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Status of the NTP HTS Initiative

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NIEHS

To meet the challenge of 21st century toxicology, the NTP Roadmap includes a major new initiative to develop a high throughput screening (HTS) program with 3 main goals:

- Identify mechanisms of action for further investigation
- Develop predictive models for in vivo biological response
- Prioritize substances for further in-depth toxicological evaluation

NIH Molecular Libraries Initiative

http://nihroadmap.nih.gov/molecularlibraries/

- The MLI is using HTS methods to identify small molecules that can be optimized as chemical probes to study the functions of genes, cells, and biochemical pathways.
- In mid-2005, NTP became a formal participant in the MLI by establishing a collaboration the Drs. Chris Austin and Jim Inglese of the NIH Chemical Genomics Center (NCGC) (http://www.ncgc.nih.gov/)
- Thus, the NTP has the opportunity to link data generated from HTS assays for biological activity to data produced by the NTP's toxicology testing program.

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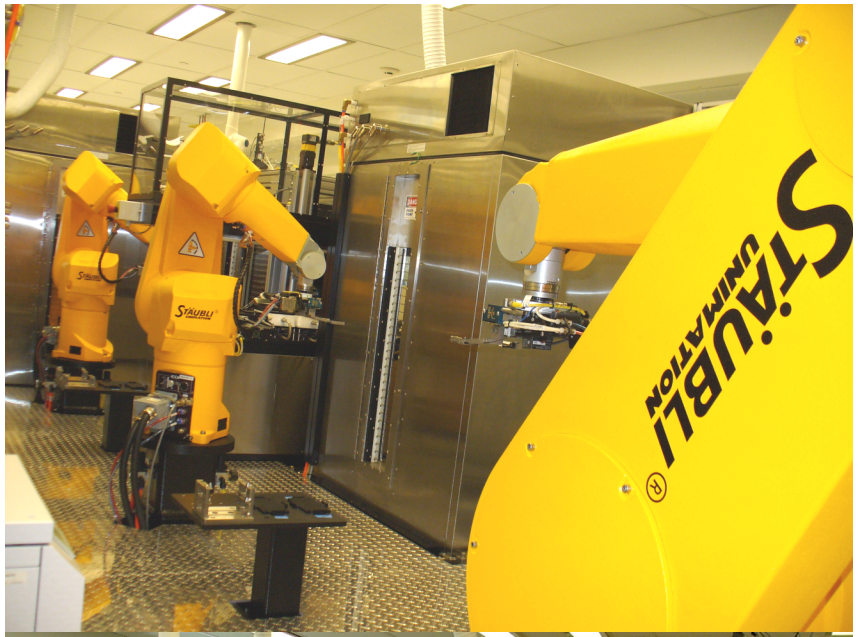

The NTP "1408"

- Includes nearly every chemical class
- All have pre-existing toxicity data from traditional *in vitro* and/or *in vivo* tests
  - 372 from NTP inventories (out of 2392 entries)
  - Remainder from NTP Ames tests and reference substances identified by NICEATM for the validation of alternative *in vitro* test methods
- Molecular weights range from ~100 to ~400
- Includes solvents, fire retardants, preservatives, flavoring agents, plasticizers, therapeutic agents, inorganic and organic pollutants, drinking water disinfection byproducts, pesticides, and natural products
- Provided as 10 mM solutions dissolved in DMSO

NCGC HTS Criteria

Criteria	Biochemical	Cell-based
*Plate Format **	96-well or higher density plate NCGC: 1536-well format Assay volume 2 -6 ul	96-well or higher density plate NCGC: 1536-well format Assay volume 4 -6 ul
Assay Steps	≤10 steps with 96 -well plate. Steps include, reagent additions, timed incubations, plate transfers to incubator, reading, etc.	≤10 steps with 96 -well plate. Steps include, reagent additions, timed incubations, plate transfers to incubator, reading, etc.
Minimum time increments and maximum assay duration	Minimum assay window is 5 min. (i.e., earliest time point after last reagent addition)	< 24 hr is ideal; max 48 hrs. Minimum assay window is 5 min.
Reagent Addition Steps	4 maximum	4 maximum
*Reagent removal steps **	No plate coating steps	No aspiration steps
Temperature	Between RT and 37°C	Between RT and 37°C
*Demonstrated DMSO Tolerance **	0.5 – 1% DMSO	0.5-1% DMSO
Signal : Background Ratio	≥ 3-fold	≥ 3-fold
Day-to-Day variation of control (e.g., IC_{50}, EC_{50})	< 3-fold	< 3-fold
Reagent stability @ final working concentration	≥ 8 hrs @ RT or on ice bath; No on-line thawing	≥ 8 hrs @ RT or on ice bath; No on-line thawing
Validation run reagent supply	10 – 96-well plate equivalents	10 – 96-well plate equivalents
Protocol	Complete detailed protocol. Data from 96 -well or high density plate tests.	Complete detailed protocol. Detailed cell culture procedure, passage # .Data from 96 -well or high density plate tests.
Detectors	**PE ViewLux** (Top reading only: FI, TRF, FP, Abs, Luminescence) **MD Analyst** (bottom reading FI) **Acumen Explorer** (laser scanning imager)	**PE ViewLux** (Top reading only: FI, TRF, FP, Abs, Luminescence) **MD Analyst** (bottom reading FI) **Acumen Explorer** (laser scanning imager)

HTS assays supplied to the NCGC

- **Apoptosis Assays**
  - Caspase-Glo® 3/7 Assay
  - Caspase-Glo® 9 Assay
  - Caspase-Glo® 8 Assay
- **Cytotoxicity Assays**
  - CellTiter-Glo® Luminescent Cell Viability Assay (measures ATP levels)
  - Cytotox-ONE™ Homogeneous Membrane Integrity Assay (measures release of lactate dehydrogenase from membrane-damaged cells)
- **P-glycoprotein (Pgp) ATPase Assay (aka MDR1 or ABCB1)**
  - Pgp-Glo™ Assay

NCGC testing conducted to date

- Using 15-point dose-response curves, the “1408” have been tested in the Promega CellTiter-Glo® Luminescent Cell Viability Assay using the following cell lines:
  - BJ (human foreskin fibroblast)
  - HEK293 (transformed human embryonic kidney cell line)
  - HepG2 (human hepatoma)
  - Jurkat (clone E6-1, human acute T cell leukemia)
  - MRC-5 (human lung fibroblast)
  - SK-N-SH (human neuroblastoma)

Assay Protocol for Cell Viability Assay using CellTiter-Glo Luminescent Reagent

1536 well plate format			
Sequence	Parameter	Value	Description
1	Reagent	5 ul	1000 cells/well
2	Time	3-5hr	37°C incubation
3	Reagent	20 nl	Compounds (0.5 nM-92 uM)
4	Time	40 hr	37°C incubation
5	Reagent	5 ul	CellTiter Glo reagent
6	Time	20 min	Room Temperature
7	Detector	Luminescence	Viewlux plate reader

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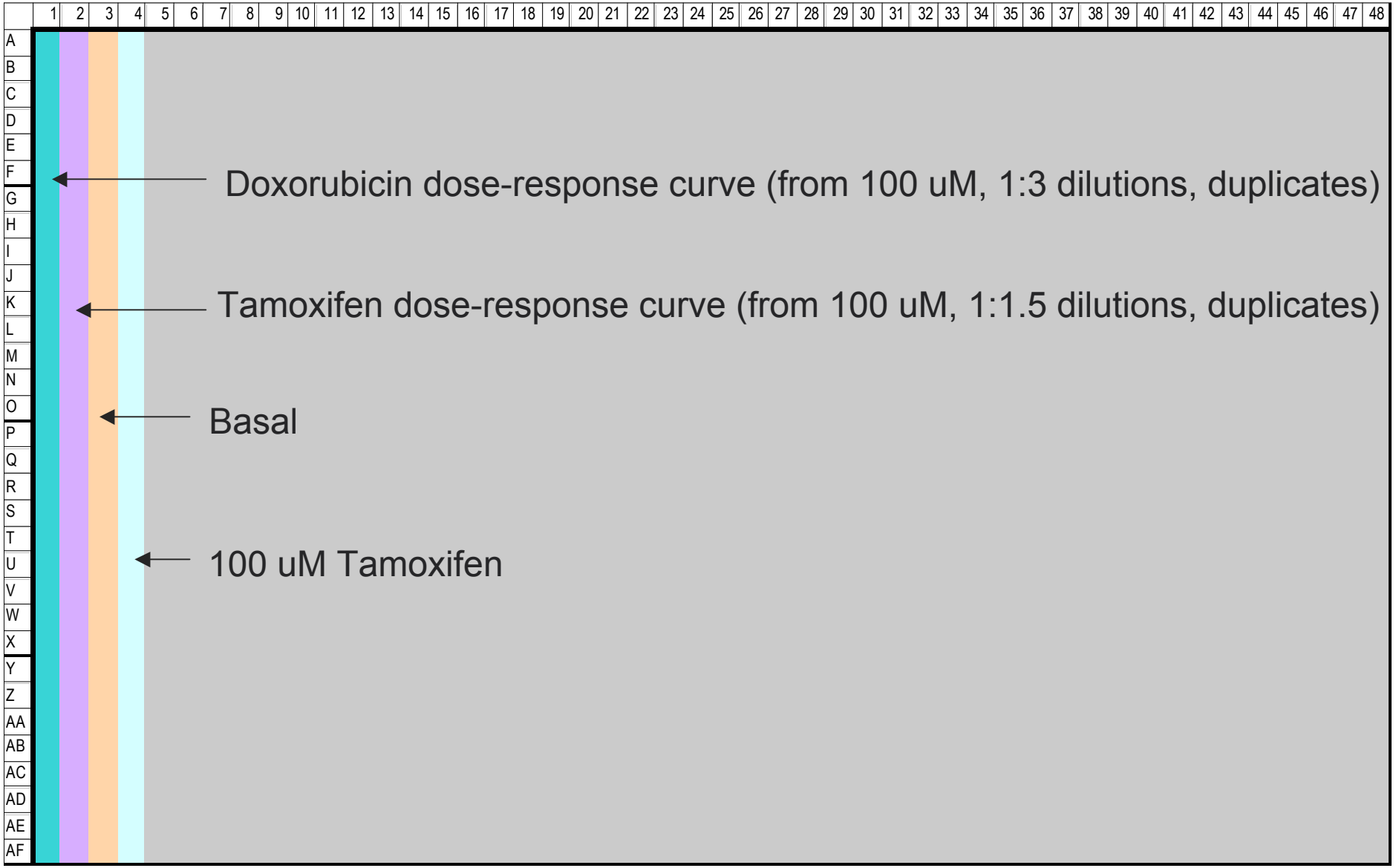
Plate Map in 1536-well Format



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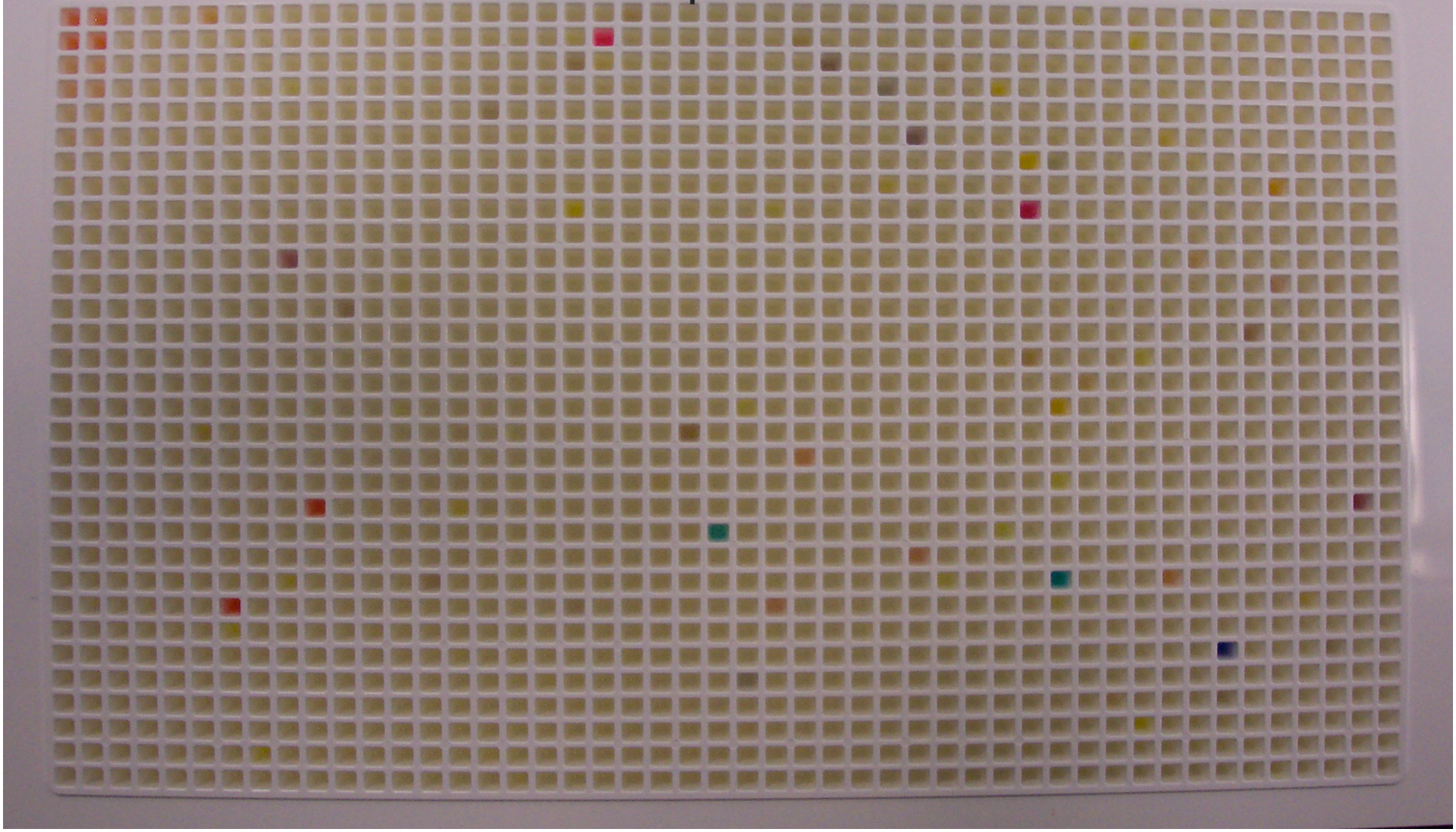
NIEHS 1408 Compound Set



Controls

Test compounds

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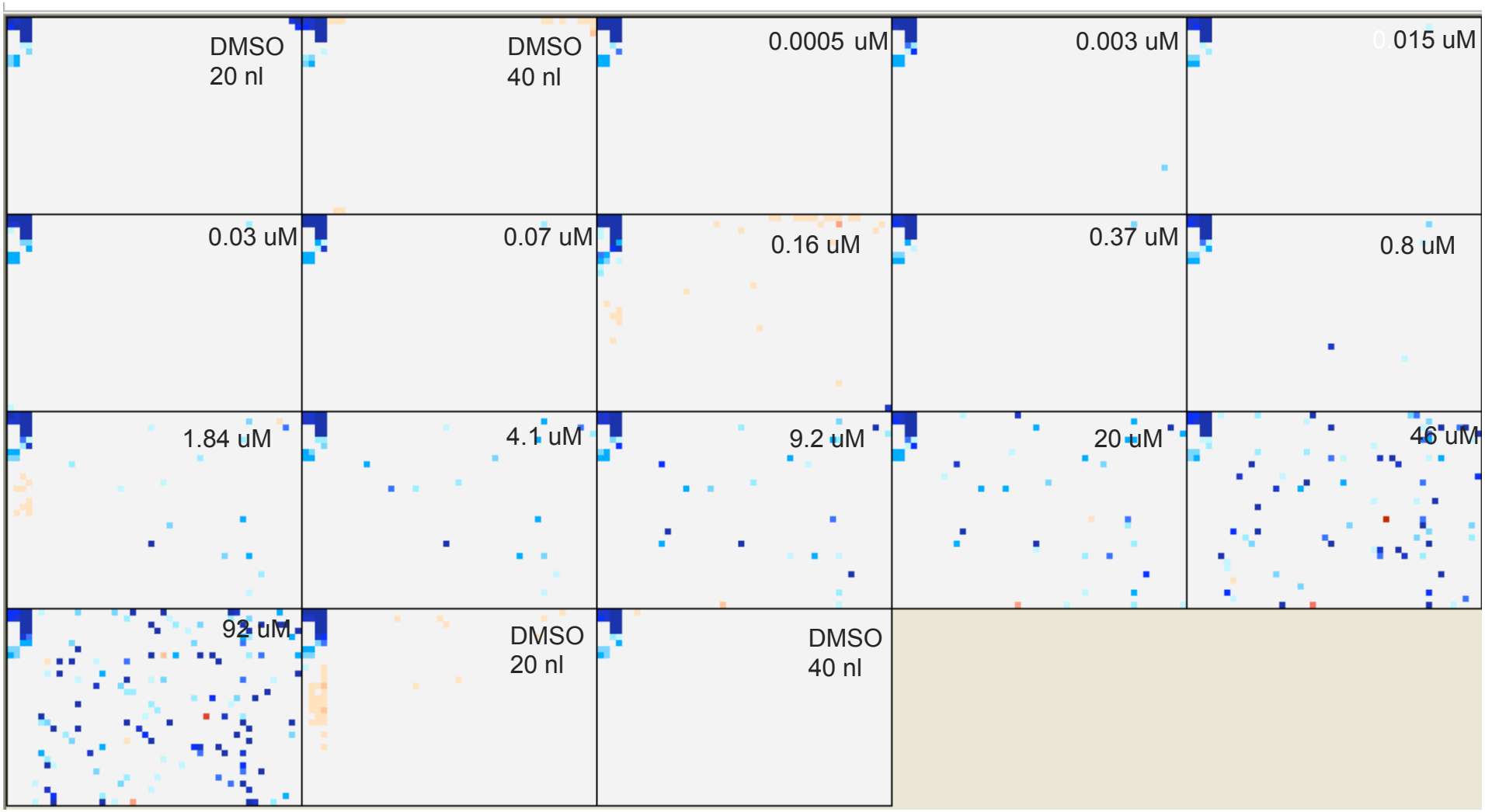
HTS results map for HepG2 cell screen



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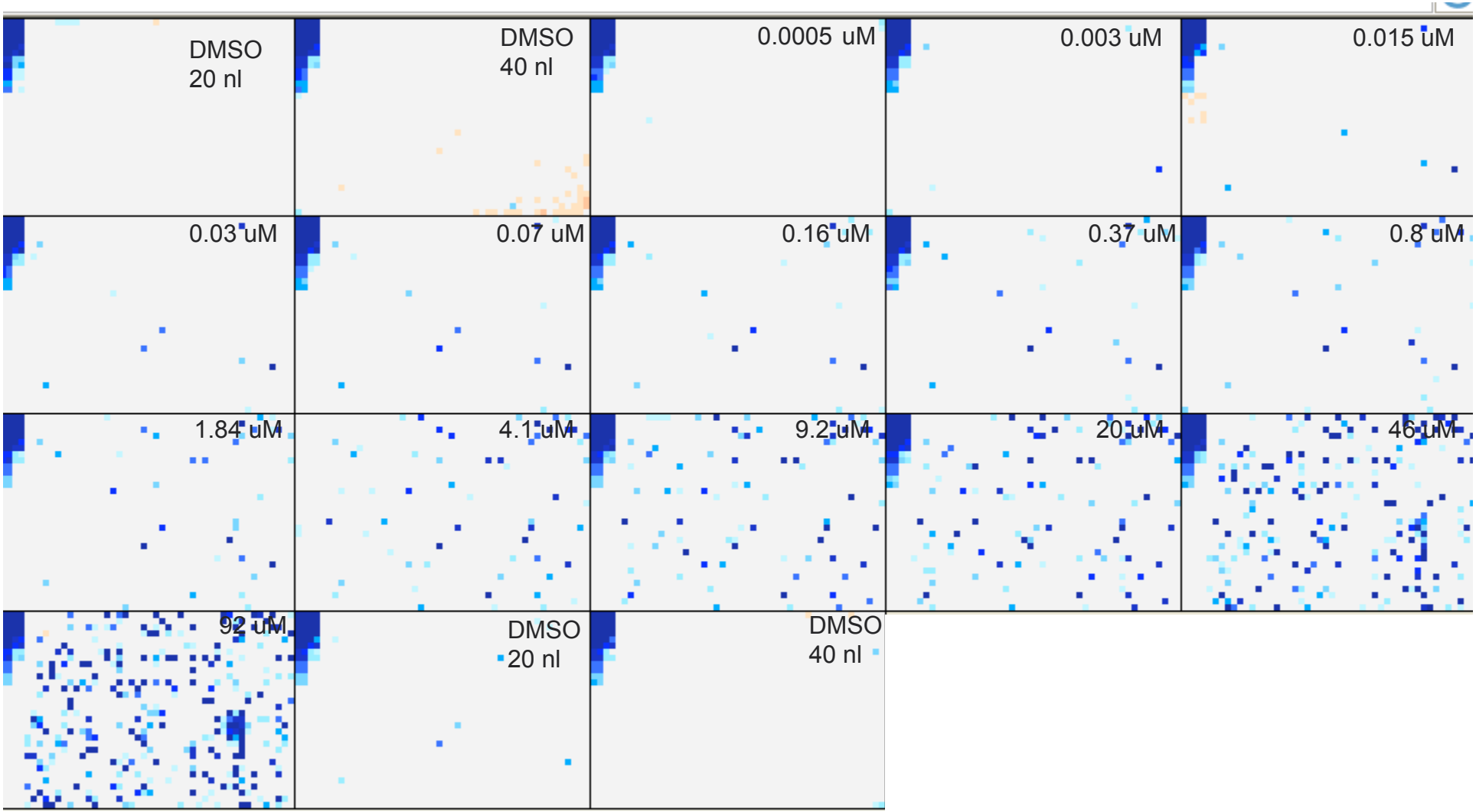
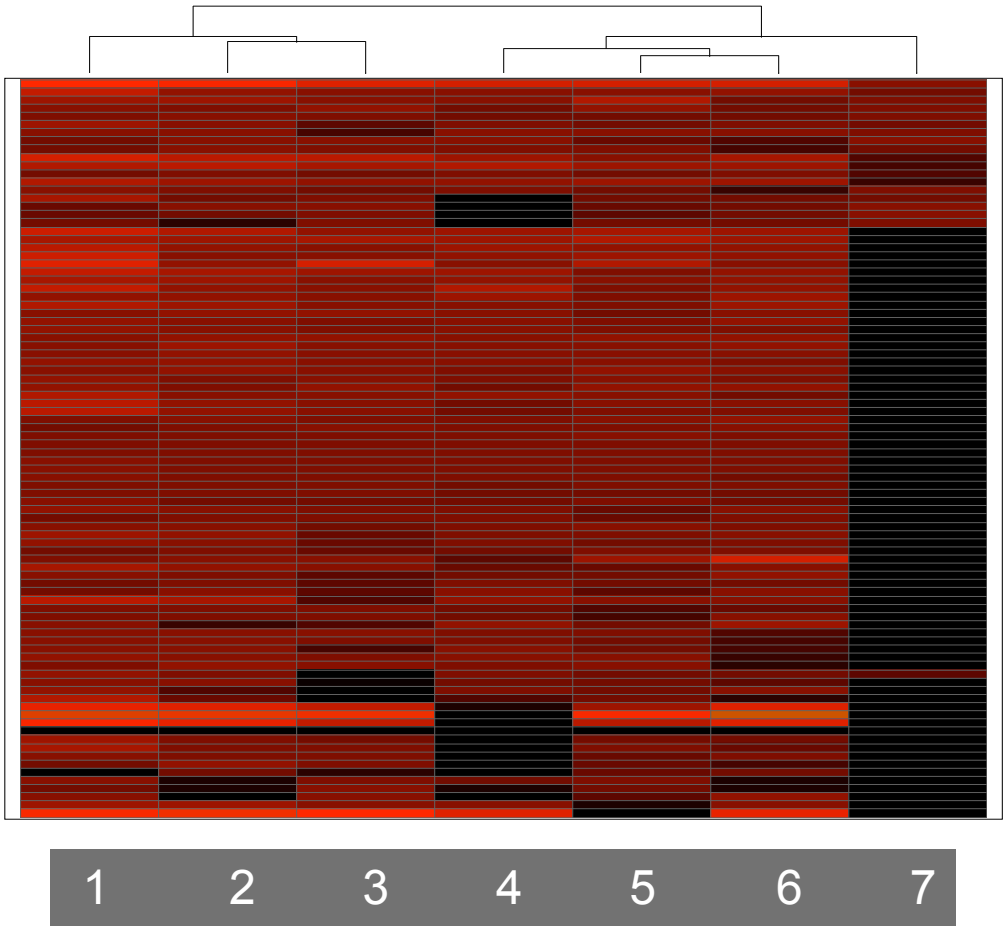
HTS results map for Jurkat cell screen



Cell Line Correlation

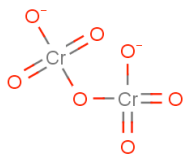
1. Jurkat
2. SK-N-SH
3. Hek 293
4. MRC5
5. HepG2
6. BJ
7. Cntrl



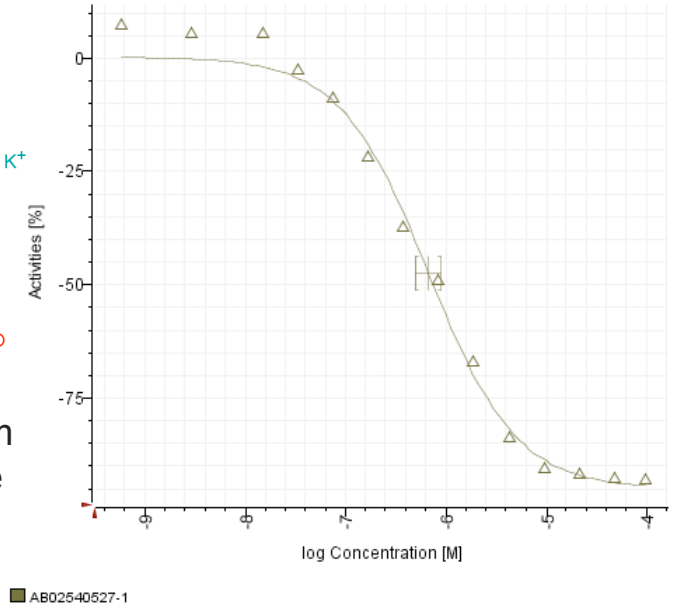
Active — Inactive

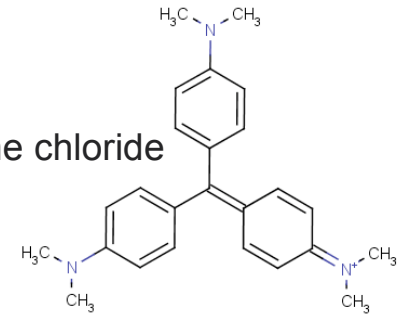
Jurkat:SK-N-SH = 0.62 R^2

AC50 Data Quality

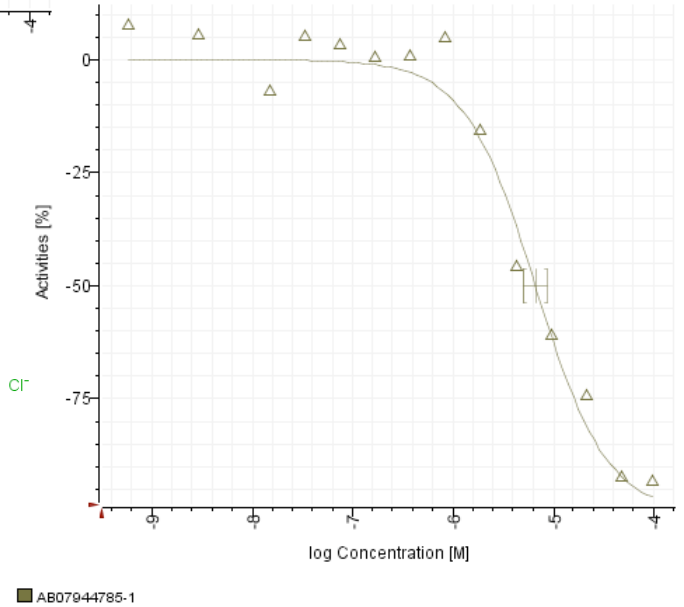


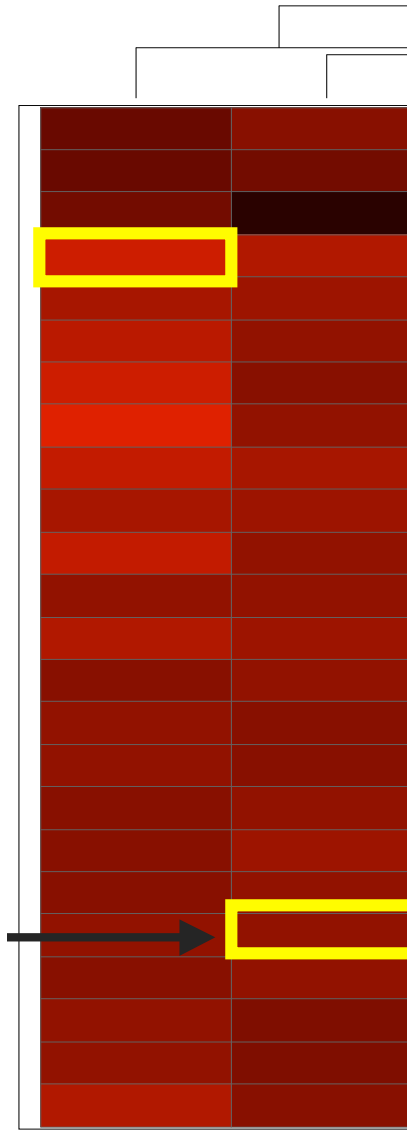
Potassium Chromate





Hexamethyl-p-rosaniline chloride (Gentian violet)





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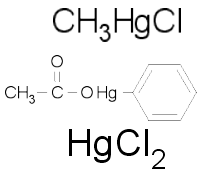
Some compounds produce similar toxicity in all six cell lines

Compound ID	Names	BJ	Hek293	HepG2	Jurkat	MRC5	SK-N-SH
AB02540519-01	Sodium dichromate dihydrate (VI)	1.98E-05	3.09E-05	4.64E-05	1.59E-06	4.2E-06	1.9E-05
AB08006152-01	4,4-Thiobis(6-t-butyl-m-cresol)	0.000044	3.37E-05	3.23E-05	1.74E-05	4E-05	2.3E-05
AB07944716-01	Zinc pyrithione	2.89E-05	4.7E-07	3.44E-06	2.28E-07	4.3E-05	2E-05
AB02540601-01	Nelfinavir mesylate	2.45E-05	2.44E-05	2.46E-05	3.12E-05	3.2E-05	2.5E-05
AB08582918-01	Digitonin	2.12E-05	2.75E-05	1.35E-05	8.75E-07	2.4E-05	2.9E-05
AB08002899-01	Sodium Dichromate Dihydrate	1.51E-05	3.18E-05	1.47E-05	2.57E-06	1.2E-05	1.7E-05
AB07944366-01	tetra-N-Octylammonium bromide	0.000014	7.17E-06	4.92E-06	7.93E-06	1E-05	9.4E-06
AB08548348-01	N,N'-Di-sec-butyl-p-phenylenediamine	1.38E-05	1.93E-05	1.35E-05	3.08E-06	2.1E-05	8.7E-06
AB07944329-01	Kepone	2.45E-05	3.02E-05	3.13E-05	3.98E-05	4E-05	1.4E-05
AB07930292-01	Methyl mercuric (II) chloride	2.31E-05	3.33E-05	3.17E-05	1.66E-06	2.5E-05	1.7E-05
AB07944715-01	Phenyl mercuric acetate	6.01E-06	2.24E-06	0.000033	5.48E-07	1.1E-05	2.2E-06
AB08080844-01	Mercuric chloride	2.81E-05	1.94E-05	8.2E-05	2.6E-05	3.3E-05	1.6E-05
AB08002816-01	Malachite Green Oxalate	3.49E-07	2.44E-07	4.94E-07	2.67E-08	4.6E-07	5.2E-08
AB07944787-01	Hexamethyl-p-rosaniline chloride (Gentian violet)	9.4E-06	5.18E-06	8.58E-06	3.84E-06	4.1E-06	1.8E-06
AB07981816-01	Pararosaniline hydrochloride	2.4E-05	2.0E-05	1.9E-05	1.5E-05	7.6E-05	4.4E-07
AB07985386-01	Captan	1.65E-05	2.69E-05	3.79E-05	5.2E-06	1.5E-05	1.3E-05
AB08001301-01	a-Solanine	4.23E-05	3.93E-05	2.37E-05	3.34E-05	4.5E-05	2.5E-05
AB02540527-01	Potassium dichromate	8.81E-06	1.92E-05	7.52E-06	6.55E-07	9.8E-06	3.9E-06
AB02540575-01	Nitazoxanide	3.19E-05	3.26E-05	3.56E-05	3.06E-05	4E-05	2.1E-05

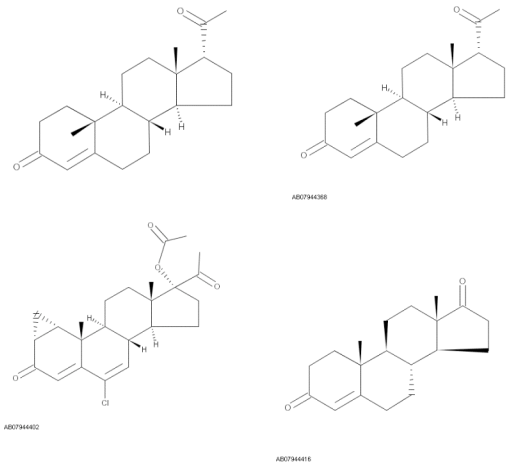


Note: Two of three mercury compounds have toxic effect in all six cell lines, one on five cell lines

Some compounds produce selective toxicity*

Compound ID	Names	Hek 293	Efficacy
AB08007382-01	Cadmium acetate, dihydrate	3.46E-05	81.18
AB02540589-01	Pentamidine isethionate	4.67E-05	38.52
AB07944402-01	Cyproterone acetate	4.56E-05	63.09
AB07944368-01	Progesterone	4.83E-05	73.14
AB07944416-01	4-Androstenedione	3.67E-05	108.9
AB07930213-01	Progesterone	4.85E-05	107.6
AB07935479-01	Econazole nitrate	4.63E-05	65.89
AB07944034-01	p -n -Nonylphenol	4.67E-05	44.55
AB08001430-01	Pentabromodiphenyl Oxide (DE-71) Repackaged	4.92E-05	47.65
AB02509328-01	Resveratrol	4.60E-05	25.39
AB08548299-01	4,6-Dinitro-o-cresol	4.75E-05	48.21
AB08582978-01	2-Methyl-1-nitroanthraquinone	3.51E-07	36.18

HEK293: 12 cpds



Compound ID	Names	HepG2	Efficacy
AB02509353-1	1,3-Diphenylguanidine	2.97E-05	100
AB08582948-1	Phenoxybenzamine HCl	3.86E-05	100

HepG2: 2 cpds

Compound ID	Names	MRC5	Efficacy
AB02509366-01	Carbendazim	2.67E-05	27.2
AB08582984-01	Azinphosmethyl (Gusathion)	4.55E-05	65.53
AB08082716-01	Nifedipine	1.95E-05	70.22
AB07990320-01	o,p'-DDD	4.61E-05	38.66
AB08000683-01	2,2',4,4',5,5'-Hexachlorobiphenyl	2.43E-05	60.13

MRC5: 5 cpds

***Compounds with ≤50 uM IC50 and ≥25% inhibition in listed cell line, but no activity in other lines**

Some compounds produce selective toxicity, cont.*

Compound ID	Names	Jurkat	Efficacy
AB08582970-1	Azobenzene	4.79E-05	100
AB08582919-1	4-Amino-4'-hydroxy-3-methyldiphenylamine	8.04E-06	97
AB02540531-1	Melphalan	4.55E-06	100
AB07944721-1	p-Quinone	3.24E-05	100
AB07944762-1	1-Naphthylamine	3.39E-05	100
AB13681075-1	Dihydromethysticin	3.79E-05	100
AB07935820-1	Pentabromophenol	4.14E-05	100
AB07981260-1	Medroxyprogesterone acetate	4.98E-05	100
AB08002895-1	Saquinavir Mesylate	4.68E-05	100
AB07985261-1	4-Chloro-3,5-dinitro-a,a,a-trifluorotoluene	3.97E-05	100
AB08548266-1	Cumene hydroperoxide	2.83E-05	100
AB07944800-1	Dichloroacetonitrile	6.95E-06	100
AB02911345-1	2,4-Hexadienal	2.85E-05	100
AB07935832-1	o-Phenylenediamine	3.65E-05	100
AB02509332-1	2,4-Decadienal	3.07E-05	100
AB08007268-1	Benzethonium chloride	2.71E-05	100
AB07981317-1	1,6-Hexanediol diacrylate	2.14E-05	100
AB07949036-1	p-Quinone dioxime (p-Benzoquinone dioxime)	4.98E-05	100
AB08001574-1	1,1,1,2-Tetrabromoethane	1.71E-05	100
AB07949335-1	Pentachlorophenol	4.76E-05	100
AB08082669-1	4-Chloro-o-phenylenediamine	1.25E-05	100
AB07981464-1	3,4-Diaminotoluene	4.11E-05	100
AB02914401-1	Actinomycin D	1.50E-09	90
AB02540539-1	cis-Dichlorodiamine platinum	3.28E-05	100
AB08003789-1	p-tert Butylcatechol	4.08E-05	100
AB08002751-1	Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)	4.69E-05	100
AB07944785-1	Glutaraldehyde (Glutaric dialdehyde)	6.45E-06	100
AB08006849-1	3,3'-Dihydroxybenzidine	3.58E-05	100
AB08582960-1	Dacarbazine	3.47E-05	100

Jurkat: 29 cpd

***Compounds with ≤50 uM IC50 and ≥25% inhibition in listed cell line, but no activity in other lines**

Some compounds produce selective toxicity, cont.*

Compound ID	Names	SK-N-SH	Efficacy
AB02509368-01	8-Hydroxyquinoline	2.81E-05	51.69
AB07985399-01	Diphenylurea	4.76E-05	28.5
AB07981003-01	1,4-Butanediol diglycidyl ether	2.77E-05	26.44
AB07930277-01	2,3,4,5-Tetrachloronitrobenzene	4.19E-05	38.27
AB07990272-01	Danthron	4.77E-05	27.98
AB07974656-01	5-Chloro-o-toluidine	4.75E-05	29.56
AB07942143-01	Dibromoacetic Acid	4.52E-05	25.34
AB02540528-01	all-trans-Retinyl acetate	4.83E-05	25.39
AB08548302-01	2,4-Dinitrophenol	4.57E-05	31.51
AB07930286-01	Apigenin	4.48E-05	46.3
AB07944776-01	Genistein (4',5,7-Trihydroxyisoflavone)	4.52E-05	56.43
AB08006134-01	Resorcinol	4.65E-05	28.44
AB07981727-01	Neopentyl glycol diglycidyl ether	4.17E-05	28.55
AB08002778-01	8-Hydroxyquinoline	2.44E-05	50.69
AB07981274-01	HC blue 2	4.59E-05	37.43
AB07981838-01	N-Acetyl-m-toluidine	4.85E-05	26.59
AB08582965-01	3,4,5-Trichlorophenol	4.60E-05	47.85

SK-N-SH:
17 cpd

Compounds with ≤50 uM IC50 and ≥25% inhibition in listed cell line, but no activity in other lines

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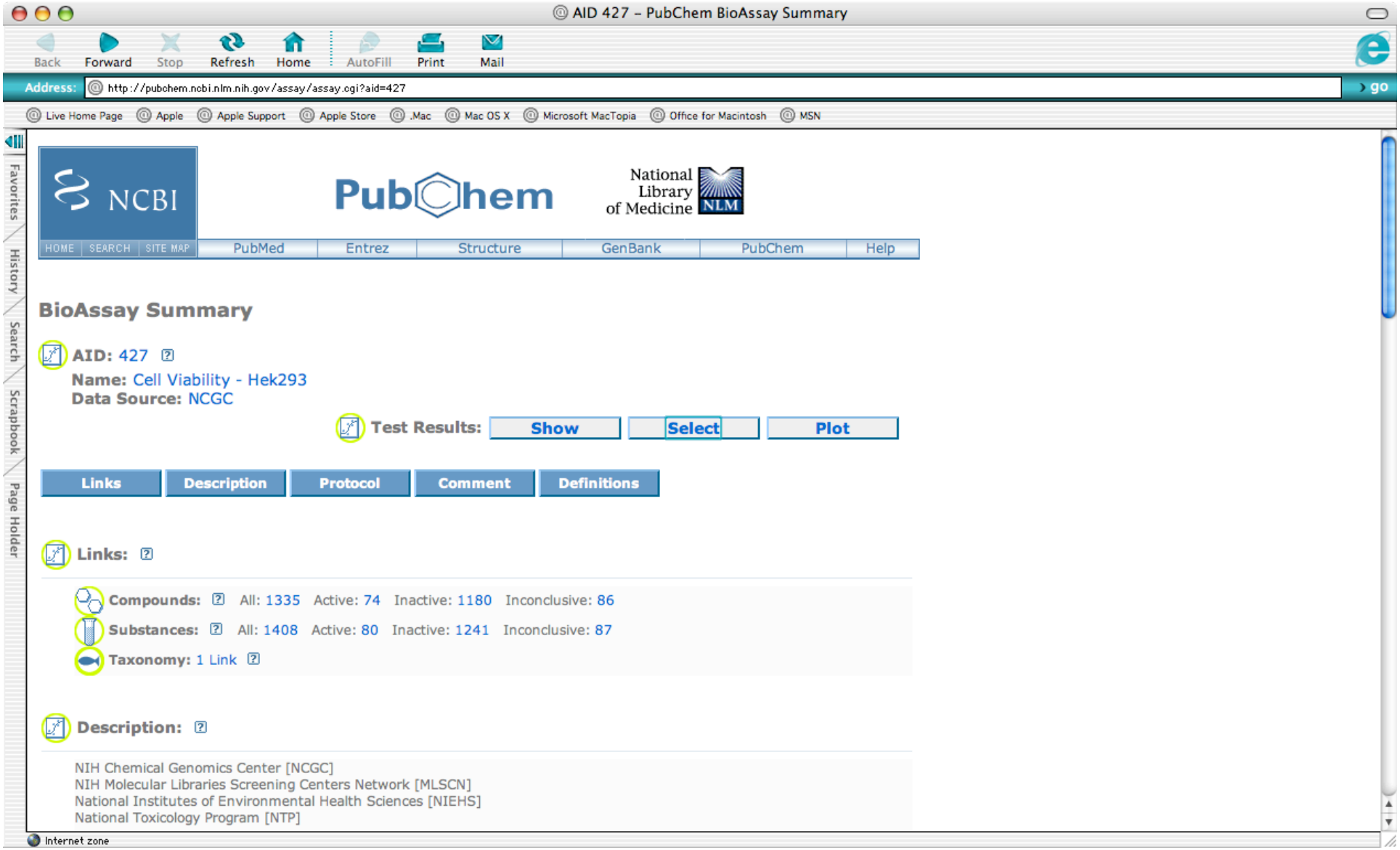

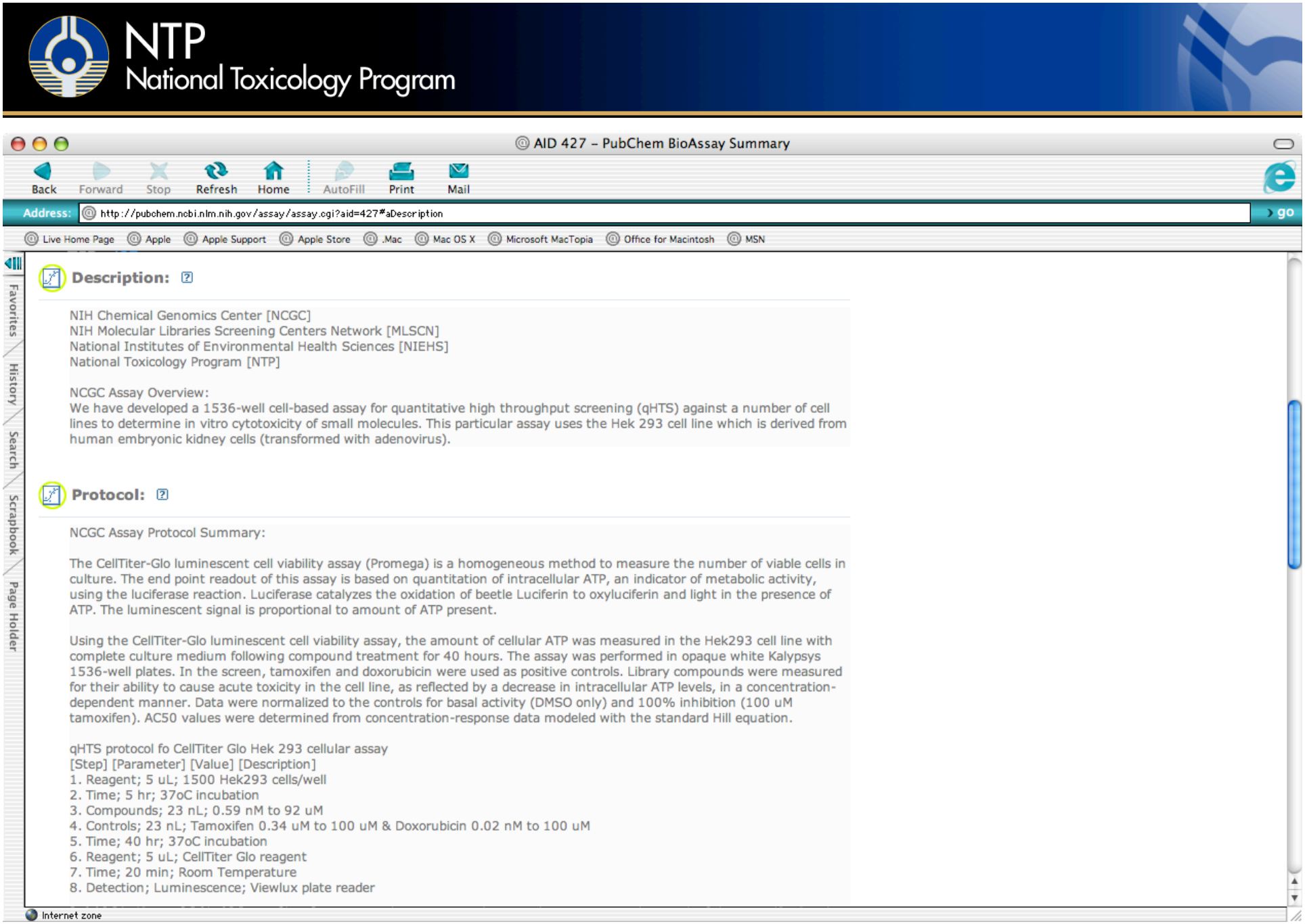
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Description:
NIH Chemical Genomics Center [NCGC]
NIH Molecular Libraries Screening Centers Network [MLSCN]
National Institutes of Environmental Health Sciences [NIEHS]
National Toxicology Program [NTP]
NCGC Assay Overview:
We have developed a 1536-well cell-based assay for quantitative high throughput screening (qHTS) against a number of cell lines to determine in vitro cytotoxicity of small molecules. This particular assay uses the Hek 293 cell line which is derived from human embryonic kidney cells (transformed with adenovirus).
Protocol:
NCGC Assay Protocol Summary:
The CellTiter-Glo luminescent cell viability assay (Promega) is a homogeneous method to measure the number of viable cells in culture. The end point readout of this assay is based on quantitation of intracellular ATP, an indicator of metabolic activity, using the luciferase reaction. Luciferase catalyzes the oxidation of beetle Luciferin to oxyluciferin and light in the presence of ATP. The luminescent signal is proportional to amount of ATP present.
Using the CellTiter-Glo luminescent cell viability assay, the amount of cellular ATP was measured in the Hek293 cell line with complete culture medium following compound treatment for 40 hours. The assay was performed in opaque white Kalypsys 1536-well plates. In the screen, tamoxifen and doxorubicin were used as positive controls. Library compounds were measured for their ability to cause acute toxicity in the cell line, as reflected by a decrease in intracellular ATP levels, in a concentration-dependent manner. Data were normalized to the controls for basal activity (DMSO only) and 100% inhibition (100 uM tamoxifen). AC50 values were determined from concentration-response data modeled with the standard Hill equation.
qHTS protocol fo CellTiter Glo Hek 293 cellular assay
[Step] [Parameter] [Value] [Description]
1. Reagent; 5 uL; 1500 Hek293 cells/well
2. Time; 5 hr; 37oC incubation
3. Compounds; 23 nL; 0.59 nM to 92 uM
4. Controls; 23 nL; Tamoxifen 0.34 uM to 100 uM & Doxorubicin 0.02 nM to 100 uM
5. Time; 40 hr; 37oC incubation
6. Reagent; 5 uL; CellTiter Glo reagent
7. Time; 20 min; Room Temperature
8. Detection; Luminescence; Viewlux plate reader
Internet zone

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AID 427 – PubChem BioAssay Summary

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Address: http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=427&q=r&queue=t&qstatus=done&reqid=565388482858256821 go

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BioAssay Results:

Select Summary

AID: 427

Name: Cell Viability - Hek293

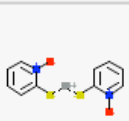
Data Source: NCGC

Results Download

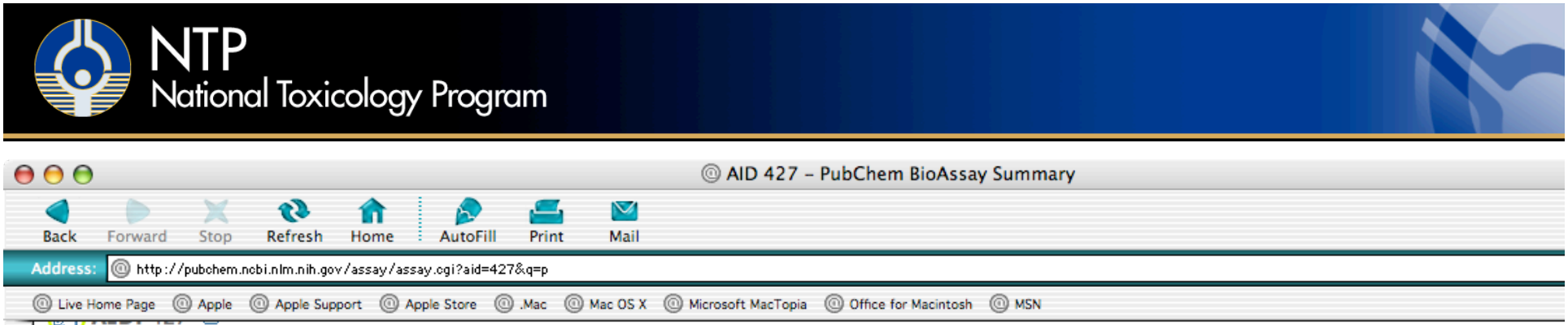
Total BioAssay Result Count: 1408 Page: 1 of 71

Display: 20 Go To Page 1

Sort: (Click the result table header to sort.)

#	Structure	SID	CID	Score	Outcome	Activity Direction	Activity Qualifier	Qualified AC50	Log of AC50	Hill Coefficient	Curve R2	Data Type	Data Analysis QC	NCGC Comment	Curve Fit Model	Hill S0	Hill Sinf	Hill dS	Log AC50 Std Error	Excluded Points	Number of Points	Activity at 0.59nM %	Activity at 2.95nM %	Activity at 14.751 %	Activity at 0.033ul %	Activi at 0.074 %
1		11076713	26041	93	Active	decreasing	=	4.7e-007	-6.328	3	1	qHTS Primary	Verified	Full Curve	4pHill (AC50,n,S0,Sinf)	7.7	-95.9	103.6	0.01594	{}	12	9	7.4	6.9	9.5	4.9
2		11076432	2724411	93	Active	decreasing	=	2.44e-007	-6.613	0.7	1	qHTS Primary	Verified	Full Curve	4pHill (AC50,n,S0,Sinf)	0.3	-100.6	100.9	0.03343	{}	11	-2.2	-1.2	-11.3	-21.1	-29.4

Link: javascript:resortassay('2984');



Name: Cell Viability - Hek293
Data Source: NCGC

Plot the BioAssay Result:

#	Name	Histogram	Value Count	Min::Max	Data Type	Unit
	Activity Outcome				String	
	Activity Ranking Score		1408	0::93	Integer	
1	Activity Direction		1408		String	
2	Activity Qualifier		1408		String	
3	Qualified AC50		1408	1.02e-09 :: 0.00922	Float	
4	Log of AC50		1408	-8.991 :: -2.035	Float	
5	Hill Coefficient		198	0.3 :: 41.3	Float	
6	Curve R2		198	0.29 :: 1	Float	
7	Data Type		1408		String	
8	Compound QC		0		String	
9	Data Analysis QC		1408		String	
10	NCGC Comment		1408		String	
11	Curve Fit Model		1408		String	
12	Hill S0		198	-1.8 :: 20.2	Float	
13	Hill Sinf		198	-2852 :: -25	Float	
14	Hill dS		198	30 :: 2851	Float	
15	Log AC50 Std Error		190	0.009786 :: 2.68757e+08	Float	
16	Excluded Points		1408		String	
17	Number of Points		1408	10 :: 12	Integer	
18	Activity at 0.59nM		1401	-20.9 :: 21.9	Float	%
19	Activity at 2.95nM		1408	-16.7 :: 25.2	Float	%
20	Activity at 14.751nM		1408	-56.2 :: 21.9	Float	%
21	Activity at 0.033uM		1408	-67.5 :: 14.8	Float	%
22	Activity at 0.074uM		1408	-70.3 :: 12.8	Float	%
23	Activity at 0.165uM		1408	-66 :: 14.9	Float	%
24	Activity at 0.369uM		1408	-68.1 :: 10.7	Float	%

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BioAssay Histogram

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Address: http://pubchem.ncbi.nlm.nih.gov/assay/histogram.cgi?dataviewtype=0&db=pcsubstance&service=cgi&TID=427_rank_2_0_0&TIDg=427_rank_2_0_0&TIDg=427_4_1_0_0

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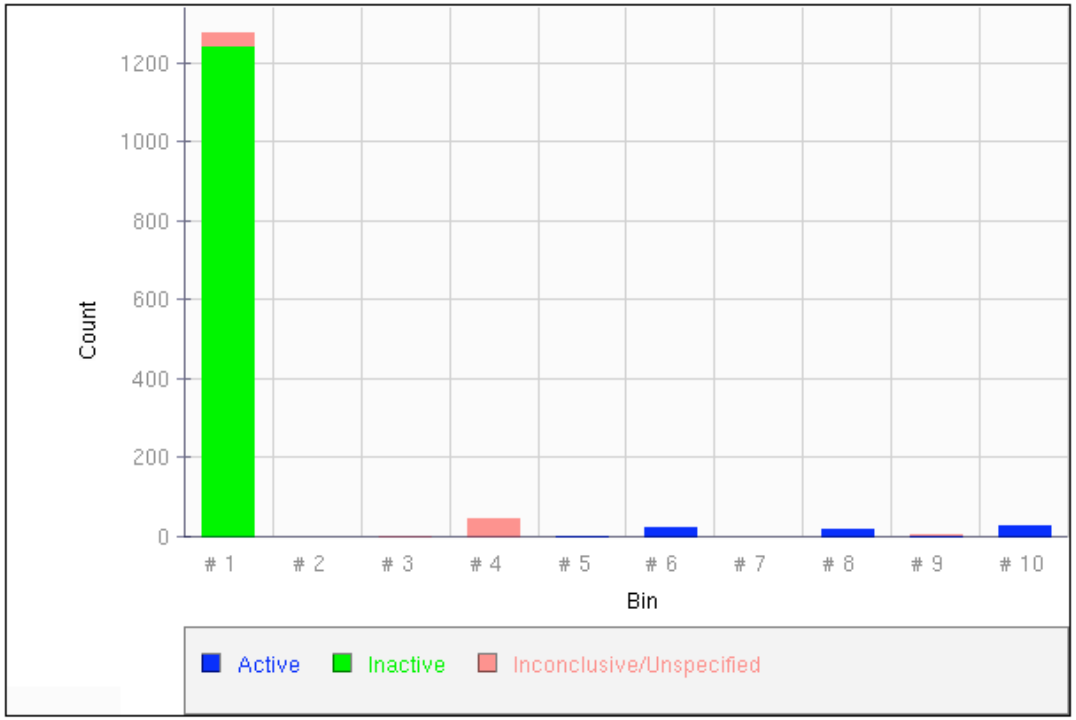
Name: Activity score

Description: Rank of activity outcome

** Click on a bar to zoom in or display BioAssay result of substances in that bin

Frequency distribution of Activity score from 0 to 93 with increment of 9.3 (total 1408 substances) color by activity



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AID 427 – PubChem BioAssay Summary

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Address: http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=427&q=graph&queue=t&preview=f&qstatus=done&reqid=954770590311019560

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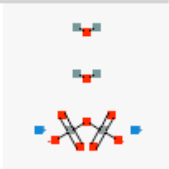
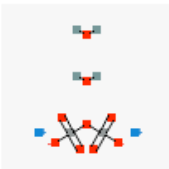
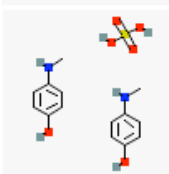
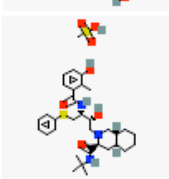
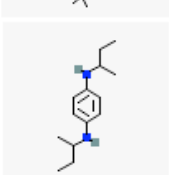
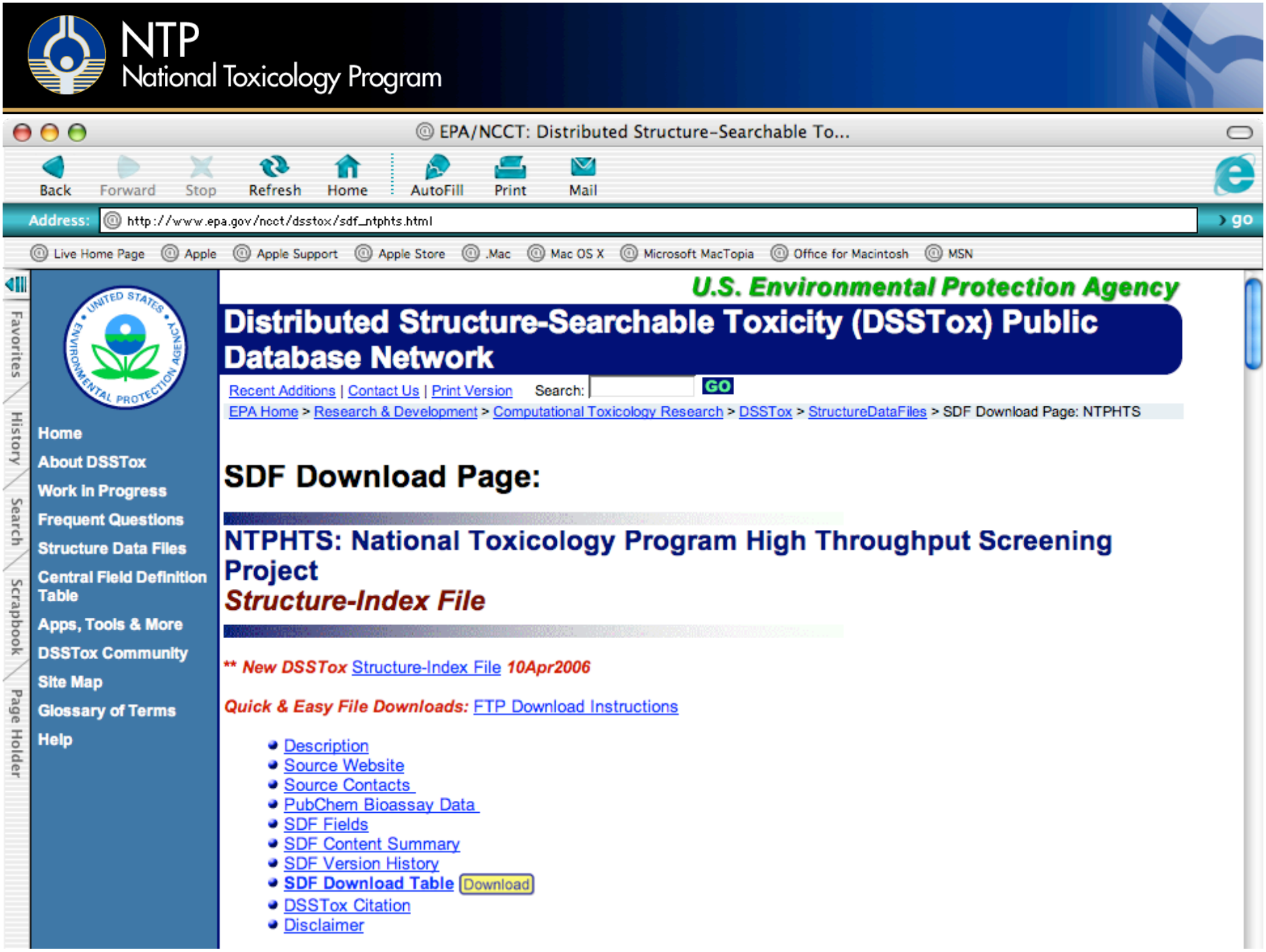
Total BioAssay Result Count: 19 Page: 1 of 1

Sort: *(Click the result table header to sort.)*

#	Structure	SID	CID	Score	Outcome	Activity Direction	Activity Qualifier	Qualified AC50	Log of AC50	Hill Coefficient	Curve R2	Data Type	Data Analysis QC	NCGC Comment	Curve Fit Model	Hill S0	Hill Sinf	Hill dS	Log AC50 Std Error	Excluded Points	Number of Points	Activity at 0.59nM %	Activity at 2.95nM %	Act 14.
1		11076643	108005	89	Active	decreasing	=	3.09e-005	-4.509	4.5	0.99	qHTS Primary	Verified	Full Curve	4pHill (AC50,n,S0,Sinf)	4.6	-92.6	97.2	0.02507	{}	12	6.6	9	
2		11076642	108005	89	Active	decreasing	=	3.18e-005	-4.498	4.5	0.99	qHTS Primary	Verified	Full Curve	4pHill (AC50,n,S0,Sinf)	-0.8	-81.1	80.3	0.02232	{}	12	0	-3.5	
3		11076527	5930	89	Active	decreasing	=	4.08e-005	-4.389	21.3	0.99	qHTS Primary	Verified	Full Curve	4pHill (AC50,n,S0,Sinf)	0.1	-96.3	96.4		{}	12	-5.7	0	
4		11076507	64142	89	Active	decreasing	=	2.44e-005	-4.612	6.8	0.99	qHTS Primary	Verified	Full Curve	4pHill (AC50,n,S0,Sinf)	1.1	-96	97.2	0.07262	{}	11	3.5	3.2	
5		11076497	7589	89	Active	decreasing	=	1.93e-005	-4.716	5.8	0.99	qHTS Primary	Verified	Full Curve	4pHill (AC50,n,S0,Sinf)	2.9	-98.4	101.2	0.022	{}	12	-0.5	5.3	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Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network
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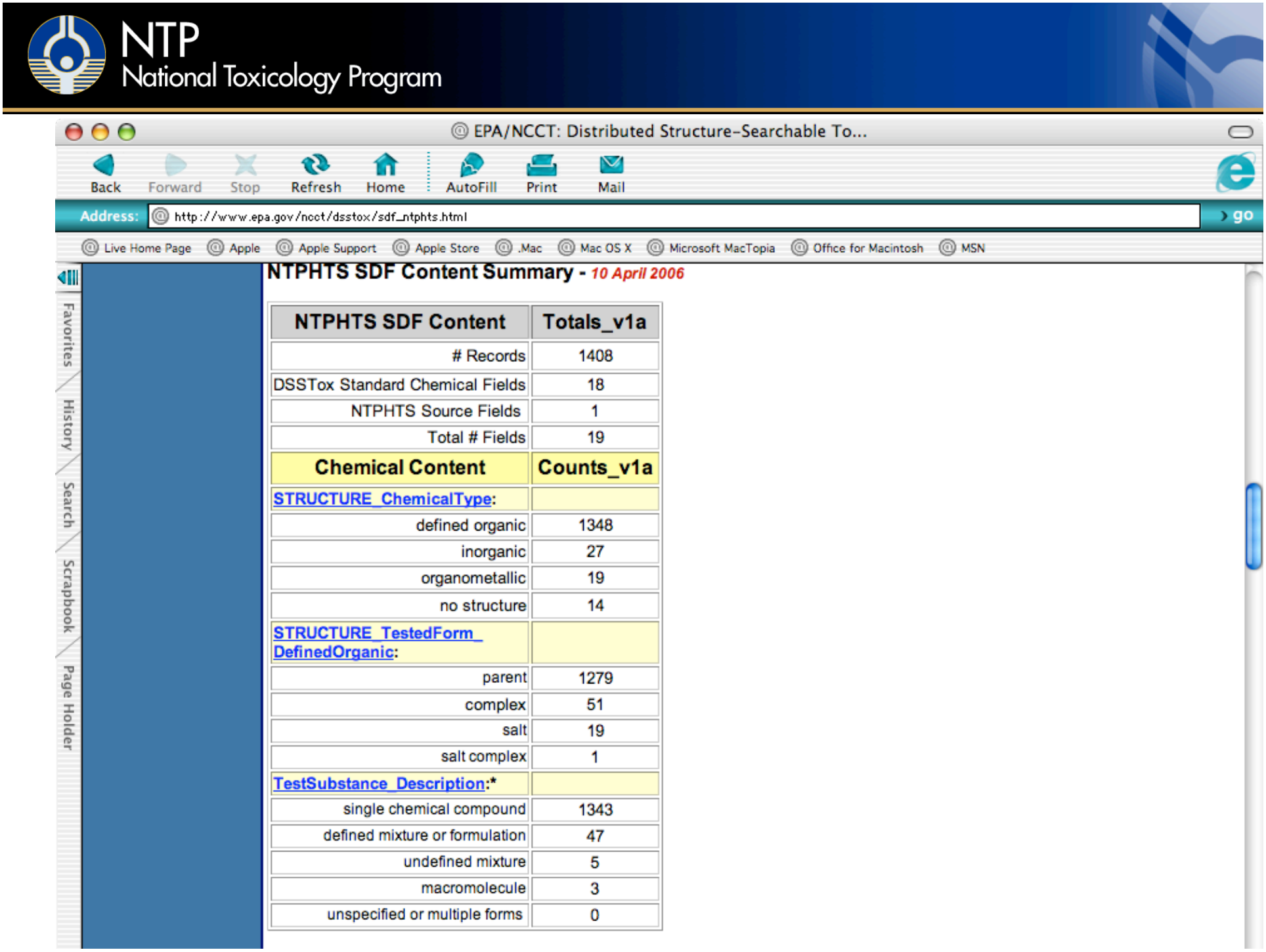


NTPHTS SDF Content Summary - *10 April 2006*

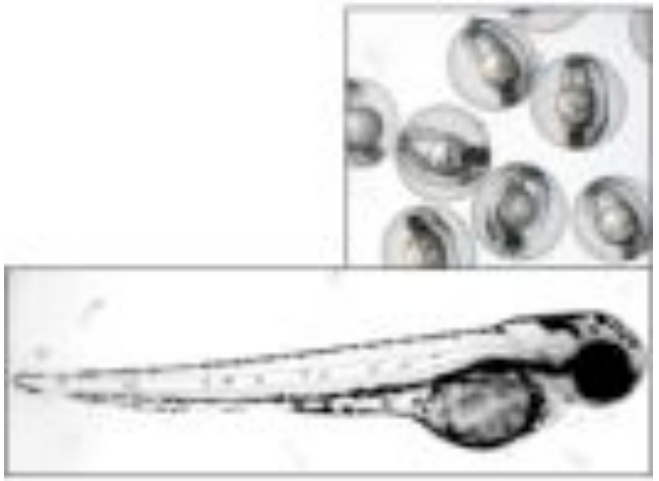
NTPHTS SDF Content	Totals_v1a
# Records	1408
DSSTox Standard Chemical Fields	18
NTPHTS Source Fields	1
Total # Fields	19
Chemical Content	**Counts_v1a**
STRUCTURE_ChemicalType:	
defined organic	1348
inorganic	27
organometallic	19
no structure	14
STRUCTURE_TestedForm_DefinedOrganic:	
parent	1279
complex	51
salt	19
salt complex	1
TestSubstance_Description:*	
single chemical compound	1343
defined mixture or formulation	47
undefined mixture	5
macromolecule	3
unspecified or multiple forms	0

- **Profile other compounds in the same cell lines?**
  - **the next NTP 1408?**
  - **the NCGC "exploratory" collection (10K)?**
  - **the DPI collection (70K)?**
- **Profile same compounds (1408) on different cells?**
  - **Different cells (primary cells, closer to physiology)**
  - **Different species**
- **Profile the same 1408 in different assays?**
  - **Apoptosis (caspase 3/7, caspase 8, caspase 9)**
  - **LDH release**
  - **Pgp**
  - **P450s (CYP1A2, CYP3A4, CYP2D6)**
  - **Pathways: AP1, STAT, NFAT, HRE, NFkB, nuclear hormone signaling**

More complex HTS systems?

C. elegans and zebrafish embryos

- **These assays allow for an assessment of developmental effects, including complex differentiation, hormonal gradients, and organ–cell communication.**
- **Proper sampling technique and automation could transform the use of these two organisms into an adjunct to HTS assays.**



NTP-EPA Collaboration on HTS Assays

- In Dec. 2005, a collaboration was established between the NTP HTS Faculty and the EPA Chemical Prioritization Community of Practice (CPCP) to jointly evaluate HTS assays and other model systems for their use in toxicological investigations and in chemical prioritization.
- In Jan, 2006, joint NTP/EPA subcommittees were established to address specific topics related to HTS
  - Toxicity targets and bioactivity assays
    - Co-Chairs: Kristine Witt (NIEHS) and Keith Houck (EPA)
  - Chemical selection
    - Co-Chairs: Cynthia Smith (NIEHS) and David Dix (EPA)
  - Informatics
    - Co-Chairs: Jennifer Fostel (NIEHS) and Ann Richard (EPA)