EPA
United States
Environmental Protection
Agency

Chemical Selection for ToxCast: EPA's Program for Predicting Toxicity and Prioritizing Chemical Testing

US EPA Community of Practice
Exposure Science for Screening and Prioritization

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

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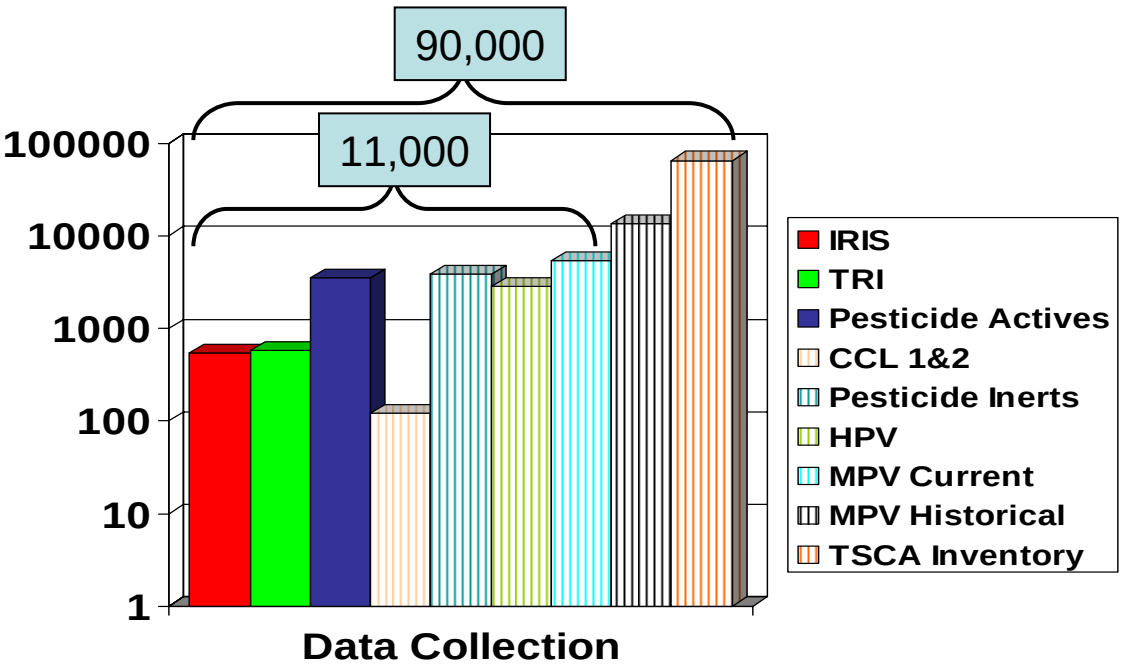
Office of Research and Development
National Center for Computational Toxicology

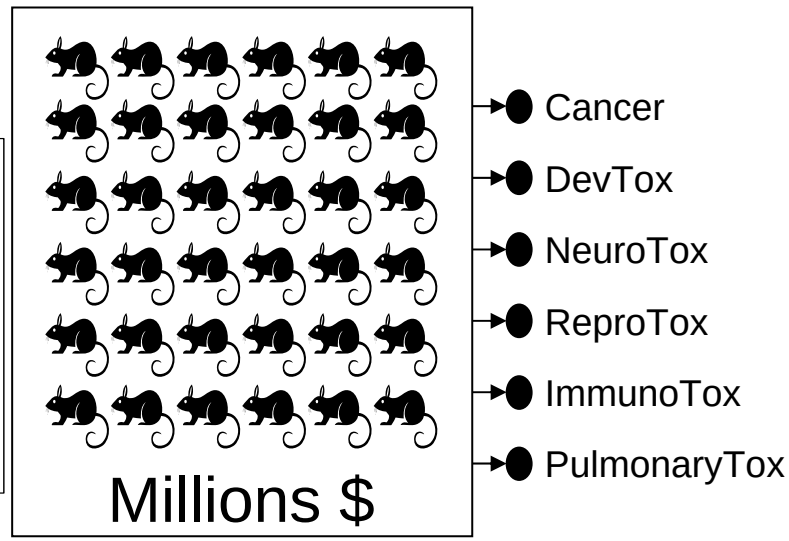
May 27, 2008

The Problem

Too Many Chemicals



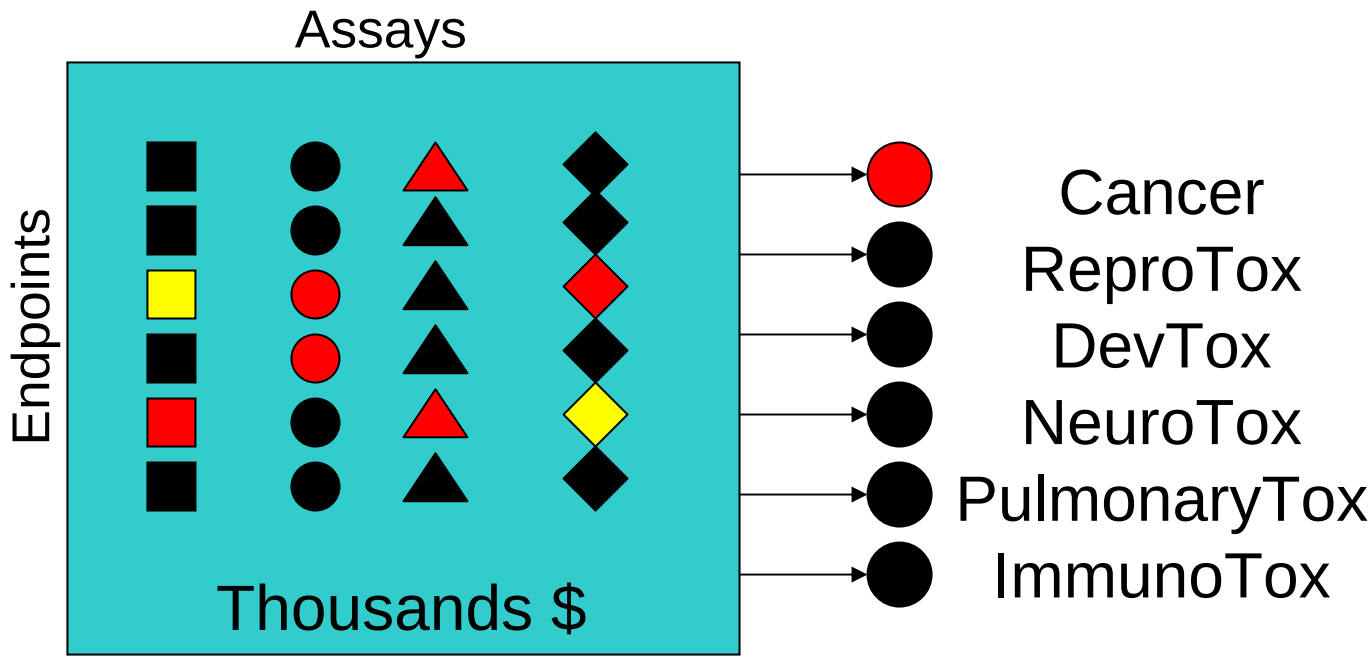
Too High a Cost



…and not enough data.

The Solution: ToxCast™

Derive classifiers or signatures from hundreds of HTS, HCS and genomics assays to predict hazard…



… and use these toxicity predictions for prioritizing further testing of environmental chemicals.

ToxCast Website: www.epa.gov/ncct/toxcast

United States Environmental Protection Agency

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You are here: EPA Home » National Center for Computational Toxicology » ToxCast™ Program

The EPA Web site will be unavailable on Sunday, March 2, 2008 from 8:00 pm until 10:00 pm ET.

ToxCast™ Program

Predicting Hazard, Characterizing Toxicity Pathways, and Prioritizing the Toxicity Testing of Environmental Chemicals

Introduction

In 2007, EPA launched ToxCast™ in order to develop a cost-effective approach for prioritizing the toxicity testing of large numbers of chemicals in a short period of time. Using data from state-of-the-art high throughput screening (HTS) bioassays developed in the pharmaceutical industry, ToxCast™ is building computational models to forecast the potential human toxicity of chemicals. These hazard predictions will provide EPA regulatory programs with science-based information helpful in prioritizing chemicals for more detailed toxicological evaluations, and lead to more efficient use of animal testing.

In its first phase, ToxCast™ is profiling over 300 well-characterized chemicals (primarily pesticides) in over 400 HTS endpoints. These endpoints include biochemical assays of protein function, cell-based transcriptional reporter assays, multi-cell interaction assays, transcriptomics on primary cell cultures, and developmental assays in zebrafish embryos. Almost all of the compounds being examined in Phase 1 of ToxCast™ have been tested in traditional toxicology tests, including developmental toxicity, multi-generation studies, and sub-chronic and chronic rodent bioassays. ToxRefDB, a relational database being created to house this information, will contain nearly $1B worth of toxicity studies in animals when completed. ToxRefDB is integrated into a more comprehensive data management system developed by NCCT called ACToR (Aggregated Computational Toxicology Resource), that manages the large-scale datasets of ToxCast™. ACToR is comprised of several independent data repositories linked to a common database of chemical structures and properties, and to tools for development of predictive HTS and genomic bioactivity signatures that strongly correlate with specific toxicity endpoints from ToxRefDB. These ToxCast™ signatures will be defined and evaluated by their ability to predict outcomes from existing mammalian toxicity testing, and identify toxicity pathways that are relevant to human health effects.

The second phase of ToxCast™ will screen additional compounds representing broader chemical structure and use classes, in order to evaluate the predictive bioactivity signatures developed in Phase I. Following successful conclusion of Phases I and II, ToxCast™ will provide EPA regulatory programs an efficient tool for rapidly and efficiently screening compounds and prioritizing further toxicity testing.

ToxCast™ Navigation

- Introduction
- ToxCast™ Chemicals
- ToxCast™ Assays
- ToxCast™ Information Management
- ToxCast™ Partnerships
- ToxCast™ Contractors
- ToxCast™ Presentations
- ToxCast™ Publications
- ToxCast™ News

United States Environmental Protection Agency

Key Components of ToxCast Proof of Concept

- Chemicals
- Traditional Toxicity Phenotypes
- HTS Assays covering Toxicity Pathways
- Data Analysis and Interpretation

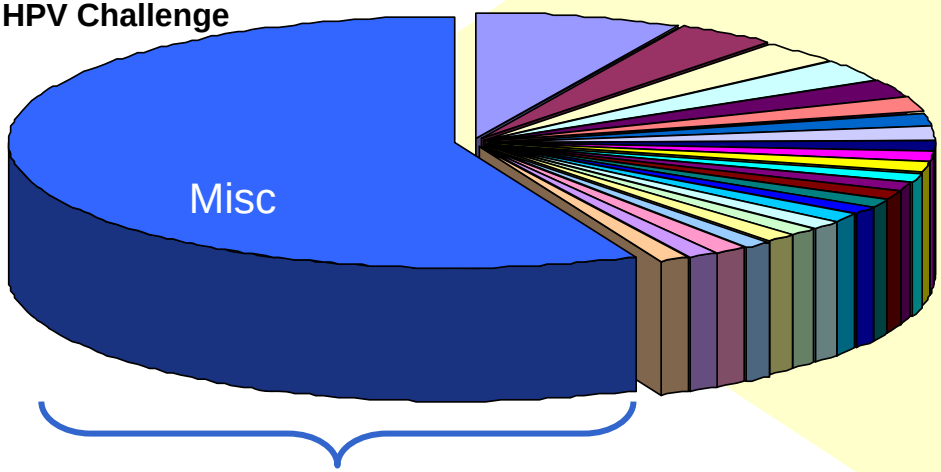
ToxCast_320: Phase I Chemicals

309 Unique Structures
Replicates for QC

291 Pesticide Actives
9 Industrial Chemicals
8 Metabolites

56/73 Proposed Tier 1 EDSP

14 HPV
11 HPV Challenge



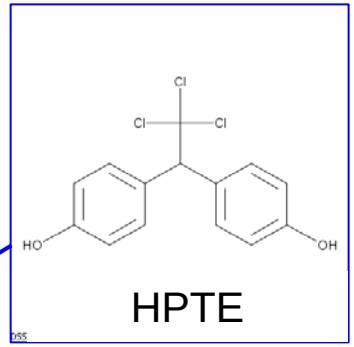
Misc MOA classes with
3 or fewer representatives

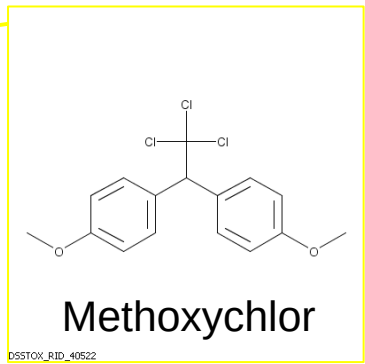
MOA Classes with
> 3 chemicals

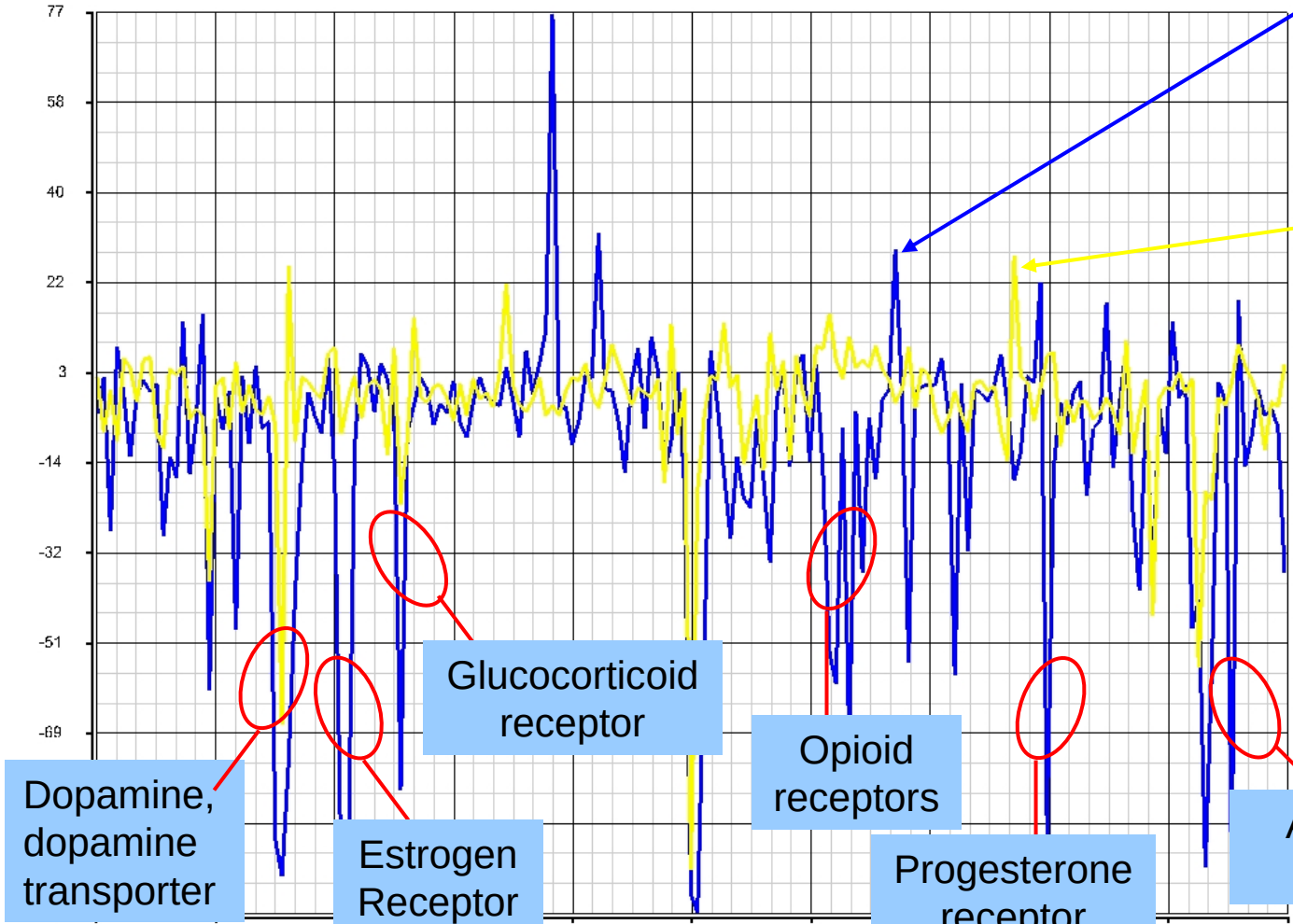
- **Acetylcholine esterase inhibitors**
- **conazole fungicides**
- **Sodium channel modulators**
- **pyrethroid ester insecticides**
- **organothiophosphate acaricides**
- **dinitroaniline herbicides**
- **pyridine herbicides**
- **thiocarbamate herbicides**
- **imidazolinone herbicides**
- **organophosphate insecticides**
- **phenyl organothiophosphate insecticides**
- **aliphatic organothiophosphate insecticides**
- **amide herbicides**
- **aromatic fungicides**
- **chloroacetanilide herbicides**
- **chlorotriazine herbicides**
- **growth inhibitors**
- **organophosphate acaricides**
- **oxime carbamate insecticides**
- **phenylurea herbicides**
- **pyrethroid ester acaricides**
- **strobilurin fungicides**
- **unclassified acaricides**
- **unclassified herbicides**

Classification based on OPPIN

Bioactivity Profiling (NovaScreen)





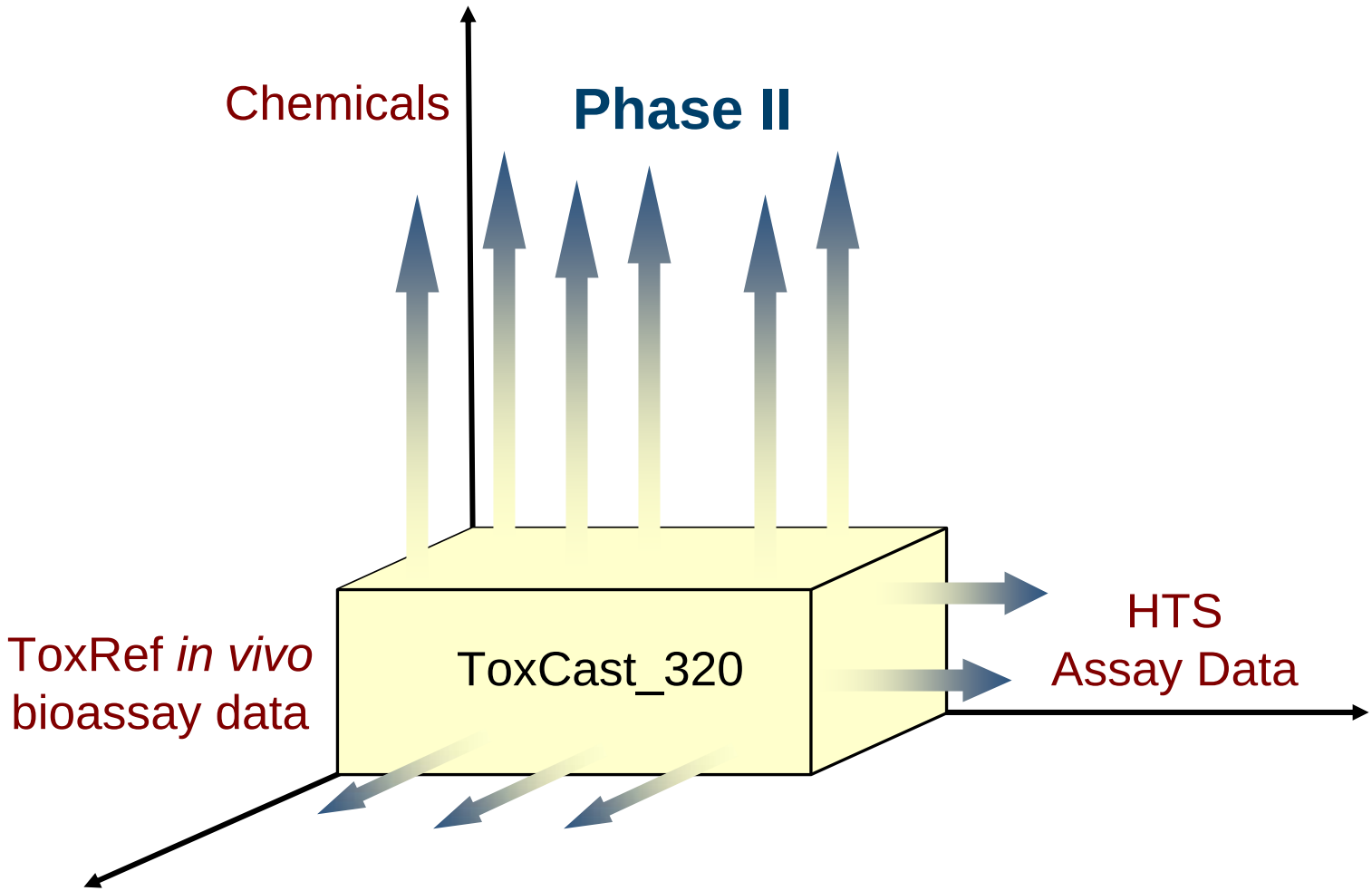


Phased Development of ToxCast

Phase	Number of Chemicals	Chemical Criteria	Purpose	Number of Assays	Cost per Chemical	Target Date
I	320	Data Rich (pesticides)	Signature Development	>400	$20k	FY07-08
IIa	>300	Data Rich Chemicals	Validation	>400	$15-20k	FY09
IIb	>100	Known Human Toxicants	Extrapolation	>400	$15-20k	FY09
IIc	>300	Expanded Structure and Use Diversity	Extension	>400	$15-20k	FY10
III	Thousands	Data poor	Prediction and Prioritization	???	$10-15k	FY11-12

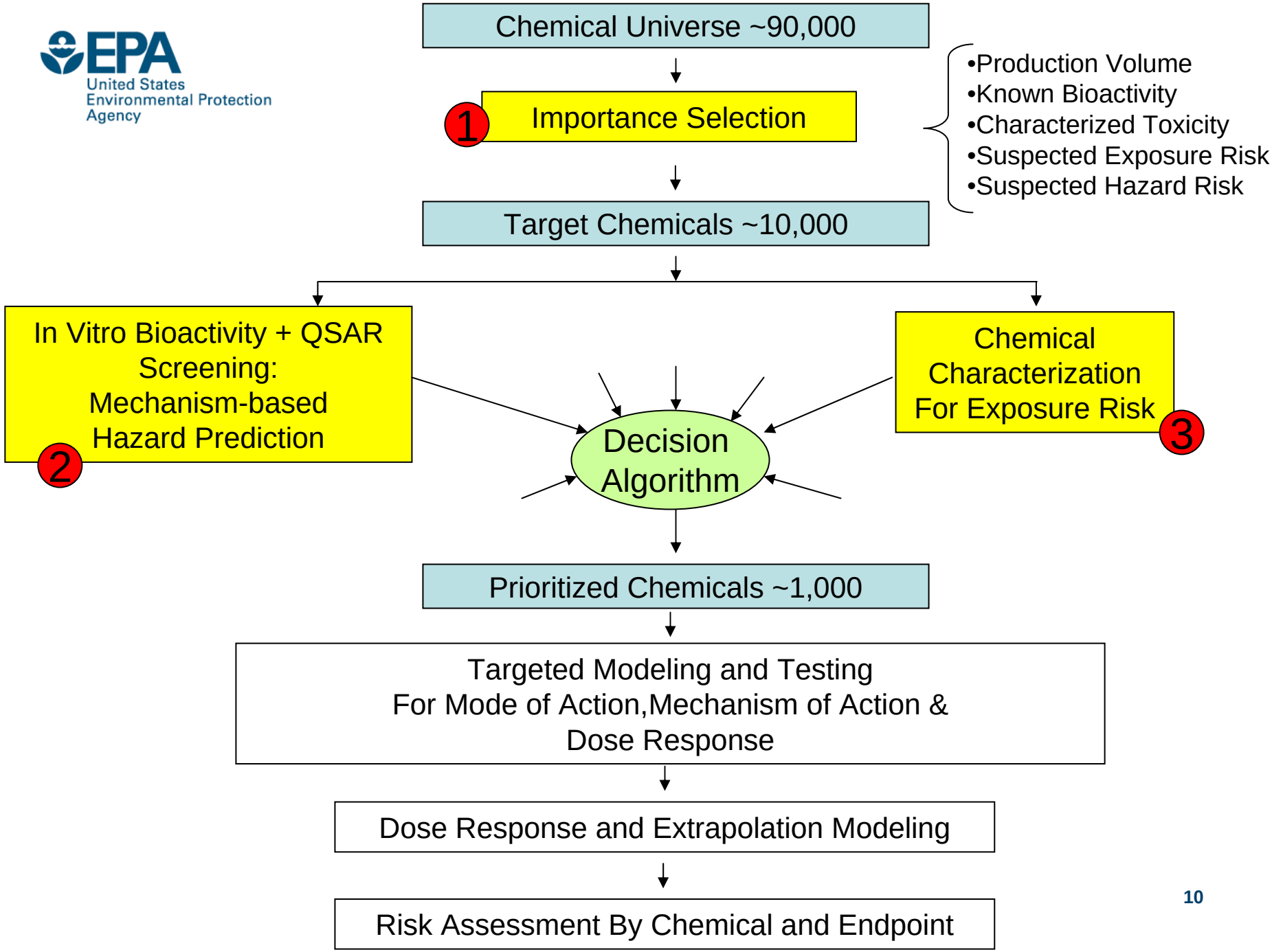
- Affordable science-based system for categorizing chemicals
- Increasing confidence as database grows
- Identifies potential mechanisms of action
- Refines and reduces animal use for hazard ID and risk assessment

ToxCast Expansion Beyond Proof of Concept

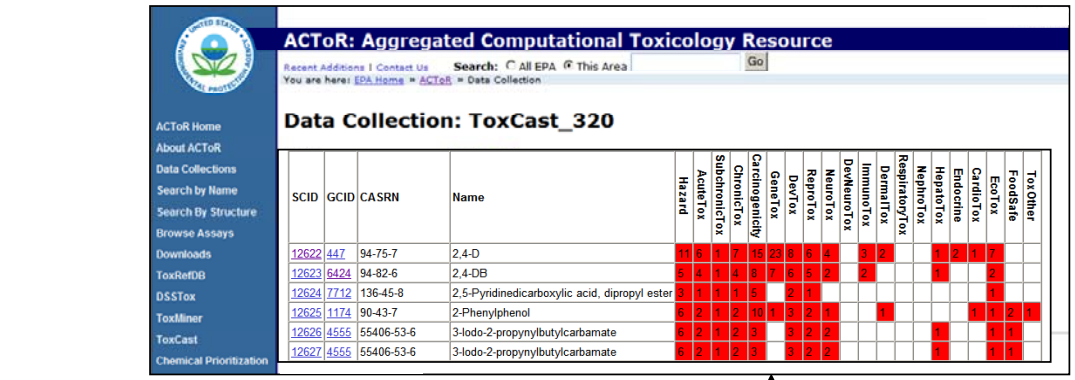


Overlap of 11,414 Candidate Across Sources

		IRIS	EPA CCL1	EPA CCL2	EPA CCL3	EPA DWSHA	EPA EDC73	EPA HPV	EPA HPV Challenge	EPA HPVIS	EPA INERTS 25b Food	EPA INERTS 25b Nonfood	EPA INERTS NONFOOD	EPA IUR (2002)	EPA Active	EPA AntiMicrobial	EPA AntiMicrobial Food Use	EPA Food Use Active	EPA Inert	EPA PCCL	EPA TRI	ToxCast_320	ToxRefDB
		536	**47**	**39**	**92**	**200**	**73**	**2539**	**1973**	**992**	**74**	**101**	**3492**	**5375**	**3474**	**754**	**26**	**1054**	**3839**	**528**	**636**	**308**	**431**
IRIS	**536**	**536**	32	26	57	176	57	147	148	55	0	0	75	185	313	71	12	208	121	190	291	123	148
EPA CCL1	**47**	32	**47**	39	13	25	6	11	11	4	0	0	6	14	25	8	1	15	9	34	27	11	16
EPA CCL2	**39**	26	39	**39**	13	19	5	10	10	4	0	0	5	13	21	7	1	14	8	28	22	10	15
EPA CCL3	**92**	57	13	13	**92**	19	9	29	30	8	0	0	10	39	46	15	6	36	20	92	60	25	31
EPA DWSHA	**200**	176	25	19	19	**200**	29	61	60	26	0	0	33	77	136	38	6	78	58	62	130	43	59
EPA EDC73	**73**	57	6	5	9	29	**73**	8	11	6	0	0	12	12	71	15	9	66	16	33	44	56	66
EPA HPV	**2539**	147	11	10	29	61	8	**2539**	1746	701	19	16	676	2187	366	167	2	163	734	237	162	13	28
EPA HPV Challenge	**1973**	148	11	10	30	60	11	1746	**1973**	703	20	13	567	1759	316	136	1	141	623	259	166	11	25
EPA HPVIS	**992**	55	4	4	8	26	6	701	703	**992**	2	4	250	747	134	66	1	58	263	91	58	8	15
EPA INERTS 25b Food	**74**	0	0	0	0	0	0	19	20	2	**74**	1	74	34	30	10	0	29	73	6	0	0	0
EPA INERTS 25b Nonfood	**101**	0	0	0	0	0	0	16	13	4	1	**101**	100	27	20	9	0	17	95	1	0	0	0
EPA INERTS NONFOOD	**3492**	75	6	5	10	33	12	676	567	250	74	100	**3492**	1126	603	298	3	326	3412	135	92	15	26
EPA IUR (2002)	**5375**	185	14	13	39	77	12	2187	1759	747	34	27	1126	**5375**	555	259	3	237	1224	302	230	23	47
EPA Active	**3474**	313	25	21	46	136	71	366	316	134	30	20	603	555	**3474**	754	26	1053	670	223	311	292	404
EPA AntiMicrobial	**754**	71	8	7	15	38	15	167	136	66	10	9	298	259	754	**754**	26	256	314	76	92	33	63
EPA AntiMicrobial Food Use	**26**	12	1	1	6	6	9	2	1	1	0	0	3	3	26	26	**26**	26	4	13	13	14	20
EPA Food Use Active	**1054**	208	15	14	36	78	66	163	141	58	29	17	326	237	1053	256	26	**1054**	331	151	192	274	351
EPA Inert	**3839**	121	9	8	20	58	16	734	623	263	73	95	3412	1224	670	314	4	331	**3839**	168	143	27	41
EPA PCCL	**528**	190	34	28	92	62	33	237	259	91	6	1	135	302	223	76	13	151	168	**528**	206	73	93
EPA TRI	**636**	291	27	22	60	130	44	162	166	58	0	0	92	230	311	92	13	192	143	206	**636**	112	144
ToxCast_320	**308**	123	11	10	25	43	56	13	11	8	0	0	15	23	292	33	14	274	27	73	112	**308**	304
ToxRefDB	**431**	148	16	15	31	59	66	28	25	15	0	0	26	47	404	63	20	351	41	93	144	304	**431**


Chemical Universe ~90,000
1
Importance Selection
•Production Volume
•Known Bioactivity
•Characterized Toxicity
•Suspected Exposure Risk
•Suspected Hazard Risk
Target Chemicals ~10,000
In Vitro Bioactivity + QSAR Screening: Mechanism-based Hazard Prediction
2
Chemical Characterization For Exposure Risk
3
Decision Algorithm
Prioritized Chemicals ~1,000
Targeted Modeling and Testing For Mode of Action,Mechanism of Action & Dose Response
Dose Response and Extrapolation Modeling
Risk Assessment By Chemical and Endpoint

ACToR: Aggregated Computational Toxicology Resource



ACToR Web Browser

ACToR API

Chemical

Chemical ID, Structure

Assay

Tabular Data, Links to Web Resources

ToxRefDB

...

DevToxDB

Specialized Toxicology Databases

Genomics

MicroArray Data

BioRefDB

Biological Reference Data

ToxMiner

Data Mining

Internet Searches

Transforming Toxicology

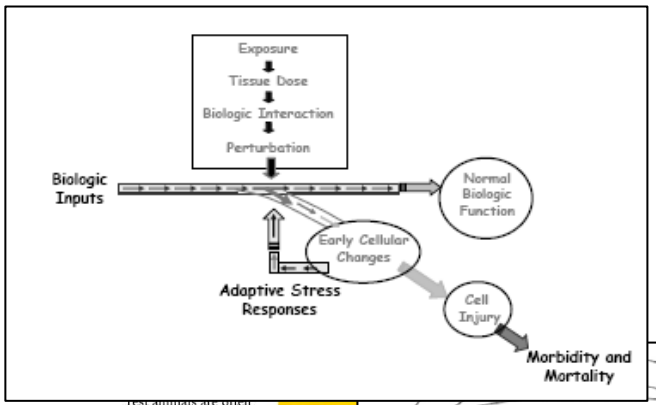
THE NATIONAL ACADEMIES

REPORT IN BRIEF

July 2007

Toxicity Testing in the 21st Century: A Vision and a Strategy

Advances in molecular biology, biotechnology, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. These advances would make toxicity testing quicker, less expensive, and more directly relevant to human exposures. They could also reduce the need for animal testing by substituting more laboratory tests based on human cells. This National Research Council report creates a far-reaching vision for the future of toxicity testing.



Test animals are often exposed to higher doses than would be expected for typical human exposures, requiring assumptions about

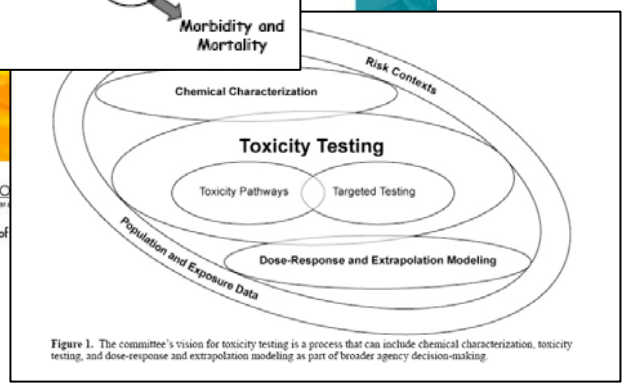


Figure 1. The committee's vision for toxicity testing is a process that can include chemical characterization, toxicity testing, and dose-response and extrapolation modeling as part of broader agency decision-making.

National Academy of Sciences • National Academy of

POLICYFORUM

TOXICOLOGY

Transforming Environmental Health Protection

We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.

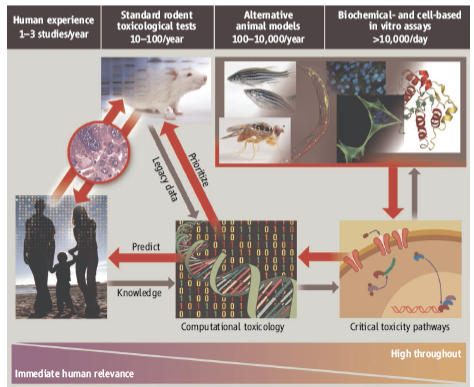
Francis S. Collins,*† George M. Gray,2* John R. Bucher3*

In 2005, the U.S. Environmental Protection Agency (EPA), with support from the U.S. National Toxicology Program (NTP), funded a project at the National Research Council (NRC) to develop a long-range vision for toxicity testing and a strategic plan for implementing that vision. Both agencies wanted future toxicity testing and assessment paradigms to meet evolving regulatory needs. Challenges include the large numbers of substances that need to be tested and how to incorporate recent advances in molecular toxicology, computational sciences, and information technology; to rely increasingly on human as opposed to animal data; and to offer increased efficiency in design and costs (*1*–*5*). In response, the NRC Committee on Toxicity Testing and Assessment of Environmental Agents produced two reports that reviewed current toxicity testing, identified key issues, and developed a vision and implementation strategy to create a major shift in the assessment of chemical hazard and risk (*6*, *7*). Although the NRC reports have laid out a solid theoretical rationale, comprehensive and rigorously gathered data (and comparisons with historical animal data) will determine whether the hypothesized improvements will be realized in practice. For this purpose, NTP, EPA, and the National Institutes of Health Chemical Genomics Center (NCGC) (organizations with expertise in experimental toxicology, computational toxicology, and high-throughput technologies, respectively) have established a collaborative research program.

EPA, NCGC, and NTP Joint Activities

In 2004, the NTP released its vision and roadmap for the 21st century (*1*), which established initiatives to integrate high-throughput screening (HTS) and other automated screening assays into its testing program. In 2005, the EPA established the National Center for Computational Toxicology (NCCT). Through these initiatives, NTP and EPA, with the NCGC, are promoting the evolution of toxicology from a predominantly observational science at the level of disease-specific models in vivo to a predominantly predictive science focused on broad inclusion of target-specific, mechanism-based, biological observations in vitro (*1*, *4*) (see figure, below).

Toxicity pathways. In vitro and in vivo tools are being used to identify cellular responses after chemical exposure expected to result in adverse health effects (*7*). HTS methods are a primary means of discovery for drug development, and screening of >100,000 compounds per day is routine (*8*). However, drug-discovery HTS methods traditionally test compounds at one concentration, usually between 2 and 10 μM, and tolerate high false-negative rates. In contrast, in the EPA, NCGC, and NTP combined effort, all compounds are tested at as many as 15 concentrations, generally ranging from ~5 nM to ~100 μM, to generate a concentration-response curve (*9*). This approach is highly reproducible, produces significantly lower false-positive and false-negative rates than the traditional HTS methods (*9*), and facilitates multiassay comparisons. Finally, an informatics platform has been built to compare results among HTS screens; this is being expanded to allow comparisons with historical toxicologic NTP and EPA data (http://ncgc.nih.gov/pub/openhts). HTS data collected by EPA and NTP, as well as by the NCGC and other Molecular Libraries Initiative centers (http://mli.nih.gov/), are being made publicly available through Web-based databases [e.g., PubChem (http://pubchem.ncbi.nlm.nih.gov)]. In addition,



Transforming toxicology. The studies we propose will test whether high-throughput and computational toxicology approaches can yield data predictive of results from animal toxicity studies, will allow prioritization of chemicals for further testing, and can assist in prediction of risk to humans.

[1]Director, National Human Genome Research Institute (NHGRI), National Institutes of Health, Bethesda, MD 20892; [2]Assistant Administrator for the Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460; [3]Associate Director, U.S. National Toxicology Program, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC 27709, USA.

*The views expressed here are those of the individual authors and do not necessarily reflect the views and policies of their respective agencies.

†Author for correspondence. E-mail: francisc@mail.nih.gov

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