.0	uM
BioSeek	BSK_3C_Proliferation_up	HUVEC_IL_1b_TNF_a_IFN_g_24_Proliferation_up	Homo sapiens		1.48	uM
BioSeek	BSK_4H_MCP1_up	HUVEC_IL_4_Histamine_24_CCL2_MCP_1_up	Homo sapiens	CCL2	13.3	uM
BioSeek	BSK_SM3C_Proliferation_up	SMC_IL_1b_TNF_a_IFN_g_24_Proliferation_up	Homo sapiens		40.0	uM
Cellumen	CLM_CellLoss_72hr	Cellumen Cell Number	Homo sapiens		166.0	uM
CellzDirect	CLZD_CYP2B6_48	CellzDirect CYP2B6	Homo sapiens	CYP2B6	6.23	uM
CellzDirect	CLZD_CYP3A4_48	CellzDirect CYP3A4	Homo sapiens	CYP3A4	2.37	uM
CellzDirect	CLZD_HMGCS2_6	CellzDirect HMGCS2	Homo sapiens	HMGCS2	0.253	uM
CellzDirect	CLZD_HMGCS2_48	CellzDirect HMGCS2	Homo sapiens	HMGCS2	6.5	uM
Novascreen	NVS_ENZ_hBACE	Novascreen Human Beta-site APP Cleaving Enzyme (BACE) 1	Homo sapiens	BACE1 BACE2	5.3	uM
Novascreen	NVS_ENZ_hTie2	Novascreen Human Tie2	Homo sapiens	TEK	36.0	uM
Novascreen	NVS_GPCR_hPY2	Novascreen Human P2Y	Homo sapiens	P2RY1 P2RY2 P2RY12 P2RY14 P2RY10 P2RY11	32.0	uM
NHEERL Zebrafish	ZF_Total_Score_AC50	ZF_Total_Score_AC50	Danio rerio		0.333	uM
NHEERL Zebrafish	ZF_Total_Score_EMAX	ZF_Total_Score_EMAX	Danio rerio		3.2	uM
NHEERL Zebrafish	ZF_Total_Score_W	ZF_Total_Score_W	Danio rerio		20.6	uM
NHEERL Zebrafish	ZF_Total_Score_R2	ZF_Total_Score_R2	Danio rerio		0.203	uM

ToxCast (Actor) – PFOS (part 1)

Source	Assay	Assay Name	Species	Gene	Value	Units
Attagene	ATG_ERa_TRANS	Attagene Factorial trans Era	Homo sapiens	ESR1	26.0	uM
Attagene	ATG_NRF2_ARE_CIS	Attagene Factorial cis NRF2/ARE	Homo sapiens	NFE2L2	18.0	uM
Attagene	ATG_PPARg_TRANS	Attagene Factorial trans PPARg	Homo sapiens	PPARG	26.0	uM
Attagene	ATG_PXRE_CIS	Attagene Factorial cis PXRE	Homo sapiens	NR1I2	18.0	uM
Attagene	ATG_RARa_TRANS	Attagene Factorial trans RARa	Homo sapiens	RARA	3.9	uM
BioSeek	BSK_BE3C_IP10_down	BrEPI_IL_1b_TNF_a_IFN_g_24_CXCL10_IP_10_down	Homo sapiens	CXCL10	13.3	uM
BioSeek	BSK_BE3C_hLADR_down	BrEPI_IL_1b_TNF_a_IFN_g_24_HLA_DR_down	Homo sapiens	HLA-DRA	13.3	uM
BioSeek	BSK_BE3C_SRB_down	BrEPI_IL_1b_TNF_a_IFN_g_24_SRB_down	Homo sapiens		40.0	uM
BioSeek	BSK_BE3C_uPA_down	BrEPI_IL_1b_TNF_a_IFN_g_24_uPA_down	Homo sapiens	PLAU	1.48	uM
BioSeek	BSK_KF3CT_IP10_down	HEK_HDFn_IL_1b_TNF_a_IFN_g_TGF_b_24_CXCL10_IP_10_down	Homo sapiens	CXCL10	1.48	uM
BioSeek	BSK_KF3CT_IL1a_down	HEK_HDFn_IL_1b_TNF_a_IFN_g_TGF_b_24_IL_1alpha_down	Homo sapiens	IL1A	40.0	uM
BioSeek	BSK_KF3CT_MMP9_down	HEK_HDFn_IL_1b_TNF_a_IFN_g_TGF_b_24_MMP_9_down	Homo sapiens	MMP9	4.44	uM
BioSeek	BSK_SAg_CD38_down	HUVEC_PBMC_SEB_TSST_24_CD38_down	Homo sapiens	CD38	40.0	uM
BioSeek	BSK_3C_uPAR_down	HUVEC_IL_1b_TNF_a_IFN_g_24_CD87_uPAR_down	Homo sapiens	PLAUR	40.0	uM
BioSeek	BSK_3C_Proliferation_down	HUVEC_IL_1b_TNF_a_IFN_g_24_Proliferation_down	Homo sapiens		40.0	uM
BioSeek	BSK_3C_Vis_down	HUVEC_IL_1b_TNF_a_IFN_g_24_Visual_down	Homo sapiens		13.3	uM
BioSeek	BSK_BE3C_uPAR_up	BrEPI_IL_1b_TNF_a_IFN_g_24_CD87_uPAR_up	Homo sapiens	PLAUR	1.48	uM
BioSeek	BSK_BE3C_MMP1_up	BrEPI_IL_1b_TNF_a_IFN_g_24_MMP_1_up	Homo sapiens	MMP1	13.3	uM
BioSeek	BSK_hDFCGF_IL8_up	HDFn_IL_1b_TNF_a_IFN_g_EGF_FGF_PDGFbb_24_CXCL8_IL_8_up	Homo sapiens	IL8	4.44	uM
BioSeek	BSK_hDFCGF_CollagenIII_up	HDFn_IL_1b_TNF_a_IFN_g_EGF_FGF_PDGFbb_24_Collagen_III_up	Homo sapiens	COL3A1	4.44	uM
BioSeek	BSK_hDFCGF_MCSF_up	HDFn_IL_1b_TNF_a_IFN_g_EGF_FGF_PDGFbb_24_M_CSF_up	Homo sapiens	CSF1	1.48	uM
BioSeek	BSK_SAg_Eselectin_up	HUVEC_PBMC_SEB_TSST_24_CD62E_E_Selectin_up	Homo sapiens	SELE	40.0	uM
Cellumen	CLM_CellLoss_24hr	Cellumen Cell Number	Homo sapiens		149.0	uM
Cellumen	CLM_CellLoss_72hr	Cellumen Cell Number	Homo sapiens		140.0	uM
Cellumen	CLM_MicrotubuleCSK_24hr	Cellumen a-tubulin	Homo sapiens	TUBA1A	179.0	uM
Cellumen	CLM_Hepat_DNATexture_1hr	Cellumen_Hepat_DNATexture	Ratus Norvegicus		69.1	uM
Cellumen	CLM_Hepat_Steatosis_24hr	Cellumen_Hepat_Steatosis	Ratus Norvegicus		166.0	uM
CellzDirect	CLZD_CYP2B6_24	CellzDirect CYP2B6	Homo sapiens	CYP2B6	10.7	uM
CellzDirect	CLZD_CYP2B6_48	CellzDirect CYP2B6	Homo sapiens	CYP2B6	17.7	uM
CellzDirect	CLZD_CYP3A4_24	CellzDirect CYP3A4	Homo sapiens	CYP3A4	28.8	uM
CellzDirect	CLZD_CYP3A4_48	CellzDirect CYP3A4	Homo sapiens	CYP3A4	28.9	uM
CellzDirect	CLZD_HMGCS2_6	CellzDirect HMGCS2	Homo sapiens	HMGCS2	29.1	uM
CellzDirect	CLZD_UGT1A1_6	CellzDirect UGT1A1	Homo sapiens	UGT1A1	30.2	uM
Gentronix	GreenScreen	GreenScreen	Homo sapiens	GADD45A	100.0	uM
Novascreen	NVS_ADME_hCYP2C18	Novascreen Human CYP2C18	Homo sapiens	CYP2C18	2.0	uM
Novascreen	NVS_ADME_hCYP2C19	Novascreen Human CYP2C19	Homo sapiens	CYP2C19	16.0	uM
Novascreen	NVS_ADME_hCYP2C9	Novascreen Human CYP2C9	Homo sapiens	CYP2C9	0.078	uM

ToxCast (Actor) – PFOS (part 2)

Novascreen	NVS_ADME_rCYP2C11	Novascreen Rat CYP2C11	Rattus norvegicus	Cyp2c	0.059	uM
Novascreen	NVS_ENZ_hBACE	Novascreen Human Beta-site APP Cleaving Enzyme (BACE) 1	Homo sapiens	BACE1 BACE2	0.53	uM
Novascreen	NVS_ENZ_hMMP13	Novascreen Human MMP13	Homo sapiens	MMP13	34.0	uM
Novascreen	NVS_ENZ_hMMP3	Novascreen Human MMP3	Homo sapiens	MMP3	15.0	uM
Novascreen	NVS_ENZ_hBTK	Novascreen Human BTK	Homo sapiens	BTK	17.0	uM
Novascreen	NVS_ENZ_hTrkA	Novascreen Human TrkA	Homo sapiens	NTRK1	32.0	uM
Novascreen	NVS_ENZ_hZAP70	Novascreen Human ZAP70	Homo sapiens	ZAP70	13.0	uM
Novascreen	NVS_ENZ_hCSF1R	Novascreen Human CSF1R	Homo sapiens	CSF1R	34.0	uM
Novascreen	NVS_ENZ_hEGFR	Novascreen Human EGFR	Homo sapiens	EGFR	16.0	uM
Novascreen	NVS_ENZ_hFGFR1	Novascreen Human FGFR1	Homo sapiens	FGFR1	24.0	uM
Novascreen	NVS_ENZ_hFGFR3	Novascreen Human FGFR3	Homo sapiens	FGFR3	39.0	uM
Novascreen	NVS_ENZ_hInsR	Novascreen Human InsR	Homo sapiens	INSR	42.0	uM
Novascreen	NVS_ENZ_hMet	Novascreen Human Met	Homo sapiens	MET	43.0	uM
Novascreen	NVS_ENZ_hVEGFR1	Novascreen Human VEGFR1	Homo sapiens	FLT1	8.2	uM
Novascreen	NVS_ENZ_hVEGFR3	Novascreen Human VEGFR3	Homo sapiens	FLT4	8.1	uM
Novascreen	NVS_ENZ_hTie2	Novascreen Human Tie2	Homo sapiens	TEK	5.0	uM
Novascreen	NVS_ENZ_hRAF1	Novascreen Human RAF1	Homo sapiens	RAF1	31.0	uM
Novascreen	NVS_ENZ_hAurA	Novascreen Human AurA	Homo sapiens	AURKA	25.0	uM
Novascreen	NVS_ENZ_hSGK1	Novascreen Human SGK1	Homo sapiens	SGK1	26.0	uM
Novascreen	NVS_ENZ_hMsk1	Novascreen Human Msk1	Homo sapiens	RPS6KA5	45.0	uM
Novascreen	NVS_ENZ_hPKA	Novascreen Human PKA	Homo sapiens	PRKACA	40.0	uM
Novascreen	NVS_ENZ_hMAPKAPK5	Novascreen Human MAPKAPK5	Homo sapiens	MAPKAPK5	44.0	uM
Novascreen	NVS_ENZ_hMARK1	Novascreen Human MARK1	Homo sapiens	MARK1	34.0	uM
Novascreen	NVS_ENZ_hIKKa	Novascreen Human IKKa	Homo sapiens	CHUK	25.0	uM
Novascreen	NVS_ENZ_hCK1a	Novascreen Human CK1a	Homo sapiens	CSNK1A1	26.0	uM
Novascreen	NVS_ENZ_hCK1D	Novascreen Human CK1D	Homo sapiens	CSNK1D	25.0	uM
Novascreen	NVS_ENZ_hCDK6	Novascreen Human CDK6	Homo sapiens	CDK6	17.0	uM
Novascreen	NVS_ENZ_rDYRK1a	Novascreen Rat DYRK1a	Rattus norvegicus	Dyrk1a	19.0	uM
Novascreen	NVS_ENZ_hMAPK1	Novascreen Human MAPK1	Homo sapiens	MAPK1	47.0	uM
Novascreen	NVS_ENZ_hPI3Ka	Novascreen Human PI3Ka	Homo sapiens	PIK3CA PIK3R1	6.8	uM
Novascreen	NVS_ENZ_hPTEN	Novascreen Human PTEN	Homo sapiens	PTEN	17.0	uM
Novascreen	NVS_ENZ_hPTPN13	Novascreen Human PTP-BAS	Homo sapiens	PTPN13	30.0	uM
Novascreen	NVS_ENZ_hACP1	Novascreen Human LMPTP-A	Homo sapiens	ACP1	25.0	uM
Novascreen	NVS_ENZ_hPTPN1	Novascreen Human PTP-1b	Homo sapiens	PTPN1	33.0	uM
Novascreen	NVS_ENZ_hPTPN12	Novascreen Human PTP-PEST	Homo sapiens	PTPN12	28.0	uM

ToxCast (Actor) – PFOS (part 3)

Novascreen	NVS_ENZ_hPTPN12	Novascreen Human PTP-PEST	Homo sapiens	PTPN12	28.0	uM
Novascreen	NVS_ENZ_hPTPN6	Novascreen Human PTP-SHP1	Homo sapiens	PTPN6	21.0	uM
Novascreen	NVS_ENZ_hPTPN11	Novascreen Human PTP-SHP2	Homo sapiens	PTPN11	14.0	uM
Novascreen	NVS_ENZ_hPTPRM	Novascreen Human PTP-MU	Homo sapiens	PTPRM	41.0	uM
Novascreen	NVS_ENZ_hPTPRF	Novascreen Human PTP-LAR	Homo sapiens	PTPRF	19.0	uM
Novascreen	NVS_ENZ_hPPP1CA	Novascreen Human PP-1a	Homo sapiens	PPP1CA	23.0	uM
Novascreen	NVS_ENZ_hPPP2CA	Novascreen Human PP-2A	Homo sapiens	PPP2CA	6.0	uM
Novascreen	NVS_ENZ_hPDE5	Novascreen Human PDE5	Homo sapiens	PDE5A	29.0	uM
Novascreen	NVS_ENZ_hHDAC3	Novascreen Human HDAC3	Homo sapiens	HDAC3 NCOR2	28.0	uM
Novascreen	NVS_GPCR_hAdra2C	Novascreen Human Adra2C	Homo sapiens	ADRA2C	8.8	uM
Novascreen	NVS_GPCR_h5HT5A	Novascreen Human 5HT5A	Homo sapiens	HTR5A	23.0	uM
Novascreen	NVS_GPCR_h5HT6	Novascreen Human 5HT6	Homo sapiens	HTR6	43.0	uM
Novascreen	NVS_GPCR_h5HT7	Novascreen Human 5HT7	Homo sapiens	HTR7	18.0	uM
Novascreen	NVS_GPCR_gLTB4	Novascreen Guinea Pig LTB4	Cavia porcellus		13.0	uM
Novascreen	NVS_GPCR_gLTD4	Novascreen Guinea Pig LTD4	Cavia porcellus	Cysltr1	48.0	uM
Novascreen	NVS_GPCR_hPY2	Novascreen Human P2Y	Homo sapiens	P2RY1 P2RY2 P2RY12 P2RY14 P2RY10 P2RY11	12.0	uM
Novascreen	NVS_GPCR_hAdoRA2a	Novascreen Human AdoRA2a	Homo sapiens	ADORA2A	6.9	uM
Novascreen	NVS_NR_hRAR_Antagonist	Novascreen Human RAR Antagonist	Homo sapiens	RARA	43.0	uM
Novascreen	NVS_NR_hPPARg	Novascreen Human PPARg	Homo sapiens	PPARG	16.0	uM
Novascreen	NVS_NR_hPXR	Novascreen Human PXR	Homo sapiens	NR1I2	38.0	uM
Novascreen	NVS_NR_hCAR_Antagonist	Novascreen Human CAR Antagonist	Homo sapiens	NR1I3	42.0	uM
Novascreen	NVS_NR_bPR	Novascreen Bovine PR	Bos taurus	PGR	48.0	uM
Novascreen	NVS_NR_hAR	Novascreen Human AR	Homo sapiens	AR	39.0	uM
Novascreen	NVS_NR_rAR	Novascreen Rat AR	Rattus norvegicus	Ar	15.0	uM
Novascreen	NVS_NR_hGR	Novascreen Human GR	Homo sapiens	NR3C1	3.5	uM
NHEERL Zebrafish	ZF_Total_Score_AC50	ZF_Total_Score_AC50	Danio rerio		32.9	uM
NHEERL Zebrafish	ZF_Total_Score_AC10	ZF_Total_Score_AC10	Danio rerio		16.0	uM

ToxCast (Actor - ToxRefDb) - PFOS

ToxRefDB	DEV_rabbit_Developmental	DEV_rabbit_Developmental (dLEL_rabbit)	Oryctolagus cuniculus	2.5	mg/kg/day
ToxRefDB	DEV_rabbit_Maternal	DEV_rabbit_Maternal (mLEL_rabbit)	Oryctolagus cuniculus	1.0	mg/kg/day
ToxRefDB	DEV_rabbit_Developmental_GeneralFetal	Developmental rabbit Developmental GeneralFetal	Oryctolagus cuniculus	2.5	mg/kg/day
ToxRefDB	DEV_rabbit_Maternal_GeneralMaternal	Developmental rabbit Maternal GeneralMaternal	Oryctolagus cuniculus	1.0	mg/kg/day
ToxRefDB	DEV_rabbit_Maternal_PregnancyRelated	Developmental rabbit Maternal PregnancyRelated	Oryctolagus cuniculus	2.5	mg/kg/day
ToxRefDB	DEV_rabbit_Developmental_GeneralFetal_FetalWeightReduction	Developmental Rabbit General FetalWeightReduction	Oryctolagus cuniculus	2.5	mg/kg/day
ToxRefDB	DEV_rabbit_Maternal_GeneralMaternal_Systemic	Developmental Rabbit Maternal Systemic	Oryctolagus cuniculus	1.0	mg/kg/day
ToxRefDB	DEV_rabbit_Maternal_PregnancyRelated_MaternalPregLoss	Developmental Rabbit PregnancyRelated MaternalPregLoss	Oryctolagus cuniculus	2.5	mg/kg/day
ToxRefDB	DEV_rabbit_Prenatal_Loss	Combined Developmental_PregnancyRelated_EmbryoFetalLoss AND Maternal_PregnancyRelated_MaternalPregLoss	Oryctolagus cuniculus	5.6	mg/kg/day

Mode of Action and Pathways

- Anchor data to pathways
- Map transcriptomics data to Pathways
- Map *in vitro* data to Pathways
- Enriched Analysis on transcriptomics data
- Enriched analysis on *in vitro* data
- Heterogenous enrichment
- Pathway analysis and visualisation
- Results shown based on CTD omics data and InCroMap software

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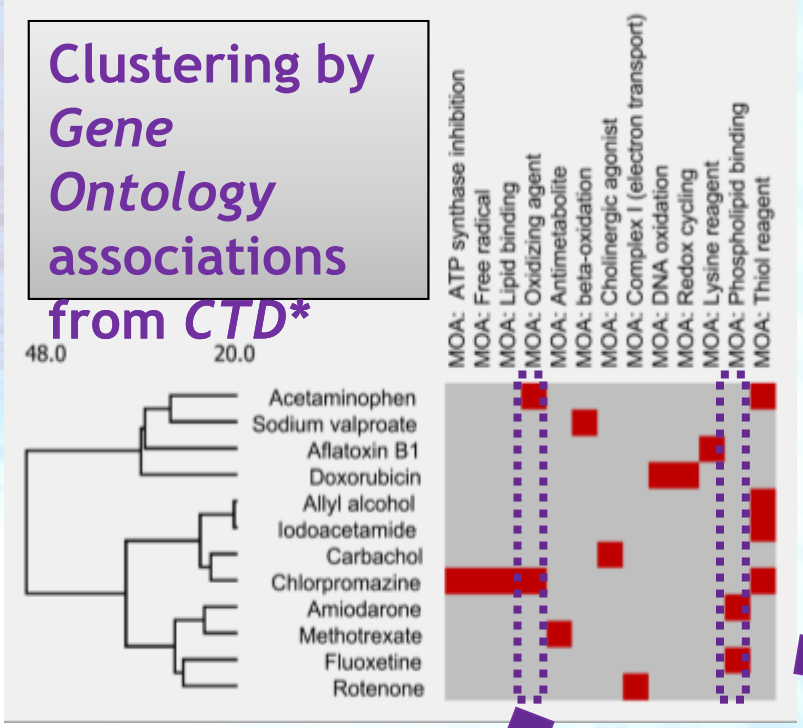
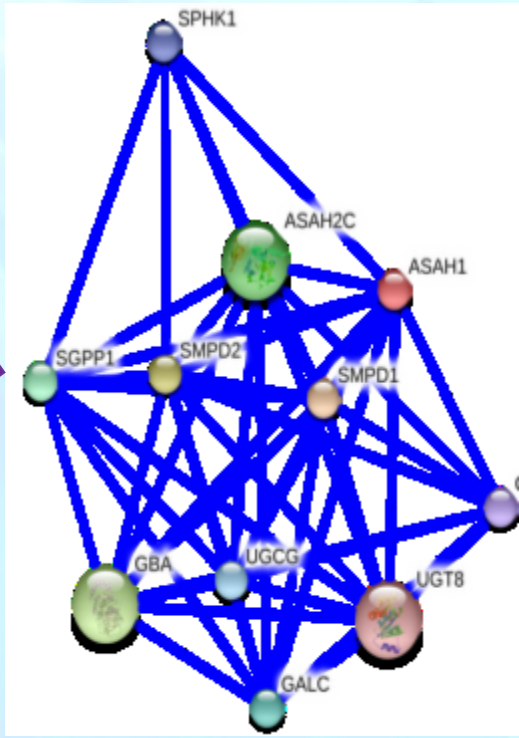
Public Data Analysis

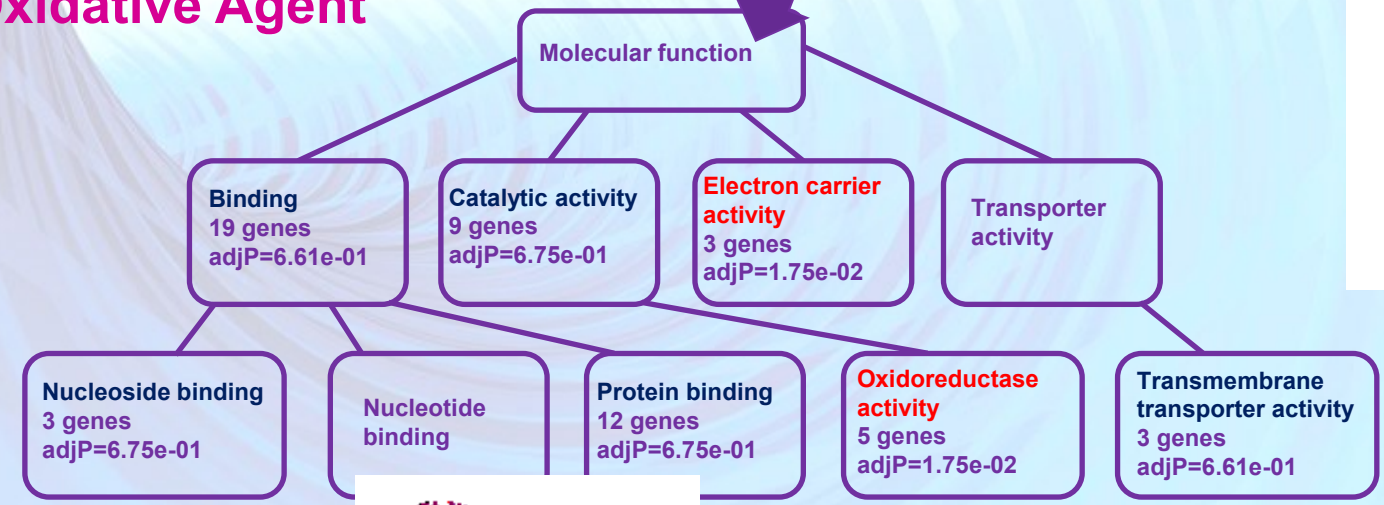
Clustering by *Gene Ontology* associations from *CTD**



Phospholipid Binding



Oxidative Agent



**CTD = Comparative Toxicogenomics Database (www.ctd.org)*

OpenTox

Karolinska Institutet

Kohonen P. et al. The ToxBank Data Warehouse: Supporting the Replacement of In Vivo Repeated Dose Systemic Toxicity Testing. Mol. Inf.17 JAN 2013.

PubChem *in vitro* Data - Benzoapyrene

	Compound	CasNR	GeneID	
2	Benzoapyrene	50-32-8	113037	Acetylcholinesterase
3	Benzoapyrene	50-32-8	113978	Amine oxidase [flavin-containing] A
4	Benzoapyrene	50-32-8	13177715	Arrestin, beta 1 [Homo sapiens]
5	Benzoapyrene	50-32-8	3041653	Aryl hydrocarbon receptor
6	Benzoapyrene	50-32-8	269849759	Cellular tumor antigen p53
7	Benzoapyrene	50-32-8	117144	Cytochrome P450 1A2
8	Benzoapyrene	50-32-8	4503385	DRD2 gene product [Homo sapiens]
9	Benzoapyrene	50-32-8	7705682	GMNN gene product [Homo sapiens]
10	Benzoapyrene	50-32-8	15607504	Probable fructose-bisphosphate aldolase Fba [Mycobacterium tuberculosis H37R
11	Benzoapyrene	50-32-8	119533	Receptor tyrosine-protein kinase erbB-2
12	Benzoapyrene	50-32-8	125370	Tyrosine-protein kinase Fyn
13	*Benzoapyrene*	*50-32-8*	*269849759*	*Cellular tumor antigen p53*
14	*Benzoapyrene*	*50-32-8*	*20149576*	*NFE2L2 gene product [Homo sapiens]*
15	*Benzoapyrene*	*50-32-8*	*122921310*	*Chain A, The Structure Of Wild-Type Human Hadh2 (17beta- Hydroxysteroid Deh*
16	*Benzoapyrene*	*50-32-8*	*62362414*	*ABL1 gene product [Homo sapiens]*
17	*Benzoapyrene*	*50-32-8*	*15607504*	*Probable fructose-bisphosphate aldolase Fba [Mycobacterium tuberculosis H37R*
18	*Benzoapyrene*	*50-32-8*	*117144*	*Cytochrome P450 1A2*
19	*Benzoapyrene*	*50-32-8*	*15607504*	*Probable fructose-bisphosphate aldolase Fba [Mycobacterium tuberculosis H37R*
20	*Benzoapyrene*	*50-32-8*	*25952111*	*TNF gene product [Homo sapiens]*

Actives obtained from data mining with IST AOP search Tool. Actives shown in red italics are based on a Tanimoto-based similarity read across.

PubChem *in vitro* Data - PFOA

	Compound	CasNR	GeneID	
2	PFOA	335-67-1	296439460	ATPase family AAA domain-containing protein 5
3	PFOA	335-67-1	269849759	Cellular tumor antigen p53
4	PFOA	335-67-1	20149576	NFE2L2 gene product [Homo sapiens]
5	PFOA	335-67-1	34577122	NFKB1 gene product [Homo sapiens]
6	PFOA	335-67-1	3041727	Peroxisome proliferator-activated receptor alpha
7	PFOA	335-67-1	51095037	aryl hydrocarbon receptor [Homo sapiens]
8	PFOA	335-67-1	348019627	estrogen nuclear receptor alpha [Homo sapiens]
9	PFOA	335-67-1	325495553	farnesoid X nuclear receptor [Homo sapiens]
10	PFOA	335-67-1	311348376	glucocorticoid receptor [Homo sapiens]
11	PFOA	335-67-1	216409692	peroxisome proliferator activated receptor gamma [Homo sapiens]
12	PFOA	335-67-1	216409690	peroxisome proliferator-activated receptor delta [Homo sapiens]
13	PFOA	335-67-1	325495557	pregnane X nuclear receptor [Homo sapiens]
14	PFOA	335-67-1	5702233	pregnane X receptor [Rattus norvegicus]
15	PFOA	335-67-1	325495497	retinoid X nuclear receptor alpha [Homo sapiens]
16	PFOA	335-67-1	189491771	thyroid hormone receptor beta [Homo sapiens]
17	PFOA	335-67-1	216409708	vitamin D (1,25- dihydroxyvitamin D3) receptor [Homo sapiens]

Actives obtained from data mining with IST AOP search Tool. Actives shown in red italics are based on a Tanimoto-based similarity read across.

Pathways from CTD Omics Data - Benzoapyrene

1	path:hsa04115	p53 signaling pathway	46/4093	69/17280	3.528E-14	8.255E-12	CDK6, BID, RFWD2, ZMAT3, IGF1, SESN1, SERPINE1, MDM2, CYCS, TNFRSF10B, STEAP3, ATM, CCND3, CASP3, A
2	path:hsa05200	Pathways in cancer	133/4093	327/17280	2.65E-12	3.101E-10	CBLB, PPARD, MAPK8, NOS2, MAPK1, MDM2, BCL2L1, MAPK3, PPARG, WNT11, CDH1, TGFB2, FGFR1, LAMA5, TGFI
3	path:hsa00980	Metabolism of xenobiotics by cytochrome P450	43/4093	71/17280	2.72E-11	1.915E-9	GSTP1, CYP1B1, CYP3A5, ADH4, CYP3A4, ADH5, MGST2, CYP2C19, ALDH1A3, ADH6, CYP2S1, ALDH3A1, GSTZ1, U
4	path:hsa05215	Prostate cancer	50/4093	89/17280	3.274E-11	1.915E-9	EGFR, GSTP1, CTNNB1, NFKBIA, CREB1, AKT1, IGF1, KLK3, MAPK1, MDM2, PDGFC, PIK3R2, CREB3L3, PDGFB, MAP
5	path:hsa04380	Osteoclast differentiation	64/4093	128/17280	5.715E-11	2.675E-9	TNFRSF1A, PPP3CA, MAPK8, TREM2, LILRA2, JUND, CREB1, JUNB, MAPK1, NFATC1, MAPK14, MAPK3, PPARG, ACP
6	path:hsa00982	Drug metabolism - cytochrome P450	43/4093	73/17280	9.608E-11	3.747E-9	GSTP1, CYP3A5, FMO1, ADH4, CYP3A4, ADH5, MGST2, CYP2C19, ALDH1A3, ADH6, FMO5, ALDH3A1, CYP2A6, GST
7	path:hsa04110	Cell cycle	62/4093	128/17280	5.693E-10	1.903E-8	CDK6, MAD1L1, MDM2, YWHAH, MYC, CHEK2, PCNA, TGFB2, WEE1, MAD2L1, TGFB1, CDK2, CDK4, CDC25C, CDC1
8	path:hsa04210	Apoptosis	45/4093	86/17280	6.036E-9	1.765E-7	BID, TNFRSF1A, PPP3CA, IRAK2, BIRC3, NFKBIA, IRAK1, RIPK1, AKT1, CYCS, TNFRSF10C, TNFRSF10B, TNFRSF10
9	path:hsa04060	Cytokine-cytokine receptor interaction	102/4093	265/17280	2.275E-8	5.914E-7	IL18R1, TSLP, PRLR, TNFSF4, TGFB2, TGFB1, TNFSF13, CXCL10, TNFSF10, CCR9, VEGFA, TNFSF9, BMPR2, TNFR
10	path:hsa05220	Chronic myeloid leukemia	39/4093	73/17280	2.84E-8	6.644E-7	CDK6, CBLB, NFKBIA, AKT1, MAPK1, MDM2, PIK3R2, BCL2L1, MAPK3, MYC, TGFB2, TGFB1, CBL, SHC1, CDK4, TP53
11	path:hsa05222	Small cell lung cancer	43/4093	85/17280	4.561E-8	9.702E-7	CDK6, PTK2, LAMB4, TRAF1, BIRC3, NFKBIA, NOS2, AKT1, COL4A2, CYCS, ITGA6, PIK3R2, BCL2L1, PTGS2, MYC, A
12	path:hsa05164	Influenza A	73/4093	176/17280	6.779E-8	1.322E-6	TNFRSF1A, HSPA1A, HSPA1B, HLA-DOA, MAPK8, TLR7, PLG, MAPK1, MAPK14, MAPK3, ATF2, STAT2, PABPN1, PY
13	path:hsa05219	Bladder cancer	26/4093	42/17280	1.157E-7	2.082E-6	EGFR, MDM2, MAPK1, MAPK3, MYC, CDH1, CDK4, TP53, IL8, VEGFA, CCND1, MAP2K2, FGFR3, MAP2K1, DAPK1, E2
14	path:hsa04660	T cell receptor signaling pathway	50/4093	108/17280	1.394E-7	2.33E-6	CBLB, PPP3CA, NFATC3, MAPK1, IL2, NFATC1, MAPK14, MAPK3, ZAP70, ITK, CDK4, PIK3CB, PIK3CD, CD8B, IKBKG,
15	path:hsa05212	Pancreatic cancer	36/4093	70/17280	3.187E-7	4.971E-6	CDK6, EGFR, MAPK8, AKT1, PLD1, MAPK1, PIK3R2, BCL2L1, MAPK3, STAT3, TGFB2, TGFB1, STAT1, CDK4, TP53,
16	path:hsa04062	Chemokine signaling pathway	75/4093	189/17280	3.55E-7	5.192E-6	CCR7, TIAM1, ADCY7, MAPK1, ADCY9, BCAR1, MAPK3, PARD3, STAT3, STAT2, ITK, STAT1, GNAI1, SHC1, CXCL1
17	path:hsa05214	Glioma	34/4093	65/17280	4E-7	5.506E-6	CDK6, EGFR, IGF1, AKT1, MAPK1, MDM2, PDGFB, PIK3R2, MAPK3, CAMK2D, CALML5, SHC1, CDK4, TP53, PIK3CB,
18	path:hsa05146	Amoebiasis	48/4093	106/17280	5.327E-7	6.926E-6	PTK2, IL10, ARG1, LAMB4, SERPINB9, ARG2, NOS2, PLCB4, COL4A2, SERPINB10, ACTN1, PIK3R2, CASP3, COL1A1,
19	path:hsa04920	Adipocytokine signaling pathway	35/4093	69/17280	6.951E-7	8.561E-6	TNFRSF1A, G6PC, NFKBIA, MAPK8, PRKAB1, AKT1, PPARA, NFKBIE, ACSL6, CD36, PCK2, NFKBIB, IRS1, PCK1, AGR
20	path:hsa05223	Non-small cell lung cancer	29/4093	54/17280	1.363E-6	1.595E-5	CDK6, EGFR, AKT1, MAPK1, PIK3R2, MAPK3, CDK4, CASP9, TP53, BAD, PIK3CB, PIK3CD, FOXO3, CCND1, MAP2K2,
21	path:hsa05218	Melanoma	35/4093	71/17280	1.601E-6	1.784E-5	CDK6, EGFR, IGF1, AKT1, MAPK1, MDM2, PDGFC, PIK3R2, PDGFB, MAPK3, MET, CDH1, FGFR1, FGF2, CDK4, TP53,
22	path:hsa05221	Acute myeloid leukemia	30/4093	58/17280	2.478E-6	2.594E-5	PPARD, AKT1, MAPK1, PIK3R2, RUNX1T1, MAPK3, PIM1, MYC, PIM2, STAT3, TCF7, CEBPA, CCNA1, BAD, PIK3CB,
23	path:hsa04960	Aldosterone-regulated sodium reabsorption	24/4093	42/17280	2.575E-6	2.594E-5	PIK3CB, IRS2, ATP1A2, PIK3CD, IGF1, ATP1B2, MAPK1, NR3C2, SFN, PIK3R2, MAPK3, IRS1, SLC9A3R2, HSD11B1,
24	path:hsa00250	Alanine, aspartate and glutamate metabolism	20/4093	32/17280	2.661E-6	2.594E-5	ASS1, GFPT1, GLS2, ABAT, GLUD1, CPS1, GPT2, AGXT2, ALDH5A1, ASNS, GLS, GOT1, AGXT, GFPT2, IL4I1, ALDH
25	path:hsa05162	Measles	55/4093	134/17280	3.402E-6	3.184E-5	CDK6, HSPA1A, HSPA1B, CBLB, TLR7, IL2, STAT3, STAT2, BBC3, STAT1, TP73, CDK2, CDK4, IRF7, TNFSF10, PIK3
26	path:hsa05143	African trypanosomiasis	21/4093	35/17280	3.767E-6	3.371E-5	IDO1, IL10, HBA2, F2RL1, PLCB4, IL18, VCAM1, APOA1, IFNG, FAS, PLCB1, HP, SELE, IL1B, APOL1, PRKCB, ICAM1,
27	path:hsa04510	Focal adhesion	75/4093	200/17280	3.89E-6	3.371E-5	MAPK8, IGF1, MAPK1, COL4A2, ITGA11, RELN, PDGFB, BCAR1, MAPK3, MET, COL1A1, KDR, LAMA5, LAMA3, COL2A
28	path:hsa05210	Colorectal cancer	31/4093	62/17280	4.176E-6	3.49E-5	CTNNB1, MAPK8, AKT1, MAPK1, MSH3, CYCS, PIK3R2, MAPK3, MSH2, MYC, CASP3, MSH6, TGFB2, TCF7, JUN, TGI
29	path:hsa04976	Bile secretion	34/4093	71/17280	4.908E-6	3.96E-5	SLC22A7, KCNN2, SLC27A5, CYP3A4, ADCY7, ATP1B2, AQP9, ADCY9, BAAT, ABCB1, SLC2A1, ABCB4, ABCG8, SLC1
30	path:hsa00040	Pentose and glucuronate interconversions	20/4093	33/17280	5.159E-6	4.024E-5	UGT1A6, UGT1A7, UGT1A8, UGP2, UGT1A4, UGT1A1, UGT2B4, UGT1A9, DHDH, UGT2B7, UGDH, CRYL1, DCXR, UGT
31	path:hsa04010	MAPK signaling pathway	94/4093	268/17280	6.799E-6	5.132E-5	TNFRSF1A, PPP3CA, HSPA1A, HSPA1B, MAPK8, JUND, RRAS, MAPK1, PDGFB, MAPK14, MAPK3, PLA2G4A, NF1, MY
32	path:hsa04722	Neurotrophin signaling pathway	51/4093	127/17280	1.451E-5	1.061E-4	MAPK8, SH2B3, NTRK3, MAPK1, YWHAH, MAPK14, MAPK3, TP73, CALML5, SHC1, BAD, PIK3CB, SHC4, PIK3CD, FO
33	path:hsa04540	Gap junction	39/4093	90/17280	1.861E-5	1.299E-4	EGFR, TUBA1A, GJA1, TUBB1, ADCY7, PLCB4, MAPK1, ADCY9, PDGFC, PDGFB, TUBA8, MAPK3, PLCB1, GNAI1, GNA
34	path:hsa04914	Progesterone-mediated oocyte maturation	38/4093	87/17280	1.906E-5	1.299E-4	MAD1L1, MAPK8, RPS6KA3, ADCY7, IGF1, AKT1, MAPK1, RPS6KA1, ADCY9, PIK3R2, RPS6KA2, MAPK14, MAPK3, BU
35	path:hsa04910	Insulin signaling pathway	54/4093	138/17280	1.943E-5	1.299E-4	PKLR, CBLB, MAPK8, MAPK1, PCK2, MAPK3, PCK1, SOCS2, INSR, CALML5, RPTOR, SHC1, BAD, PIK3CB, SHC4, GYS
36	path:hsa00500	Starch and sucrose metabolism	27/4093	55/17280	2.48E-5	1.612E-4	G6PC, HK1, UGP2, PYGM, UGDH, UGT2B11, UGT2A1, PGM2L1, UGT2A3, HK2, GYS2, UGT1A8, UGT1A7, UGT1A6, UG
37	path:hsa04810	Regulation of actin cytoskeleton	76/4093	214/17280	2.742E-5	1.653E-4	TIAM1, CYFIP2, RRAS, MAPK1, ITGA11, ARPC4, GSN, PDGFB, BCAR1, MAPK3, FGFR1, PIP5K1B, MYH9, MYH10, DIA
38	path:hsa00830	Retinol metabolism	30/4093	64/17280	2.748E-5	1.653E-4	CYP3A5, CYP3A4, ADH4, RDH16, ADH5, CYP2C19, ADH6, LRAT, CYP2A6, UGT2B11, UGT2A1, CYP3A7, CYP2A7, UG
39	path:hsa05145	Toxoplasmosis	52/4093	133/17280	2.755E-5	1.653E-4	TNFRSF1A, HSPA1A, HSPA1B, HLA-DOA, MAPK8, NOS2, MAPK1, LY96, BCL2L1, MAPK14, MAPK3, PLA2G4A, STAT3
40	path:hsa04620	Toll-like receptor signaling pathway	42/4093	102/17280	3.8E-5	2.223E-4	IRF5, NFKBIA, MAPK8, TLR7, IRAK1, RIPK1, AKT1, MAPK1, TLR5, PIK3R2, LY96, CCL5, MAPK14, MAPK3, LBP, JUN,
41	path:hsa03320	PPAR signaling pathway	32/4093	71/17280	3.897E-5	2.224E-4	ME1, PPARD, SLC27A5, SORBS1, ACOX1, SCD, PPARA, PLTP, ACSL6, LPL, CD36, CYP8B1, PCK2, APOA5, PPARG, P
42	path:hsa05160	Hepatitis C	52/4093	135/17280	4.278E-5	2.384E-4	TNFRSF1A, IFIT1, MAPK8, CLDN4, CLDN2, PPARA, CLDN10, IRF1, MAPK1, MAPK14, MAPK3, STAT3, STAT2, NR1H

Pathways shown for enriched analysis of CTD Home Sapiens omics data

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Pathways from CTD Omics Data - Benzoapyrene

1	path:hsa04115	p53 signaling pathway	46/4093	69/17280	3.528E-14	8.255E-12	CDK6, BID, RFWI
2	path:hsa05200	Pathways in cancer	133/4093	327/17280	2.65E-12	3.101E-10	CBLB, PPARD, M
3	path:hsa00980	Metabolism of xenobiotics by cytochrome P450	43/4093	71/17280	2.72E-11	1.915E-9	GSTP1, CYP1B1,
4	path:hsa05215	Prostate cancer	50/4093	89/17280	3.274E-11	1.915E-9	EGFR, GSTP1, C
5	path:hsa04380	Osteoclast differentiation	64/4093	128/17280	5.715E-11	2.675E-9	TNFRSF1A, PPP3
6	path:hsa00982	Drug metabolism - cytochrome P450	43/4093	73/17280	9.608E-11	3.747E-9	GSTP1, CYP3A5,
7	path:hsa04110	Cell cycle	62/4093	128/17280	5.693E-10	1.903E-8	CDK6, MAD1L1,
8	path:hsa04210	Apoptosis	45/4093	86/17280	6.036E-9	1.765E-7	BID, TNFRSF1A,
9	path:hsa04060	Cytokine-cytokine receptor interaction	102/4093	265/17280	2.275E-8	5.914E-7	IL18R1, TSLP, PI
10	path:hsa05220	Chronic myeloid leukemia	39/4093	73/17280	2.84E-8	6.644E-7	CDK6, CBLB, NFK
11	path:hsa05222	Small cell lung cancer	43/4093	85/17280	4.561E-8	9.702E-7	CDK6, PTK2, LAM
12	path:hsa05164	Influenza A	73/4093	176/17280	6.779E-8	1.322E-6	TNFRSF1A, HSP/
13	path:hsa05219	Bladder cancer	26/4093	42/17280	1.157E-7	2.082E-6	EGFR, MDM2, MA
14	path:hsa04660	T cell receptor signaling pathway	50/4093	108/17280	1.394E-7	2.33E-6	CBLB, PPP3CA, N
15	path:hsa05212	Pancreatic cancer	36/4093	70/17280	3.187E-7	4.971E-6	CDK6, EGFR, MA
16	path:hsa04062	Chemokine signaling pathway	75/4093	189/17280	3.55E-7	5.192E-6	CCR7, TIAM1, AI
17	path:hsa05214	Glioma	34/4093	65/17280	4E-7	5.506E-6	CDK6, EGFR, IGF
18	path:hsa05146	Amoebiasis	48/4093	106/17280	5.327E-7	6.926E-6	PTK2, IL10, ARG
19	path:hsa04920	Adipocytokine signaling pathway	35/4093	69/17280	6.951E-7	8.561E-6	TNFRSF1A, G6P(
20	path:hsa05223	Non-small cell lung cancer	29/4093	54/17280	1.363E-6	1.595E-5	CDK6, EGFR, AKT
21	path:hsa05218	Melanoma	35/4093	71/17280	1.601E-6	1.784E-5	CDK6, EGFR, IGF
22	path:hsa05221	Acute myeloid leukemia	30/4093	58/17280	2.478E-6	2.594E-5	PPARD, AKT1, M
23	path:hsa04960	Aldosterone-regulated sodium reabsorption	24/4093	42/17280	2.575E-6	2.594E-5	PIK3CB, IRS2, AT
24	path:hsa00250	Alanine, aspartate and glutamate metabolism	20/4093	32/17280	2.661E-6	2.594E-5	ASS1, GFPT1, GI
25	path:hsa05162	Measles	55/4093	134/17280	3.402E-6	3.184E-5	CDK6, HSPA1A,
26	path:hsa05143	African trypanosomiasis	21/4093	35/17280	3.767E-6	3.371E-5	IDO1, IL10, HBA2

Pathways shown for enriched analysis of CTD Home Sapiens omics data

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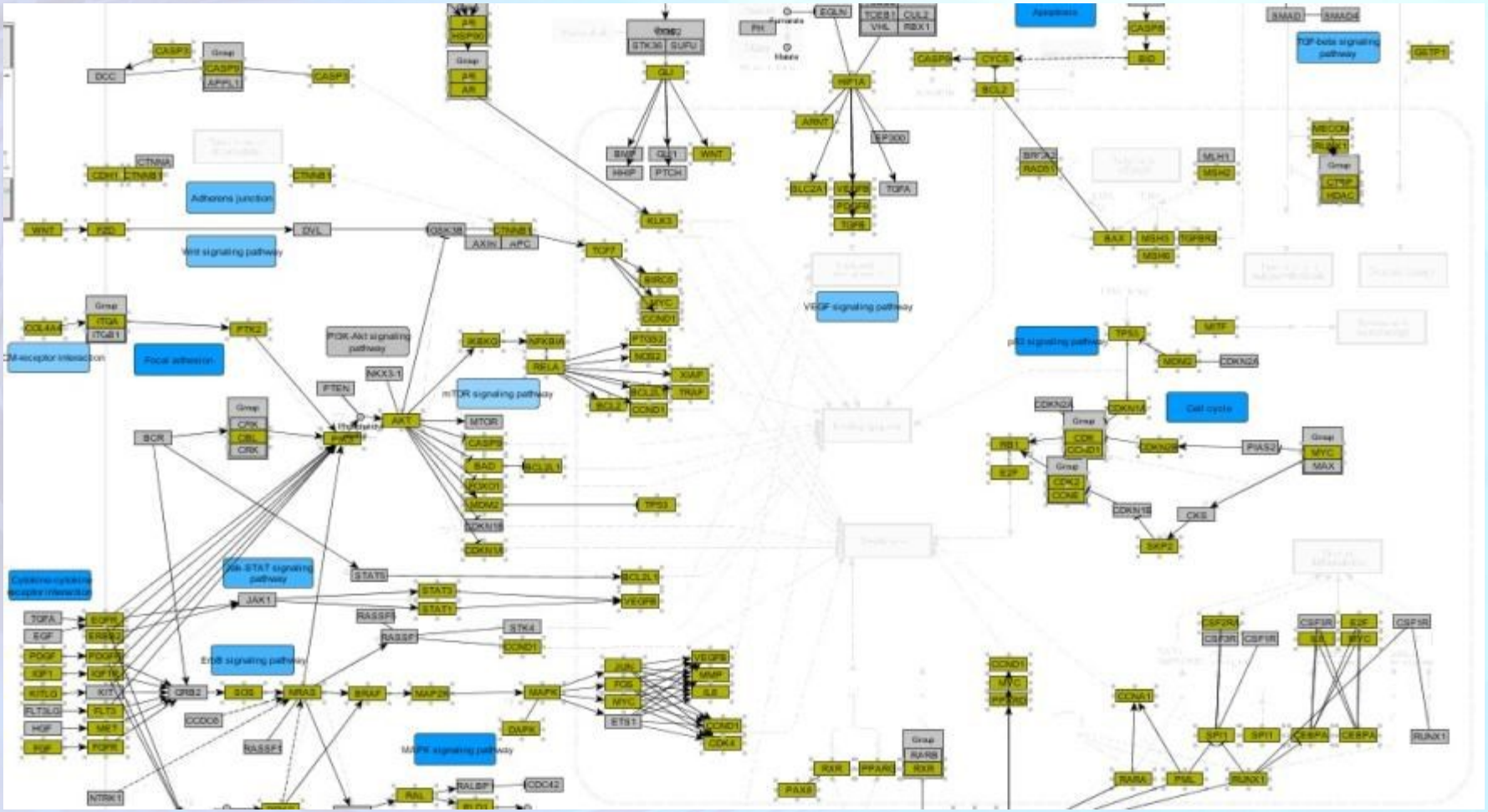
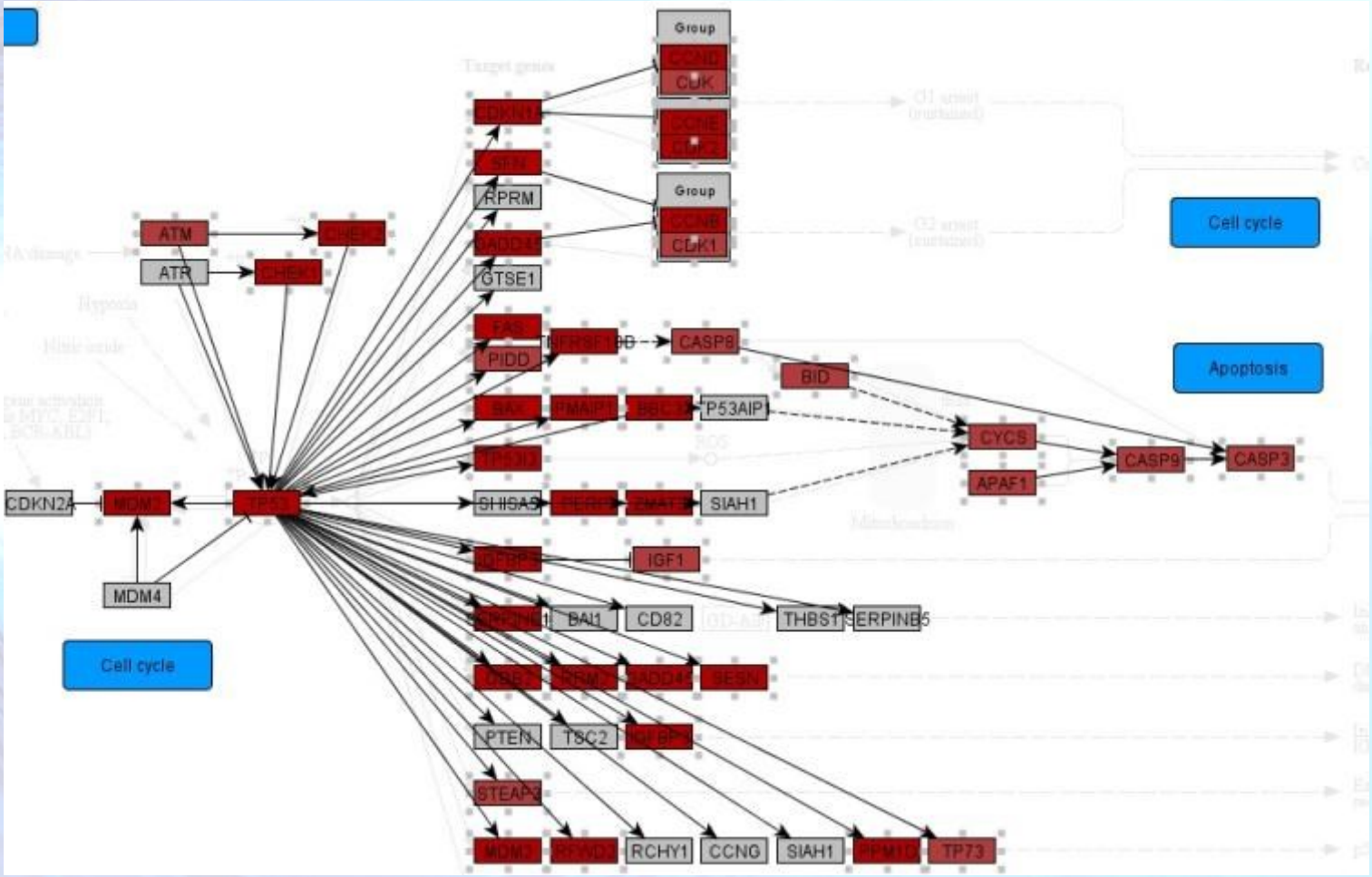
Cancer Pathways - Benzoapyrene



Pathway data shown based on enriched analysis of CTD Homo Sapiens omics data

OpenTox

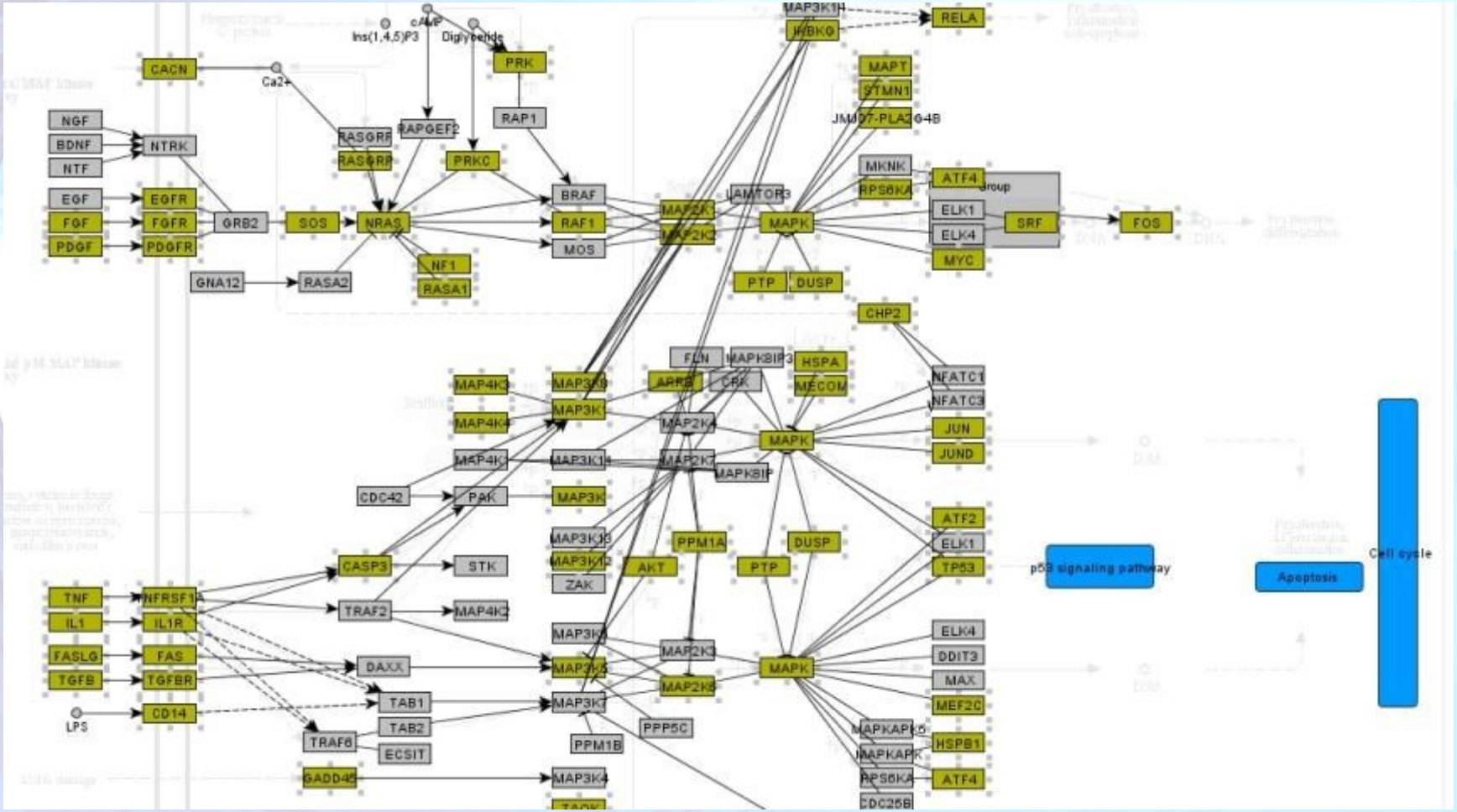
p53 Pathway - Benzoapyrene



Pathway data shown based on enriched analysis of CTD Homo Sapiens omics data

OpenTox

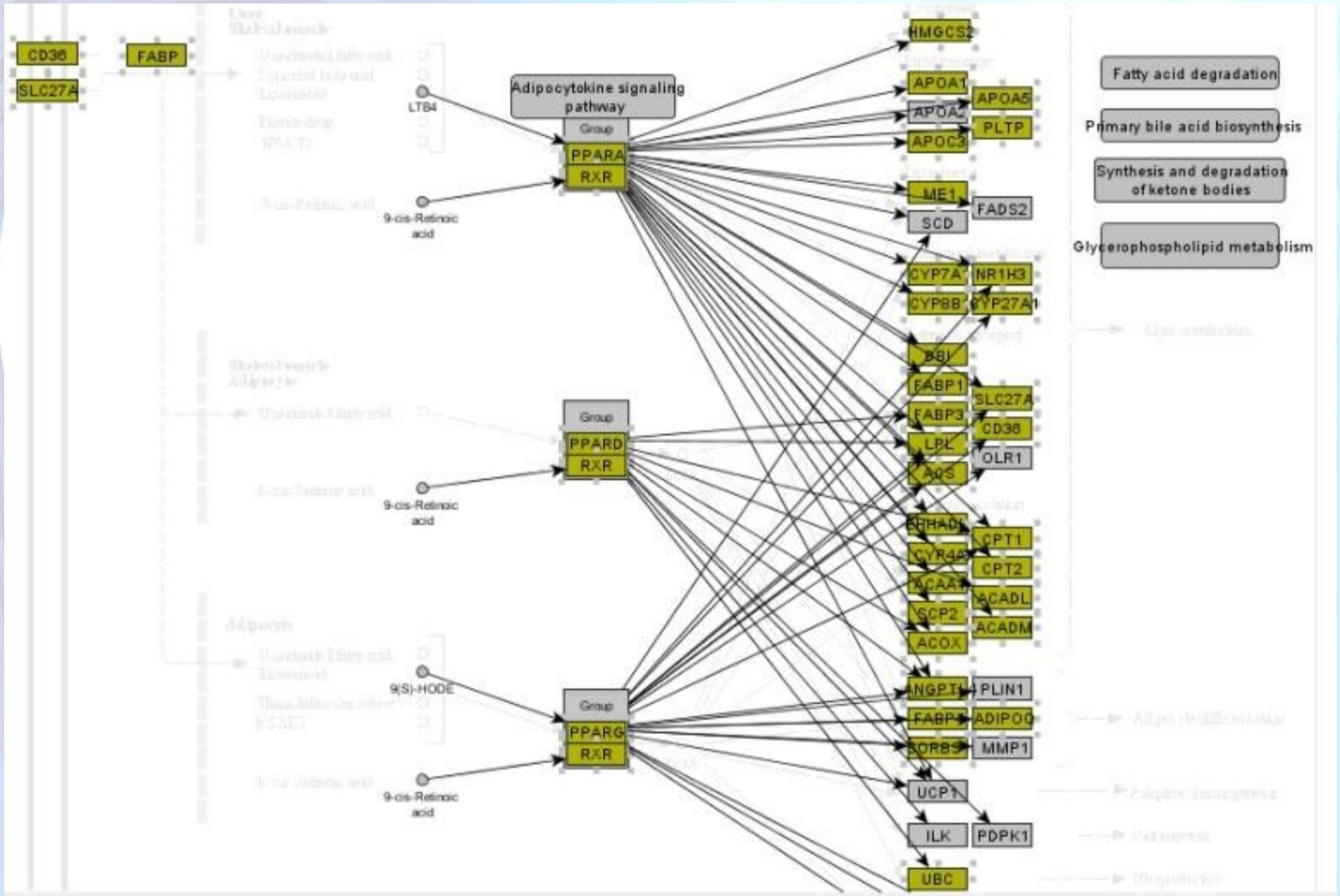
MAPK Signalling Pathway - Benzoapyrene



Pathway data shown based on enriched analysis of CTD Homo Sapiens omics data

OpenTox

PPAR Pathways - PFOS



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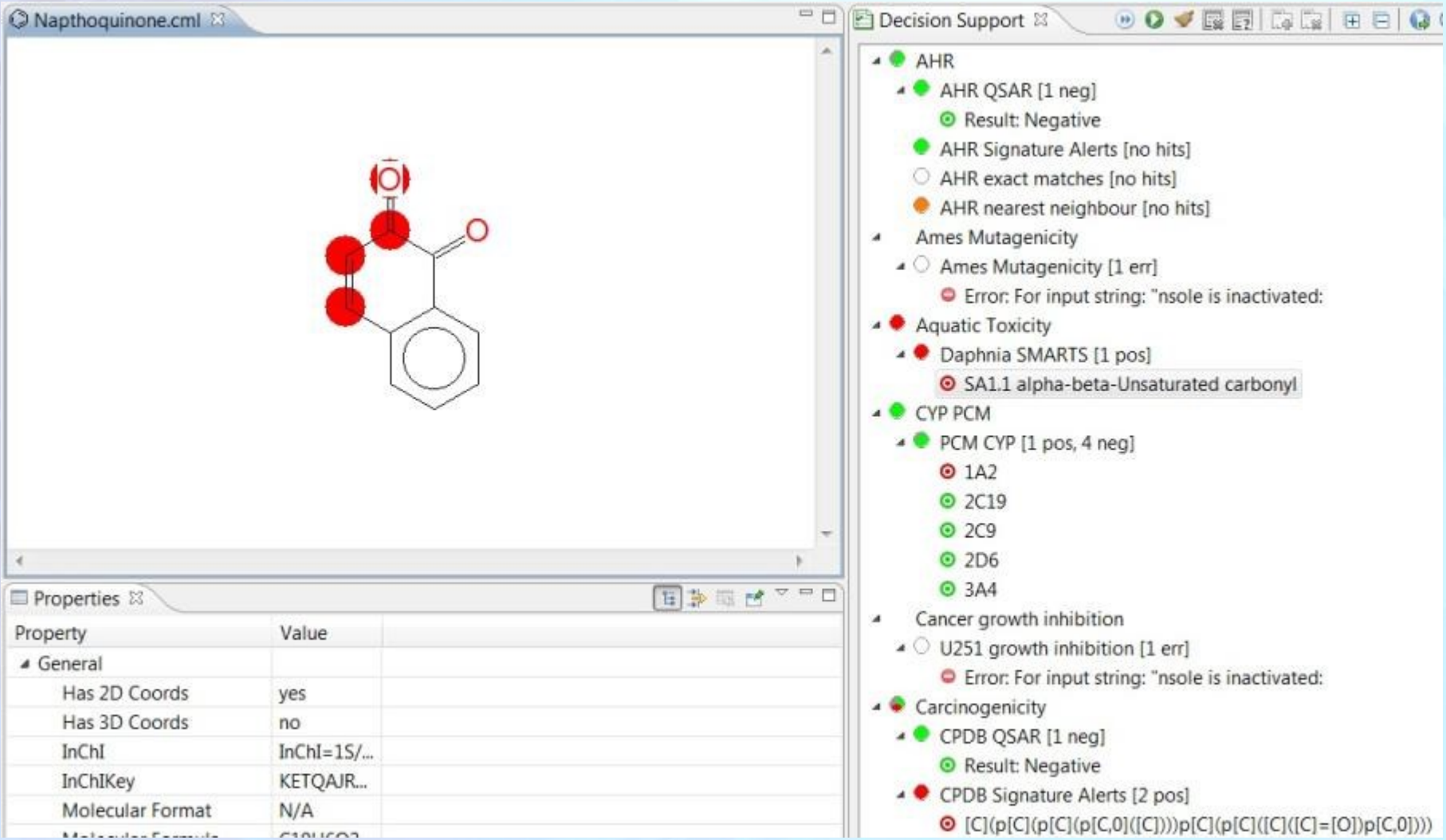
Pathways shown for enriched analysis of CTD omics data.

Bioclipse - OpenTox

- Workbench for Chemical Safety Assessment
- Interoperates in real time with distributed OpenTox web services
- Combines local and distributed models
- Explore impact on toxicities through chemical modifications
- Informs site risk assessment on influence of reactions and alternative chemical forms

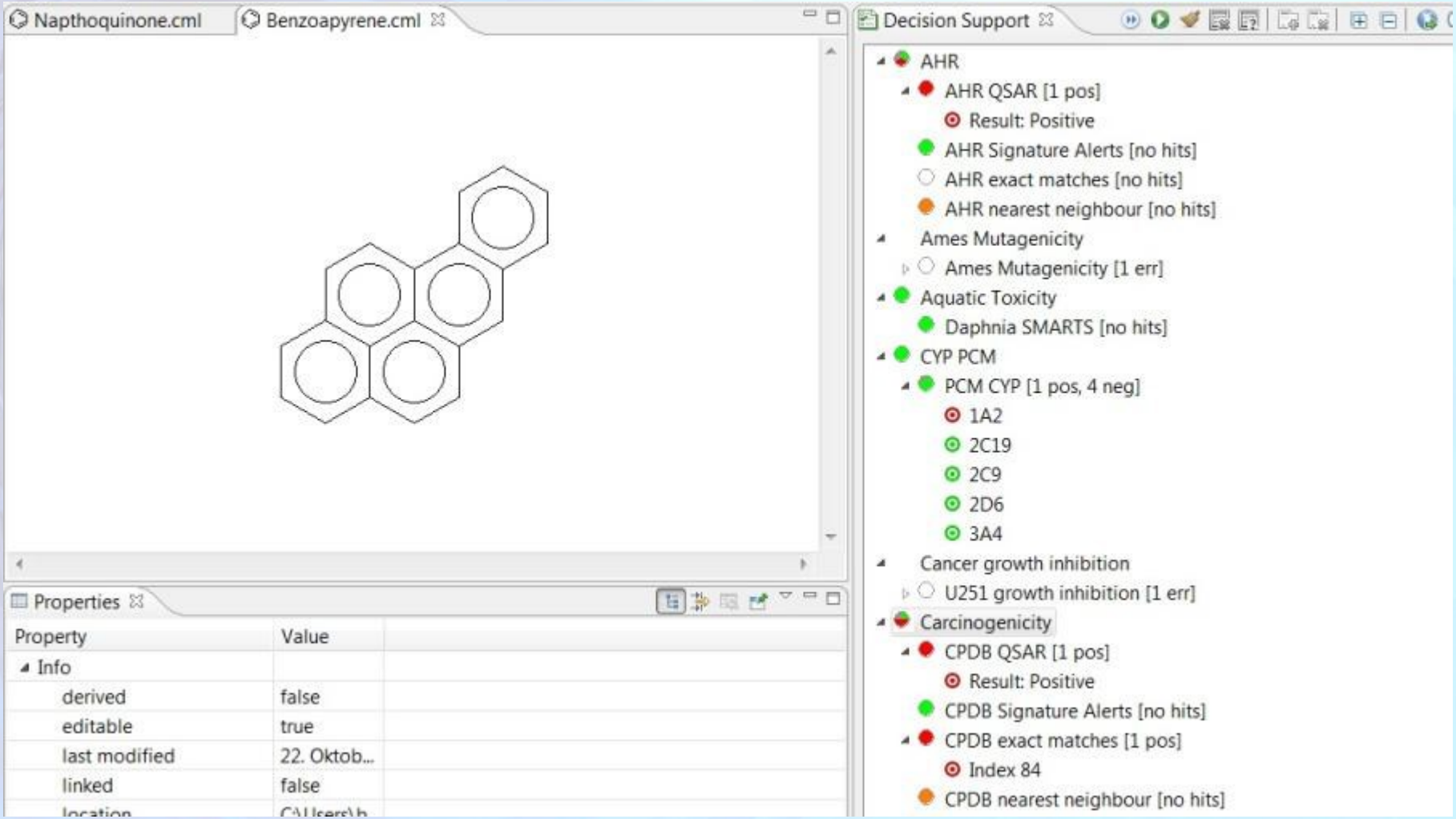
OpenTox

Bioclipse - OpenTox: 1,2-Naphthoquinone



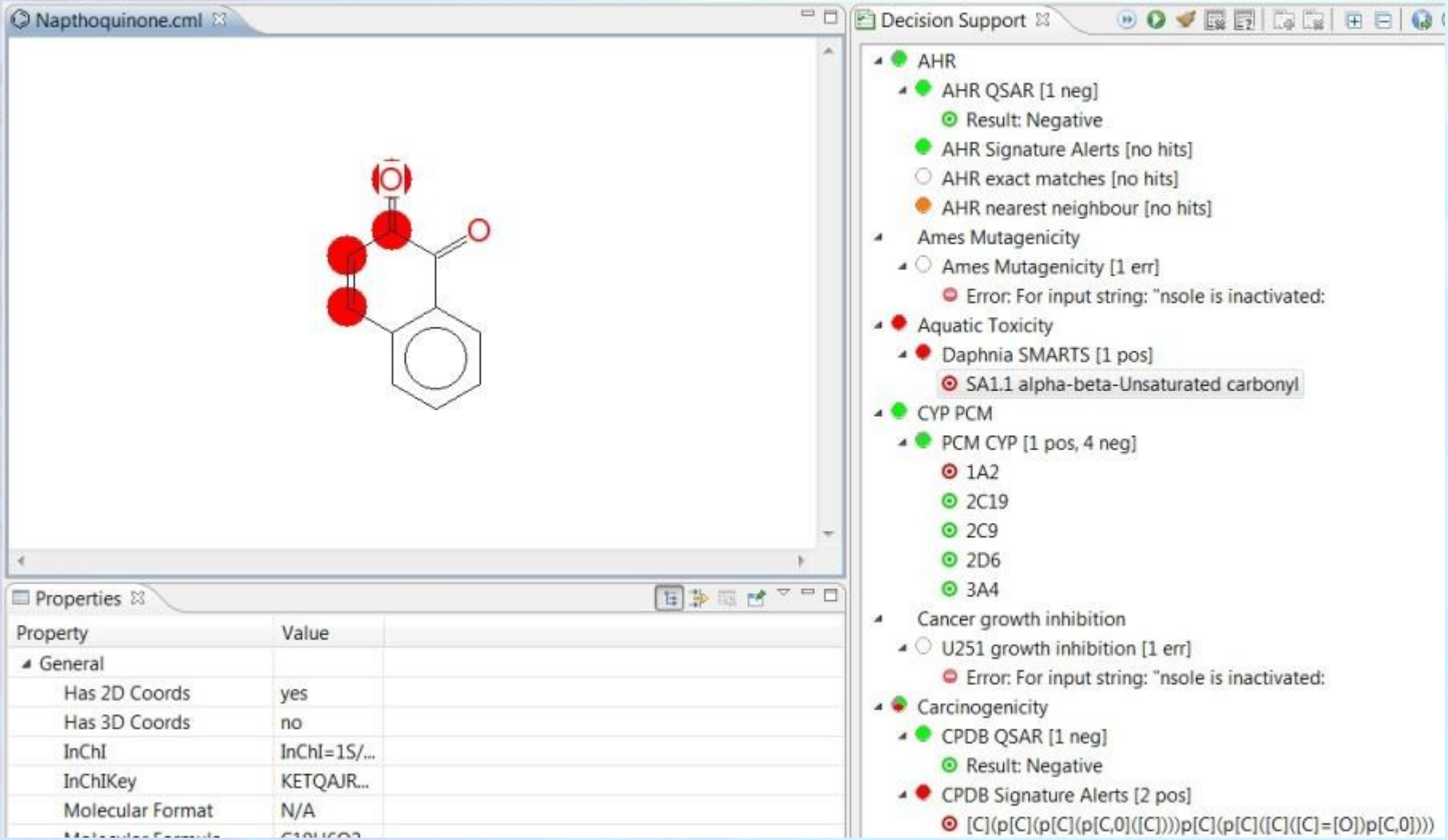
OpenTox

Bioclipse - OpenTox: benzoapyrene



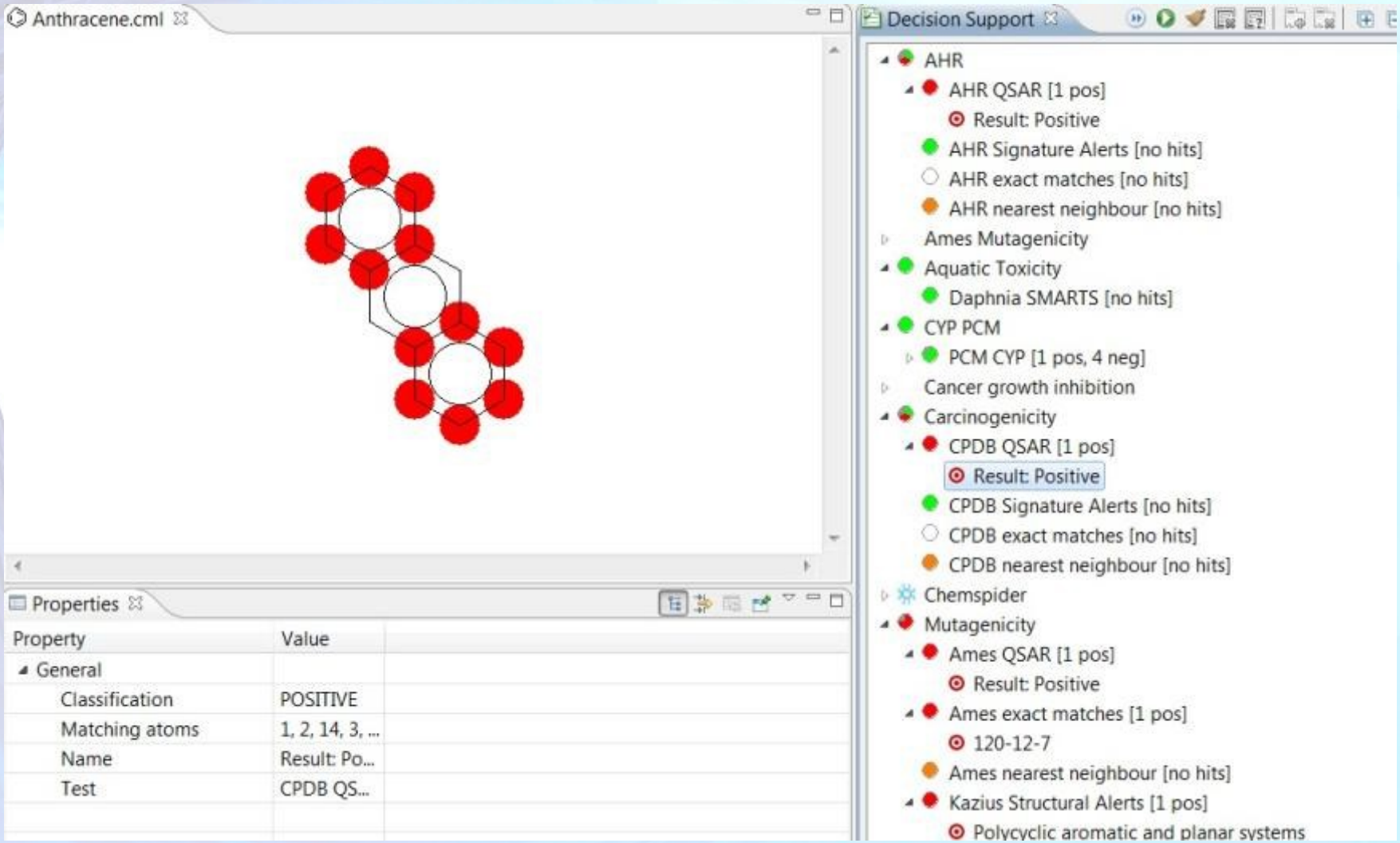
OpenTox

Bioclipse - OpenTox: benzo[a]pyren-7,8-dihydrodiol-9,10-epoxide



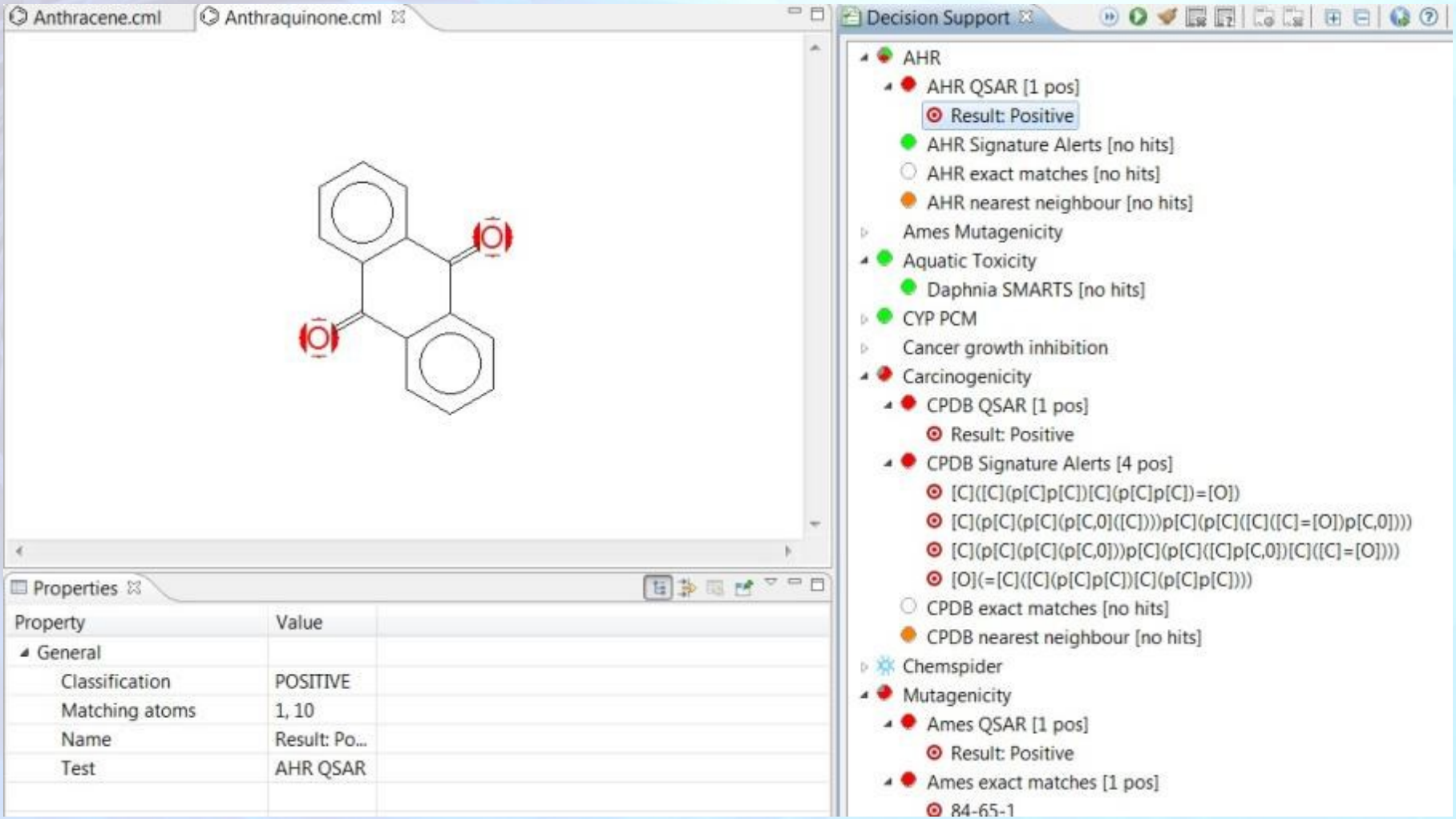
OpenTox

Bioclipse - OpenTox: Anthracene



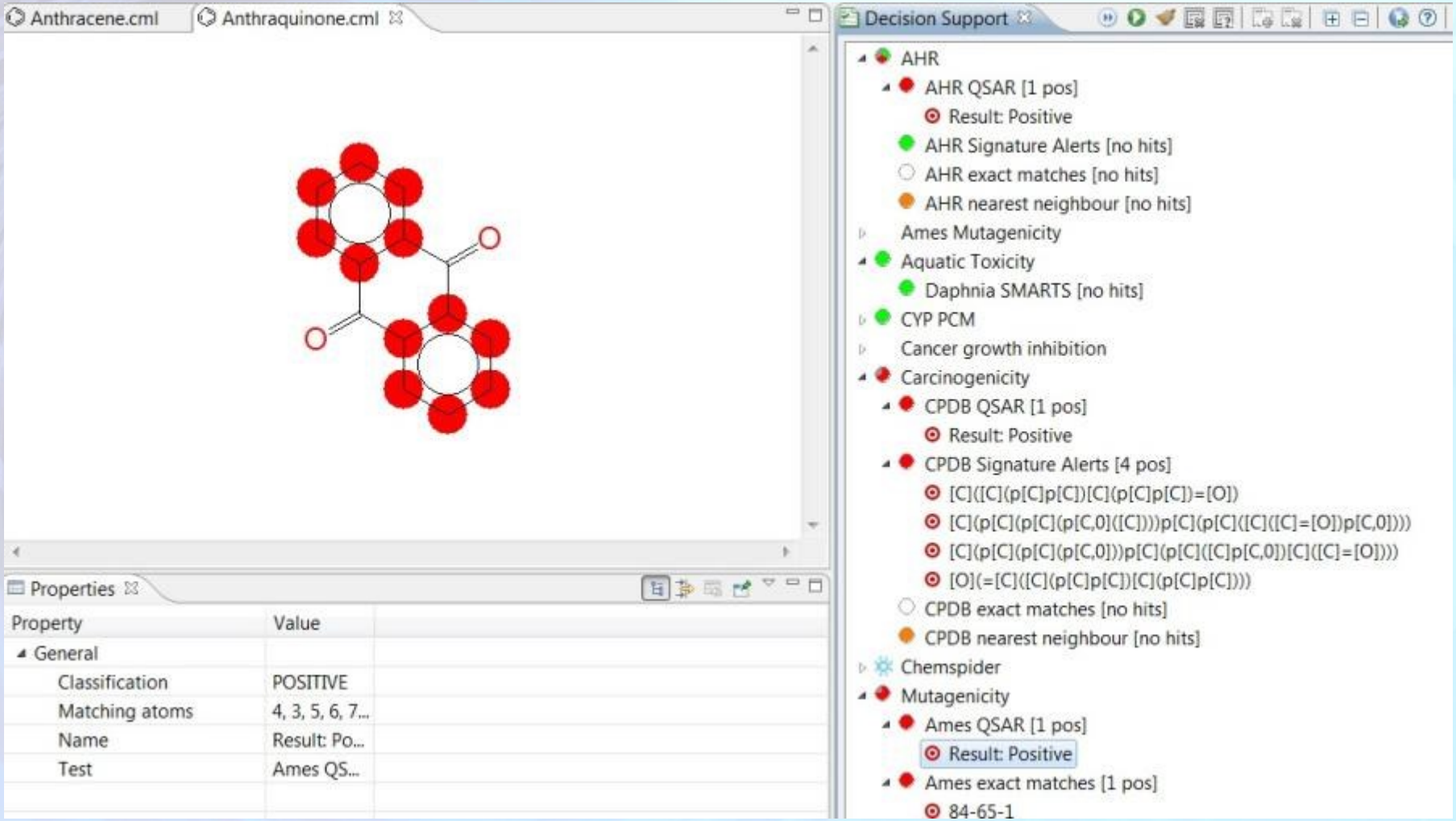
OpenTox

Bioclipse - OpenTox: Anthraquinone (1)



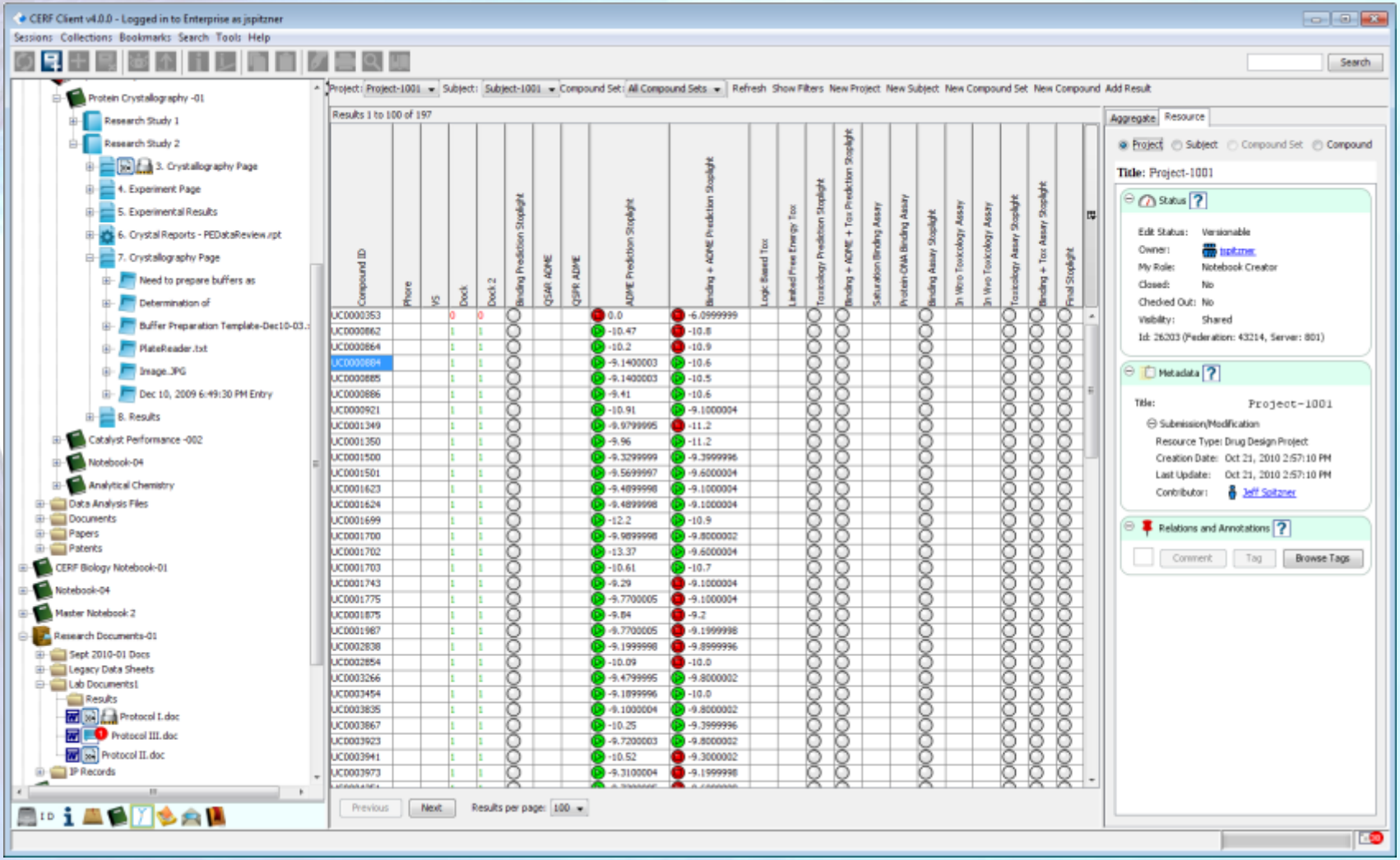
OpenTox

Bioclipse - OpenTox: Anthraquinone (2)



OpenTox

Event Driven Weight of Evidence



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Hardy and Affentranger, Drug Discovery Today. 2013 Jul;18(13-14):681-6.

Inclusion of Biokinetics components

- Need to model biokinetics and toxicodynamics to relate *in vitro* and *in silico* models to *in vivo* exposure pathways
  e.g., exposure of wild fish to chemical leached from site, human exposure through eating fish or drinking water, ADME modeling of exposed chemicals
- Need to model *in vitro* kinetics and variability
- Kinetics modeling may guide experimental design for new data creation to fill gaps for data poor chemicals
- Kinetics needed to support Weight of Evidence framework
- Toxico- kinetics and dynamics supporting determination of NOAELs/LOAELs for risk assessment purposes
- Environmental exposure modeling and time dependencies - also important for contaminated site risk assessment

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Risk Management Application

- We are developing a predictive toxicology framework to support Risk Management of Contaminated Sites
- Risk Management Evaluation may be increasingly based on *in vitro* and *in silico* information
- Need to fill data gaps and to design experiments (*in vitro*, omics) with Risk Assessment purposes in mind
- Adopt toxicity pathways-based approach
- Using reference compounds we will compare WoE approach for reference compounds discussed here cf. to traditional animal testing approach
- Most compounds have already had REACH submissions
- Most compounds are being tested in ToxCast Phase 2/Tox21
- Future is promising!

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Conclusions

- There is a significant amount of background knowledge available for chemicals of risk management and remediation interest
- There are also significant gaps for some chemicals e.g., *in vitro* assay, omics, dose-response data
- New data from programs such as ToxCast/Tox21, TG-Gates and EC programs such as SEURAT-1 and collaboration between such programs offer much promise for increasing application to new practical risk assessment framework establishment over the next 5 years
- Kinetics model development will be an important factor
- Reference compounds and models discussed here offer important test beds for practice development and establishment
- Increasing sophistication on knowledge integration will be enabling
- Community effort involving increased interaction between multi-stakeholders is a key enabler
- We are optimistic on the increasing application in practical situations involving assessment, management and remediation of contaminated sites in the years ahead.

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