Identification, prioritization and conduct of applied research and analyses impacting policy development: lessons learned from the U.S. National Toxicology Program (NTP)

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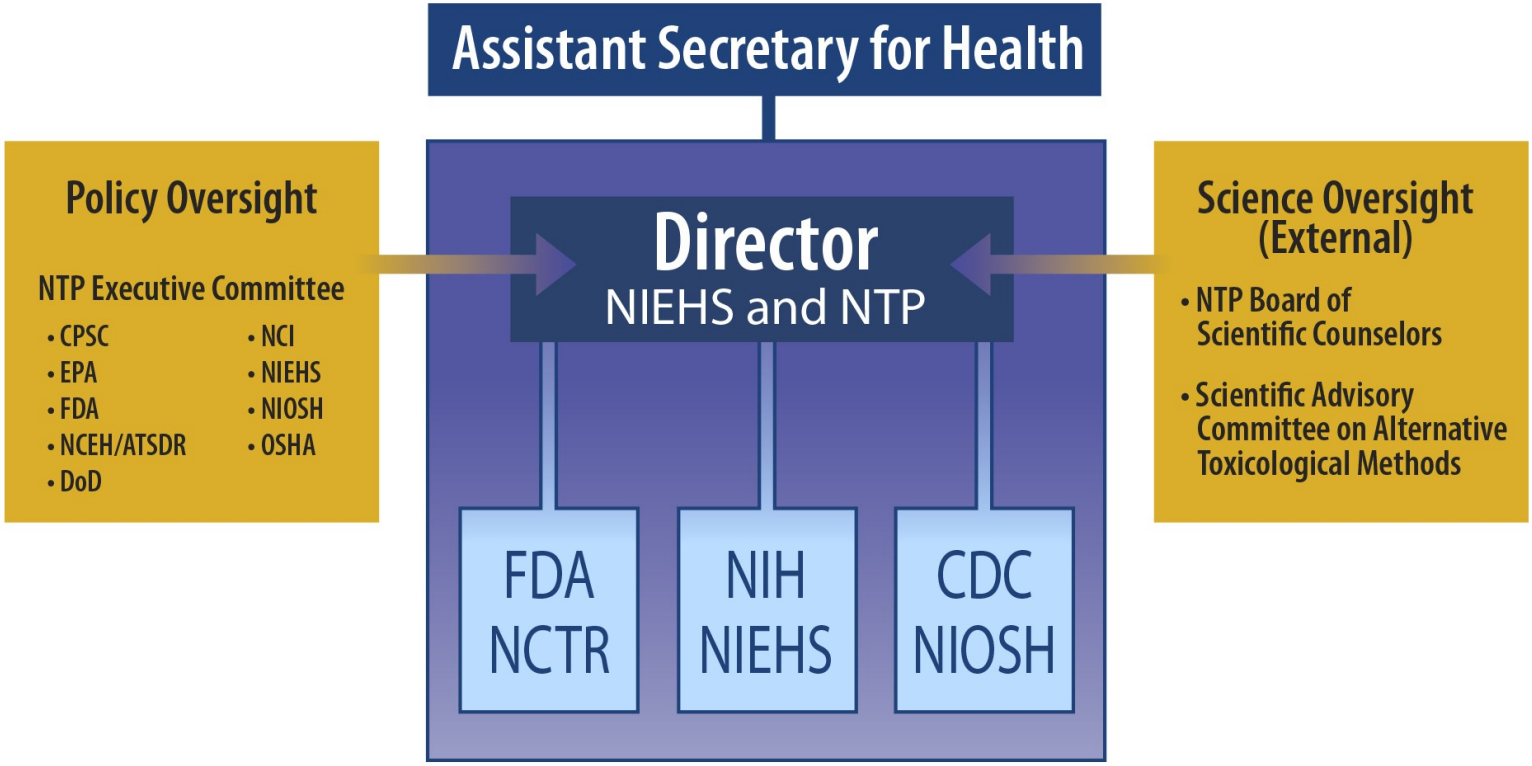
Outline

- Overview of the National Toxicology Program
  - Scientific approach
  - Operational approach
- Case examples of NTP projects
  - Chromium VI
  - Bisphenol-A
- New approaches
  - Tox 21
  - Elk River Spill
- Reflections

National Toxicology Program, DHHS

(Headquartered at NIEHS)



"Evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology."

Safety = lack of risk
Risk = hazard x exposure

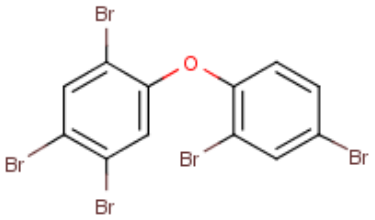
- Exposure assessment
- Hazard identification
- Hazard characterisation
- Dose-response

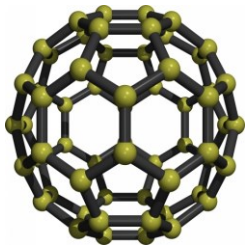
NTP Approaches

- Hazard Characterization (“Testing Program”)
  - Carcinogenicity and toxicity and evaluations
  - Primarily via *in vivo* GLP-studies
- New testing methods development and approaches
  - Quantitative high throughput screening/in vitro testing (Tox21)
  - Non-mammalian systems
  - Validation of alternative models (NICEATM/ICCVAM)
- Toxicology/Pathology Research
  - Molecular pathogenesis, informatics, genetics variability, cancer stem cells,
- Human health Hazard Assessments (literature-based analyses)
  - Report on Carcinogens (RoC)
  - Non-cancer Health Assessments (OHAT) and systematic reviews
- Exposure assessments
  - Via interagency agreements

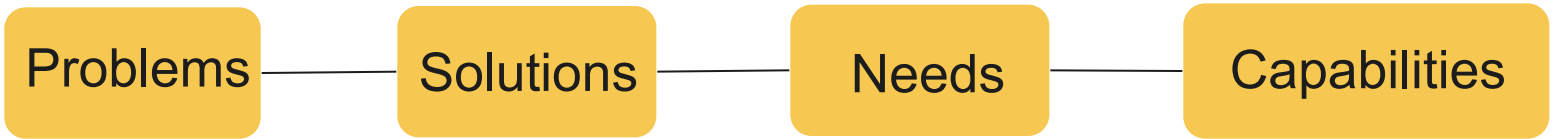
Food safety related areas of emphasis for the NTP

- Botanicals and Dietary supplements
- Endocrine active compounds
- Flame retardants
- Food derived carcinogens
- Dinking water contaminants
- Mixtures/Combined exposures
- Nanoscale materials
- Occupational exposures
- Polycyclic aromatic compounds
- Persistent environmental contaminants
- Personal care products
- Radiofrequency radiation
- Sunscreen constituents





Operational framework



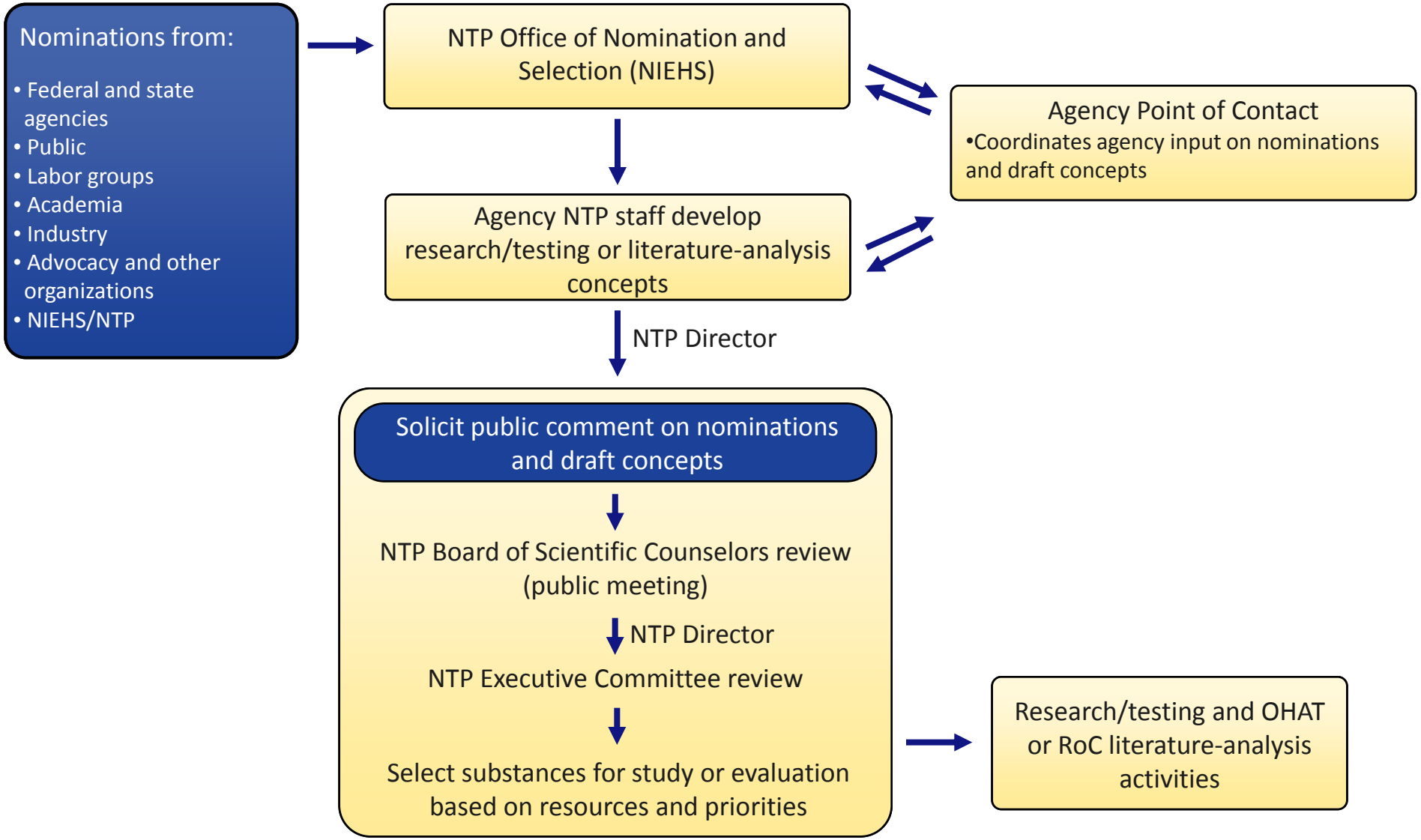
Nominations
Hypotheses
Ideas
etc

Concepts
Strategies

Study designs
Endpoints
Assays
Procedures

Contracts
Core labs
IAGs
Services

Review Process for Nominations to NTP

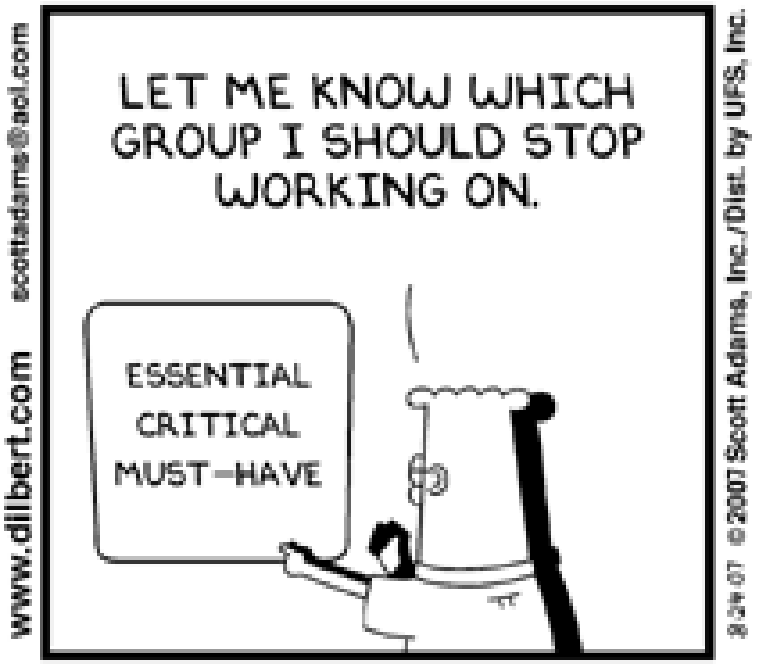


Nominations Reviewed 1998-2009

- 180 single agent nominations
- 41 'complex' nominations
  - Mixed occupational exposures
  - Structural classes
  - Functional categories
- Sources
  - NIH/NIEHS-21%
  - NIH/NCI-23%
  - Private individuals- 14%
  - FDA-11%
  - NIOSH- 8%
  - USEPA-8%
  - CPSC/OSHA/NCEH/ATSDR-8%
  - Other- 8%

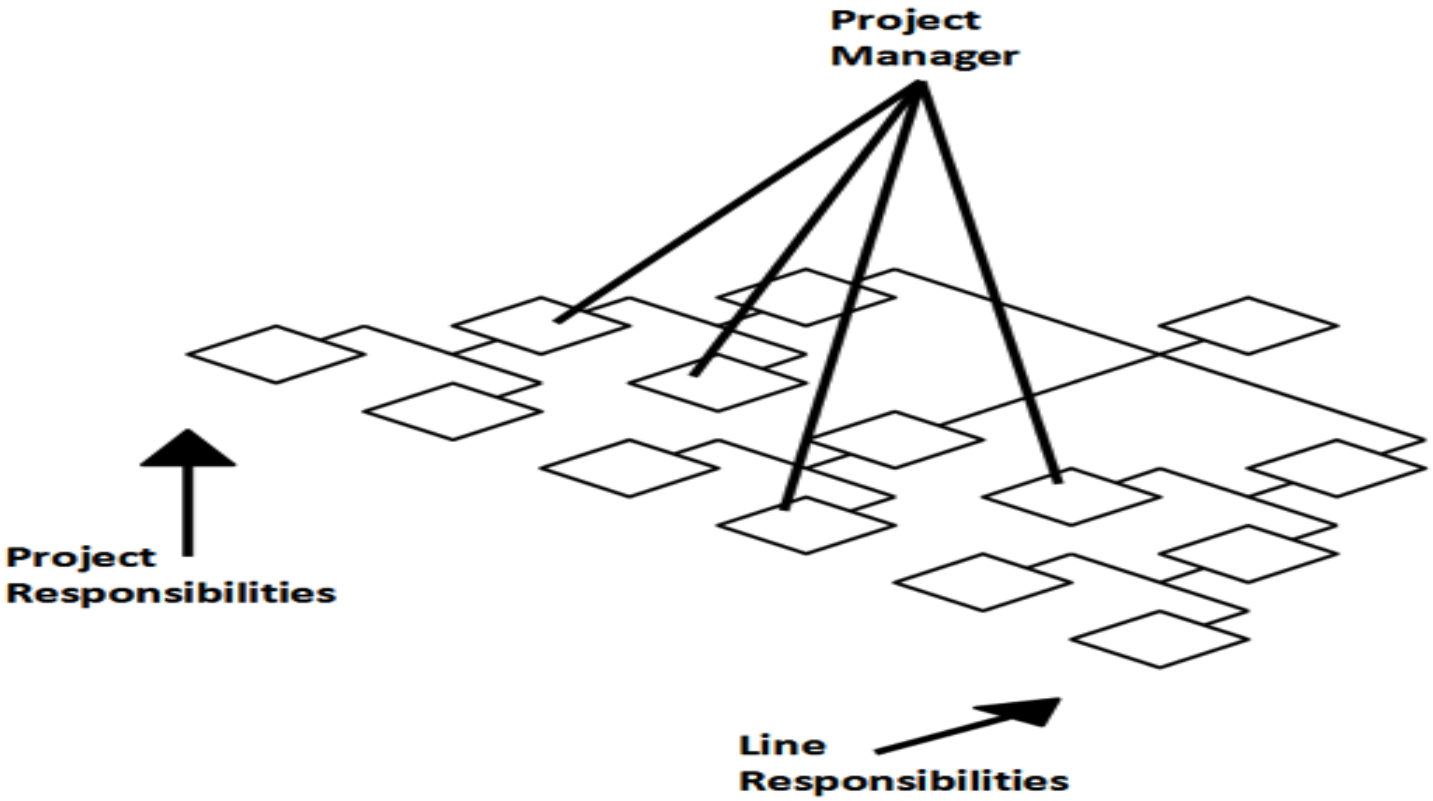
Prioritization: principles considered

- Being responsive to “nominators” question
- GLP-compliance (defensibility for regulatory decision-making)
- Transparency
- Personnel capabilities
- Operational capabilities
- Comprehensiveness needed
- Fiscal constraints
- Timeframe of data needs
- Scientific creativity



Team science model

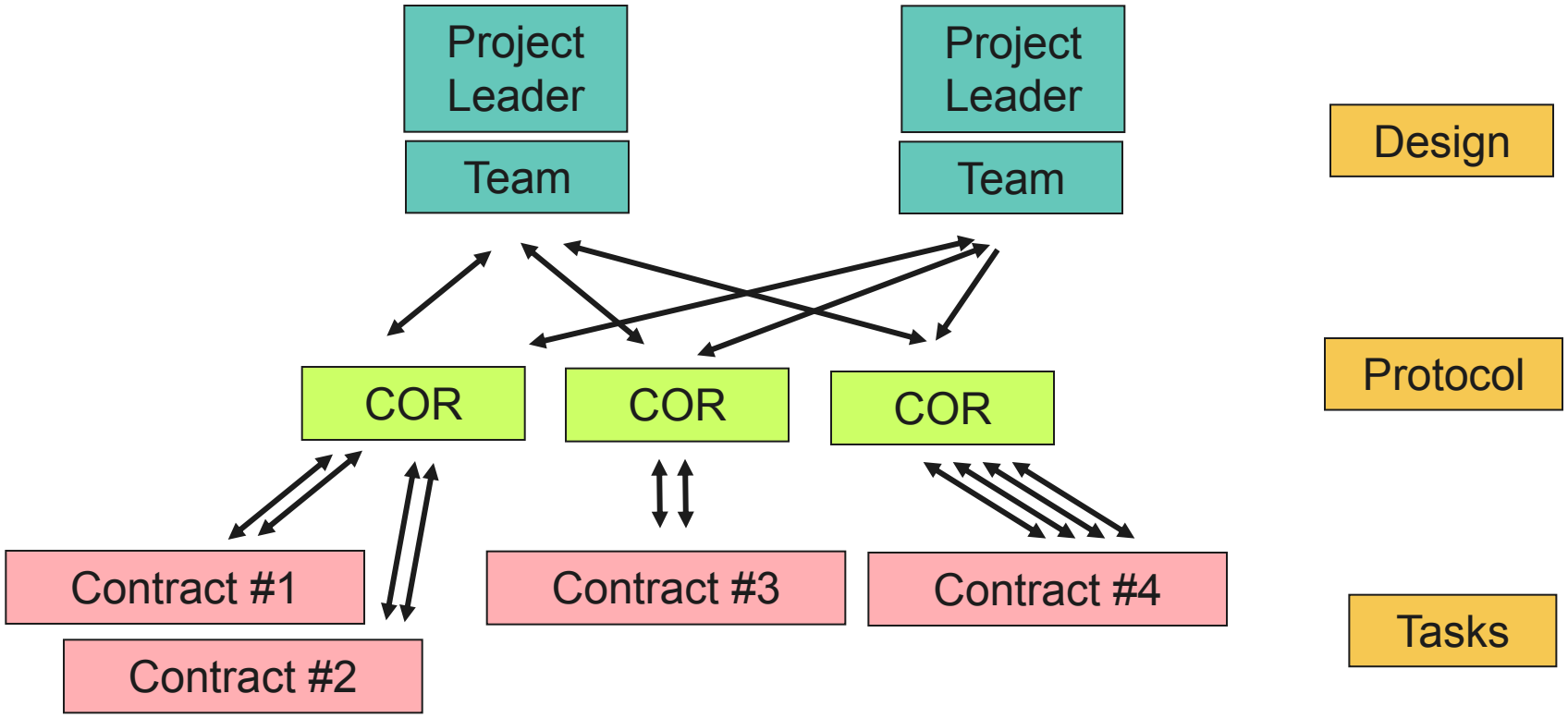
- Some groups are self contained with the organizational structure
- Many projects operate across the administrative structure
- Not “collaborations”



DNTP Operational Workflow

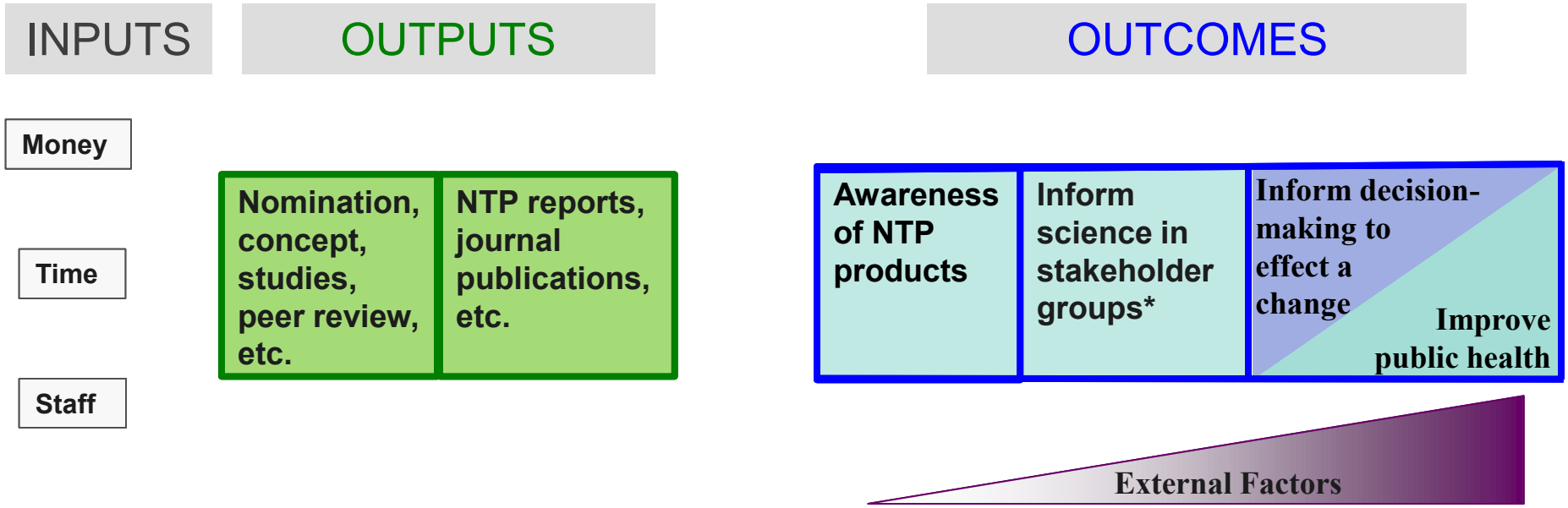
- Project-centered, centrally funded, research model
- NOT a Principal Investigator group centered research model
  - Not a specific or specific person or project
  - Not a single contract for a specific study
- Projects proceed primarily through consensus-based decision making
- Research primarily conducted in the context of NTP projects, NTP review processes and uses shared DNTP resources
- Research teams span across the administrative structure and are flexible

How work gets done



Not a single contract per project

Logic Model for NTP Studies



OUTPUTS	OUTCOMES (Impacts)		
Activities & Products	Proximal	Intermediate	Distal
Number and dates of milestones of what NTP did and produced	Number of downloads and requests for NTP products	Number and nature of citations in science publications, grants, and reports from stakeholder groups*	Citations in documents that led to a change or action in legislation, lawsuit, policy, etc.

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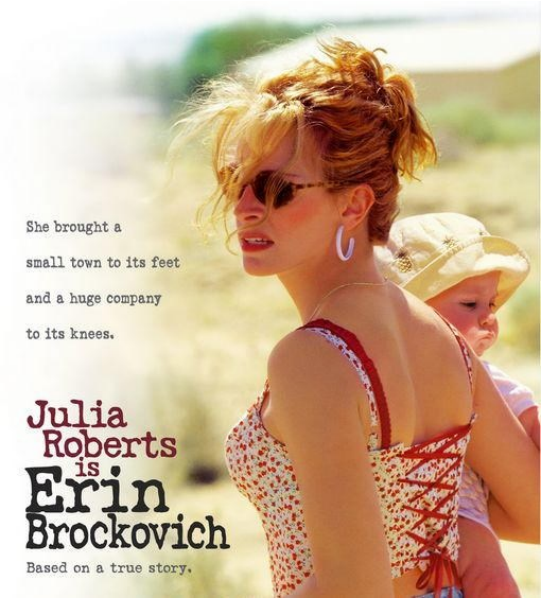
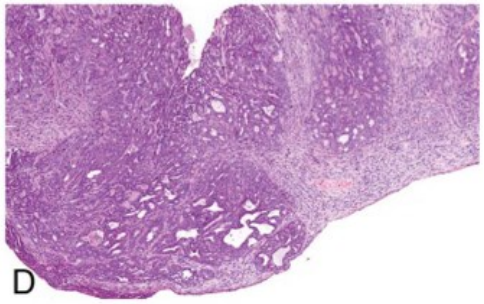
Hexavalent Chromium (VI)

- Cr VI is a drinking water contaminant
  - Cr(III) is an essential nutrient and is relatively nontoxic
- Lots of Public/media attention
- Nominated for study
  - California Congressional Delegation, the California Environmental Protection Agency, and the California Department of Health Services
- Human carcinogen by inhalation
- Lack of adequate data on the toxicity and carcinogenicity of hexavalent chromium ingested orally



Outcome of the CrVI Program

- Carcinogenic in both sexes of rats and mice
- Extensive evaluation of kinetics showed systemic exposure to CrVI based on the tissue distribution data.
- Multiple reports and publications
- Report on Carcinogens evaluation and conclusion as known human carcinogen



Impact of the NTP study and use of the data

- Basis for California's Public Health Goal for Cr(VI) in drinking water
  - dose-related increase of tumors of the small intestine in male mice
  - PHG are non-mandatory goals used for establishing drinking water standards
- NTP data used in a risk assessment conducted by the New Jersey Department of Environmental Protection in 2009
  - human cancer potency estimate for Cr(VI) by ingestion and an associated Soil Cleanup Standard of 1

Table 5. Small Intestine Tumors in Male Mice Administered Hexavalent Chromium.

Organ	Tumor Type	Concentration of Sodium Dichromate Dihydrate in Drinking Water				
		0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Small Intestine[a]	Adenomas	1/49[b,d]	1/49	1/49	5/50	17/48[f]
	Carcinomas	0/49[c]	2/49	1/49	3/50	5/48[e]
	Adenomas or Carcinomas	1/49[d]	3/49	2/49	7/50[e]	20/48[f]

[a]Includes duodenum, ileum and jejunum.
[b]Number of animals with tumors/number of animals at risk (alive at the time of the first occurrence of tumor (day 451)) and if tissue was available (not missing).
[c]Statistically significant (p=0.01) Exact trend test.
[d]Statistically significant (p<0.0001) Exact trend test.
[e]Statistically significant (p<0.05) Fisher's exact test.
[f]Statistically significant (p<0.0001) Fisher's exact test.

CrVI: an example of the need for new approaches

- Clearly addressed the issue of carcinogenic hazard by the oral route
- Project was given “front of the line status” in the various places in the NTP pipeline.
- Time from nomination to regulatory impact was over 10 years

Bisphenol-A

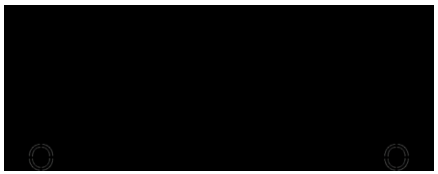
- Chemical widely used to make polycarbonate plastics & epoxy resins.
- Widespread low exposure from migration of small amounts into foods from food contact materials
- Considerable debate over risk posed by “low level” exposure.
- GLP guideline studies show no effects of concern at low doses
  - Basis for FDA regulatory decision making
- Academic “investigative/exploratory” studies show that BPA induces a variety of dysfunctions in a variety of model systems at low exposures.

CLARITY-BPA

- Consortium Linking Academic and Regulatory Insights on the Toxicity of BPA (CLARITY-BPA)
- Goal: Address scientific uncertainties about BPA toxicity, optimize BPA-focused research investments, and to generate additional data for risk assessment.
  - New collaborative research model that draws upon the strengths of academic investigation and guideline-compliant research.

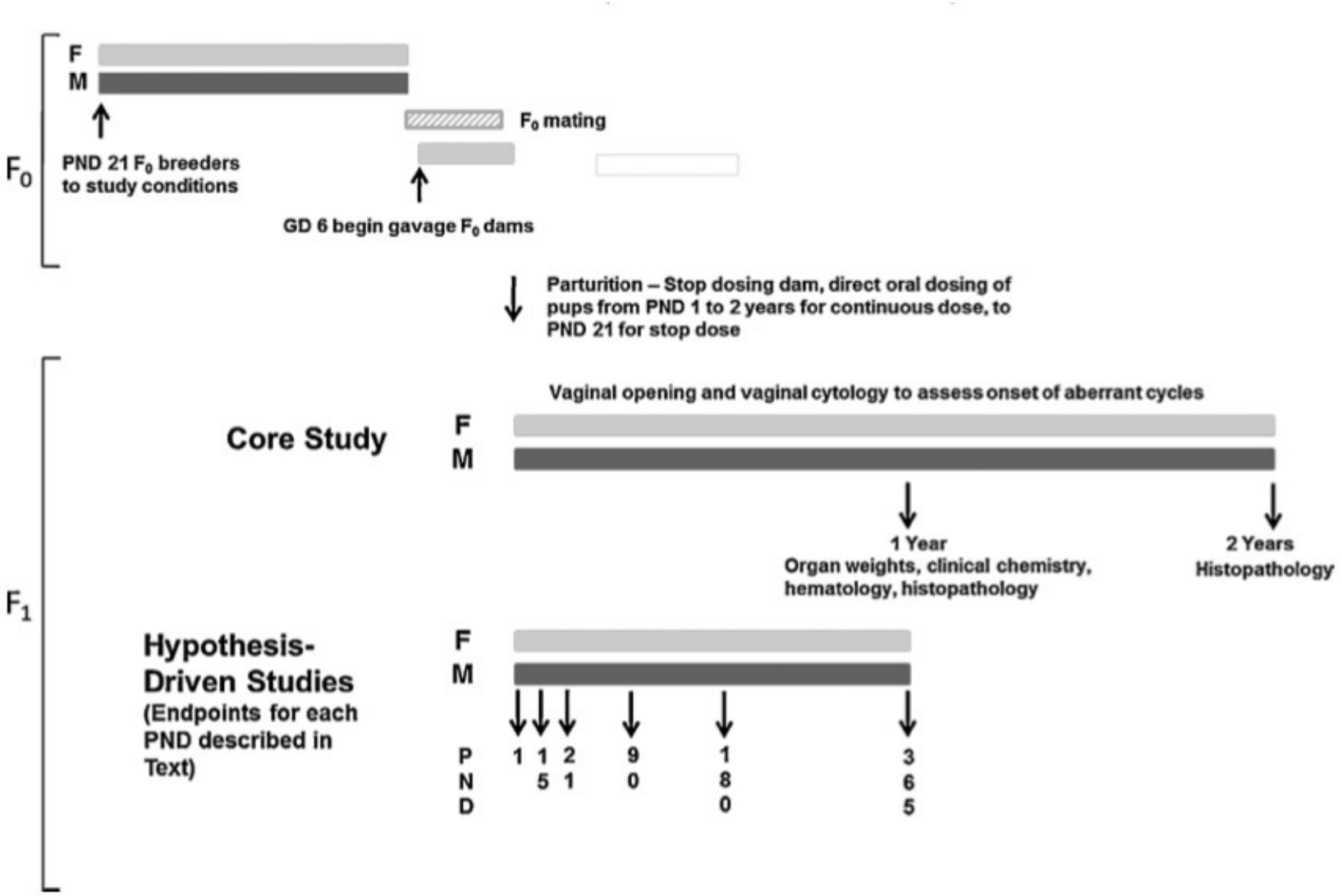
- Brings together academic researchers with federal scientists and regulators to answer critical research questions.
  - NIEHS/NTP and NIEHS/Extramural Training program
  - FDA/NCTR and CFSAN
  - 13 NIEHS-funded academic grantees

BPA-CLARITY



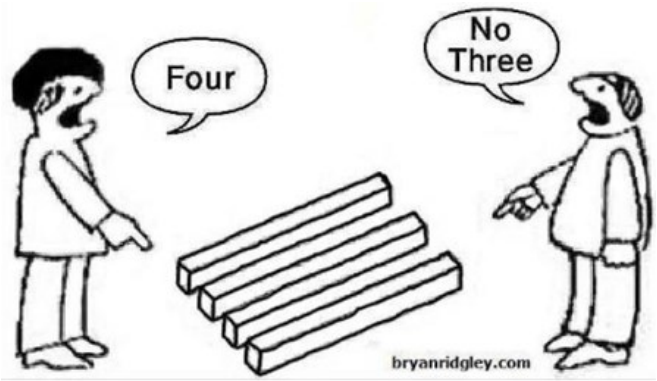
- Guideline-compliant 2-year chronic study conducted under GLP
  - Includes perinatal exposure by direct dosing of F1 pups
  - 1 year interim sacrifice (histopathology, clinical chemistry, sperm parameters) and 2 year terminal sacrifice (histopathology)
- 13 Academic grantees studies
  - Focus on a range of molecular, structural, and functional endpoints
  - Focus on reported BPA effects in animal models but not usually assessed in guideline-compliant studies

BPA-CLARITY


F
M
F0 mating
F0
PND 21 F0 breeders to study conditions
GD 6 begin gavage F0 dams
Parturition – Stop dosing dam, direct oral dosing of pups from PND 1 to 2 years for continuous dose, to PND 21 for stop dose
F1
Vaginal opening and vaginal cytology to assess onset of aberrant cycles
Core Study
F
M
1 Year
Organ weights, clinical chemistry, hematology, histopathology
2 Years
Histopathology
Hypothesis-Driven Studies
(Endpoints for each PND described in Text)
F
M
PND
1
15
21
90
180
365

BPA-CLARITY Outcomes

- Project still ongoing
- Clear differences in culture between academic science and regulatory science
  - Scientific freedom
  - Innovation
- Building/maintaining trust has been critical
  - Involvement in study design
  - Sample blinding
  - Use of independent NTP CEBS database for deposition and decoding
  - Clear “articles of collaboration”
  - Constant communication



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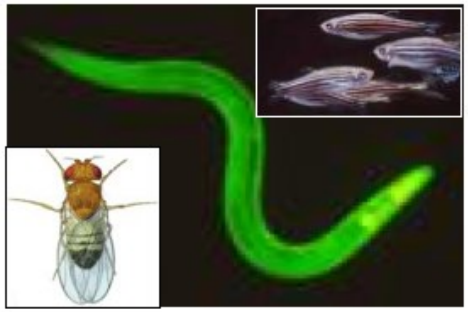
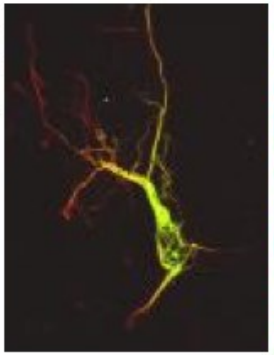
Fundamental challenge for hazard evaluation

??

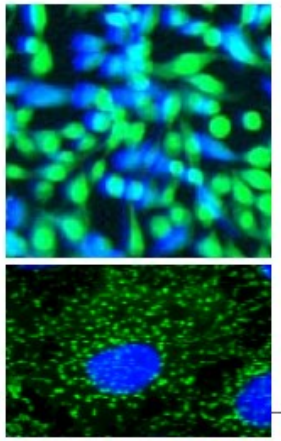
1-10's/year



100's/year



10,000's/day



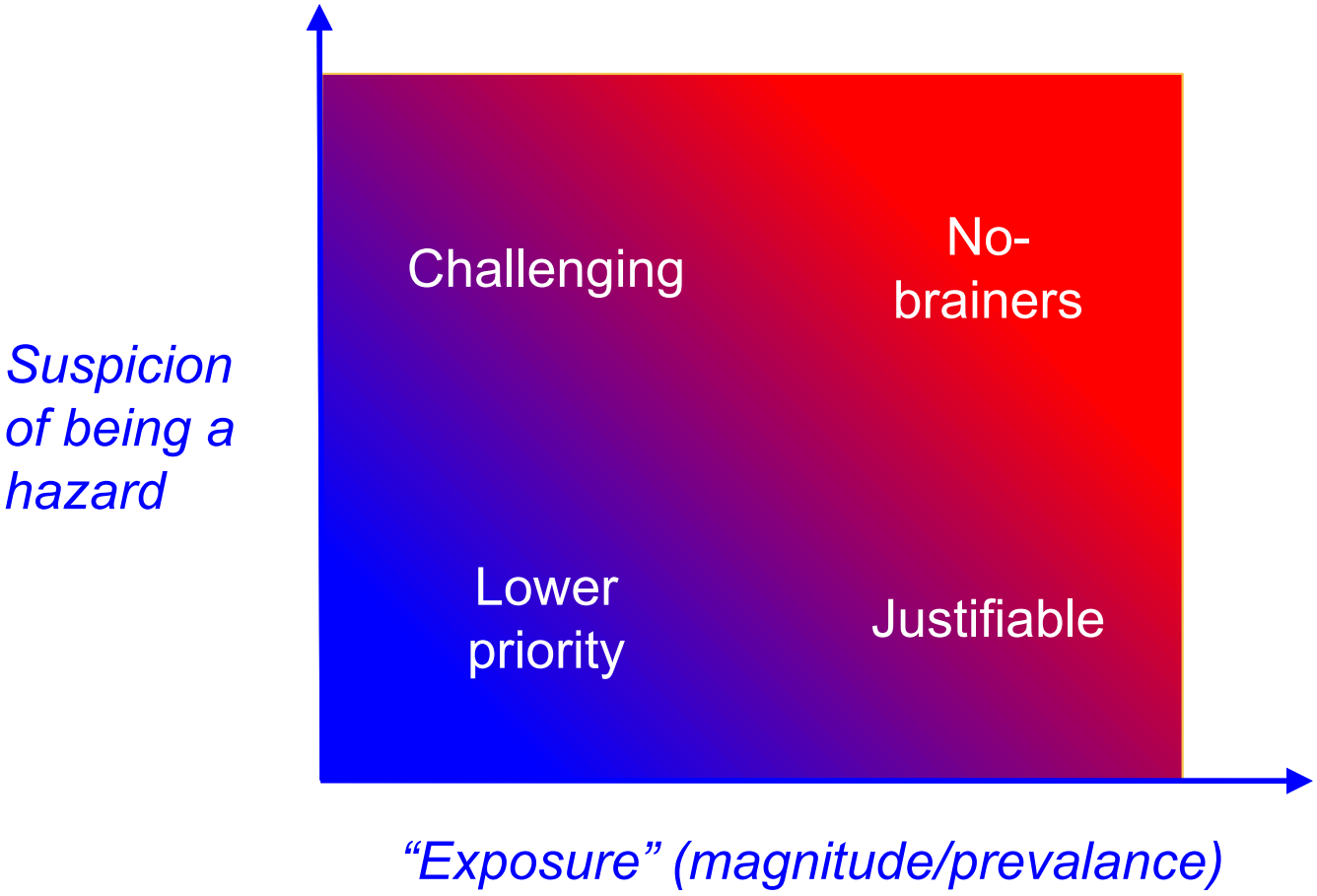
100,000's/day

Mechanisms

Immediate Human Relevance

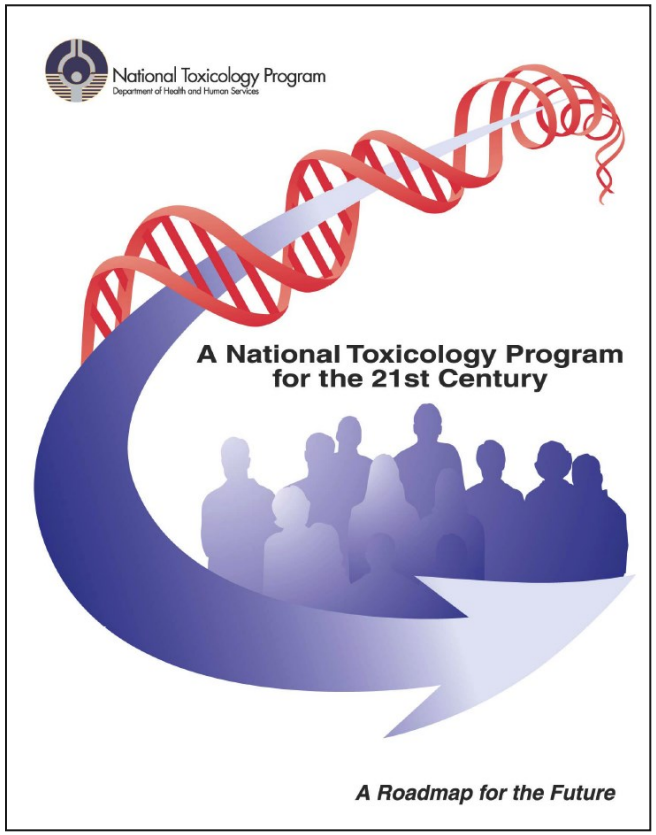
Exposure data

Hazard data


Challenging
No-brainers
Lower priority
Justifiable
Suspicion of being a hazard
"Exposure" (magnitude/prevalance)

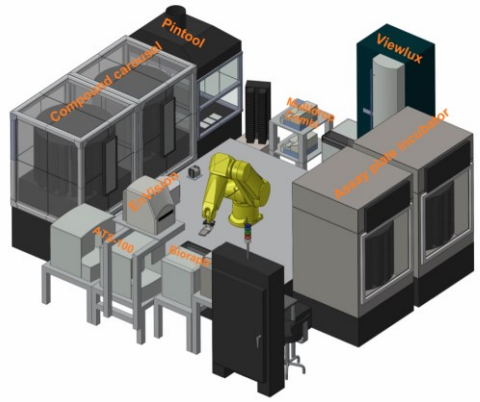
A National Toxicology Program for the 21st Century

- Roadmap to Achieve the NTP Vision
  - Released November 2004
  - http://ntp.niehs.nih.gov/go/vision
- "*To support the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target specific, mechanism-based, biological observations.*"

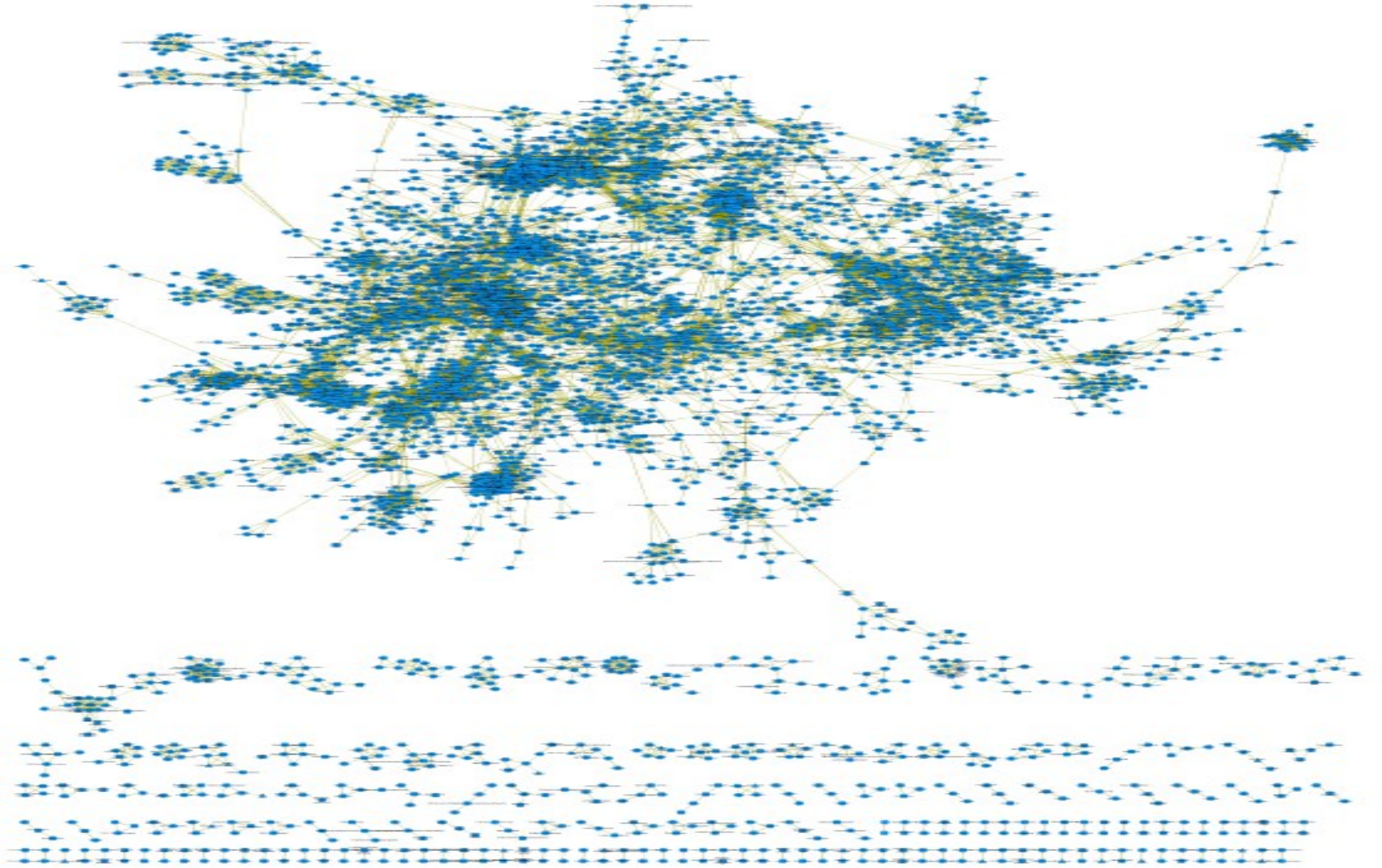


Tox21 Quantitative High Throughput Screening

- Phase I - Proof of Principle (2005-2010)
  - Robotic screens of 2700 chemcials in 15 concentrations in 140 qHTS assays representing 77 predominantly cell-based reporter gene endpoints.
  - Data made public via PubChem and CEBS
- Phase II – Expanded Screening (2010-2014)
  - 10K compound library screened 3 x at 15 concentrations in qHTS assays that focused on:
    - Nuclear receptor activation or inhibition
    - Induction of cellular stress response pathways
- Phase III (2014-onwards)
  - Incorporation of metabolic capability into screens
  - Use of high throughput genomics
  - Alternative model systems

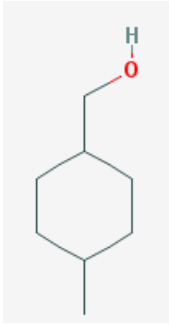


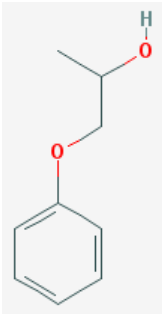
Connectivity Network map of Tox21 Assay data



West Virginia Chemical Spill: NTP Research Response

- Jan 2014; Residents of Charleston, West Virginia began to notice a “sweet smell” (like licorice) in the air and reported it to the WV Department of Environmental Protection.
- 10,000 gallons of chemicals used to process coal spilled from a storage tank
  - Mixture of multiple chemicals including 4-methylcyclohexanemethanol (MCHM), propylene glycol phenyl ether (PPH)
- CDC issues a 1 ppm screening level based on limited information
- NTP was asked to evaluate the point of departure used in the risk assessment, determine if there are life stage specific hazards and screen minor components of the mixture.





In silico SAR

In vitro HTS

Bacterial mutagenicity

Nematode Toxicity

Zebrafish Embryotoxicity

Mouse Dermal Irritancy/Hypersensitivity

Rat repeat dose Toxicogenomics

Rat Prenatal Developmental Toxicity

Proposed NTP Studies

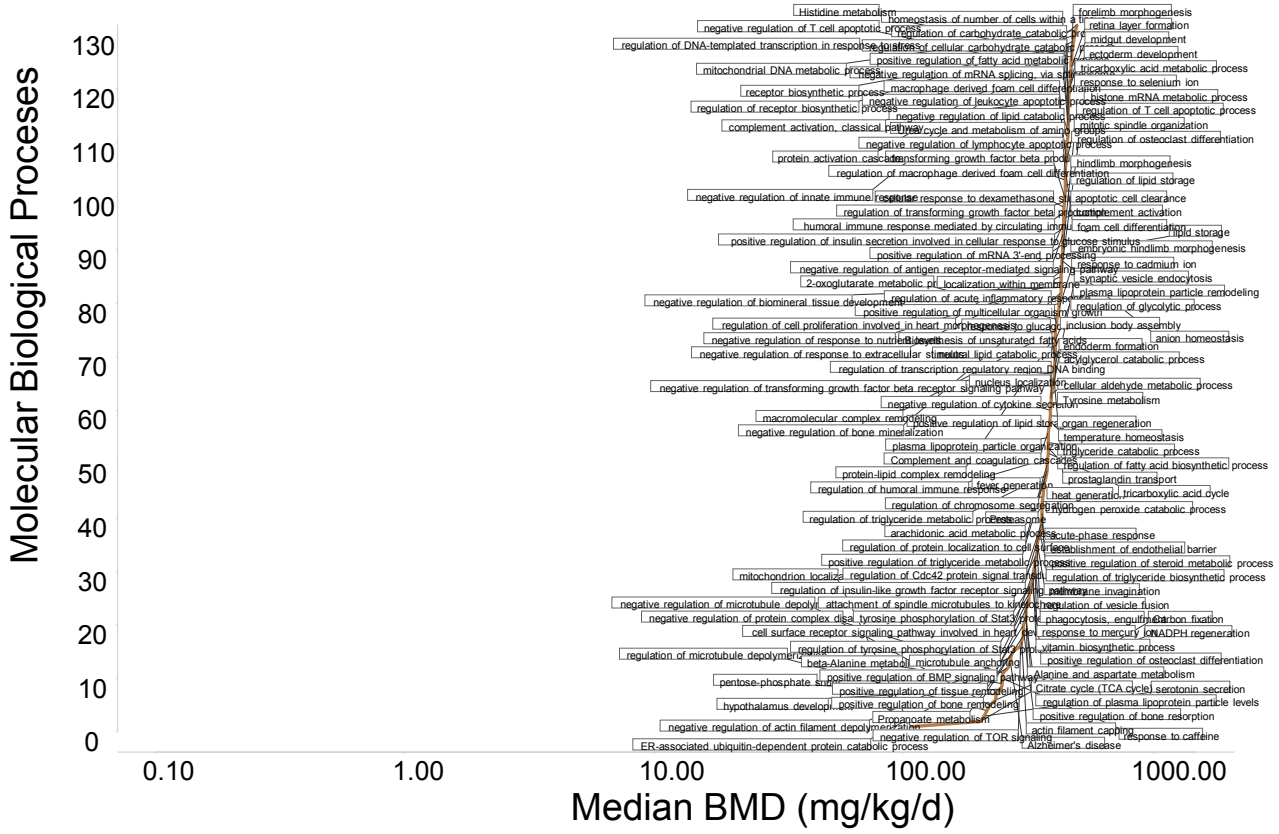
Test Article [Abbreviation, CAS Number]	Studies							
	Rat Prenatal Toxicity	Mouse Dermal Irritation and Hypersensitivity	5-Day Rat Toxicogenomic	Bacterial Mutagenicity	Zebrafish Developmental	Nematode Toxicity	High Throughput Screening	Structure Activity Relationship (SAR) Analysis
4-Methylcyclohexanemethanol [MCHM, 34885-03-5]	X	X	X	X	X	X	X	X
Dipropylene glycol phenyl ether [DiPPH, 51730-94-0]			X	X	X	X		X
Propylene glycol phenyl ether [PPH, 770-35-4]			X	X	X	X	X	X
1,4-Cyclohexanedimethanol (CHDM; 105-08-8)				X	X	X	X	X
2-Methylcyclohexanemethanol [2MCHM, 2105-40-0]				X	X	X		X
4-(Methoxymethyl)cyclohexanemethanol [MMCHM, 98955-27-2]				X	X	X		X
4-Methylcyclohexanecarboxylic acid [4331-54-8]					X	X		X
Cyclohexanemethanol, 4-[(ethenyloxy)methyl]- [114651-37-5]					X	X	X	X
Cyclohexanemethanol, alpha,alpha,4-trimethyl- [498-81-7]					X	X		X
Dimethyl 1,4-cyclohexanedicarboxylate [DMCHDC, 94-60-0]				X	X	X	X	X
Methyl 4-methylcyclohexanecarboxylate [MMCHC, 51181-40-9]				X	X	X		X
Phenoxyisopropanol [4169-04-4]					X	X	X	X
Technical product [“crude MCHM”]		X	X	X	X	X		

Summary findings

- MCHM and most of the spill chemicals were inactive in the “screening studies”
- MCHM was a mild irritant but not a sensitizer and crude MCHM was a mild irritant and weak sensitizer.
- MCHM and crude MCHM produced changes in biological activity at doses of approximately 100 mg/kg/day (approximates 1000 ppm in drinking water).
  - PPH produced changes in biological activity at doses in the range of 1 mg/kg/day (approximates 30 ppm in drinking water).
- At doses well in excess of the drinking water advisory level MCHM was toxic to developing rats. Toxicity in the developing rats was observed at dose levels where there was no maternal toxicity. The most sensitive effect in the Rat Developmental Toxicity Study of MCHM was decreased fetal weight.

5-Day Rat Toxicogenomics for MCHM

- Rat liver microarray
- Identification of BMDs for biological processes



Outcome

- Data produced by NTP to date supports a focus on MCHM in determining the health risks associated with the spill and the selection of 100 mg/kg/day as a point of departure on which to base a drinking water advisory level.

- A focus on “dose”, as opposed to a focus on a comprehensive assessment of hazard, was a pragmatic solution to the question and afforded a more rapid evaluation.

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Lessons learned from a program like NTP

- Mission driven
  - Team science/project centric model vs “Investigator-group” model
- Centralized operational funding
  - Flexibility with “capabilities”
  - Adapts multi year programs/studies within a 1 yr-cycle funding NIH budget system
- Pipeline management
  - Diverse drivers make it hard to manage priorities within such an operationally driven pipeline
- Headquartered within NIH
  - A biomedical applied research organization not a specific regulatory agency
  - Freedom to push the boundaries of what data *could* be used vs data that is *asked* for within confines of current regulatory framework

Transparency

- CEBS; all data available to individual level
  - Anyone can use ALL the data
  - People can it use it disagree with our conclusions
  - Open peer review of reports
- Literature analyses:
  - OHAT systematic review
  - Public review of PECO statements/protocol review
- Open access tools for data visualization
  - User interrogation of data
  - HAWK
- ICCVAM
  - Public forums for direct engagement
  - New approaches for more rapid ”fit for purpose” validation.

"NTP exists to develop the information and the tools that both agencies of government and industry need so that we can all live together safely in the same world."

David P. Rall, 1981

NIEHS Director 1971-1990

NTP Director 1978-1990

National Institute of Environmental Health Sciences

National Toxicology Program
U.S. Department of Health and Human Services

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