# Increasing the confidence in read-across of chemicals with *new approach methods data*

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## Acknowledgements:

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Nicole Kleinstreuer (NIEHS)

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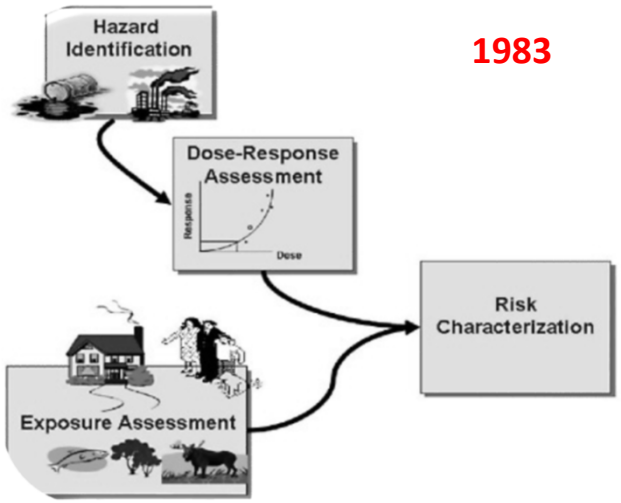
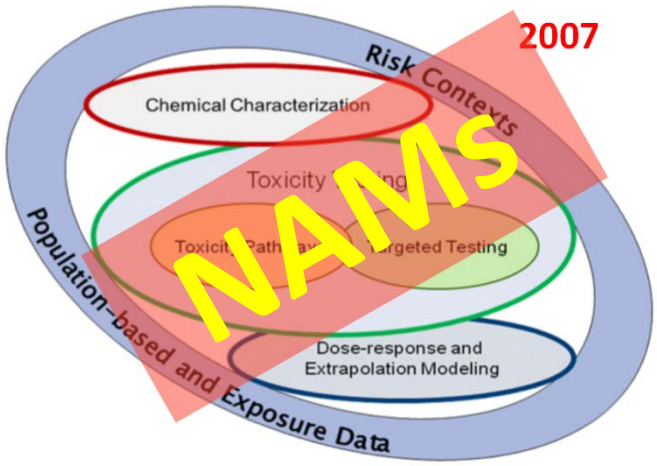
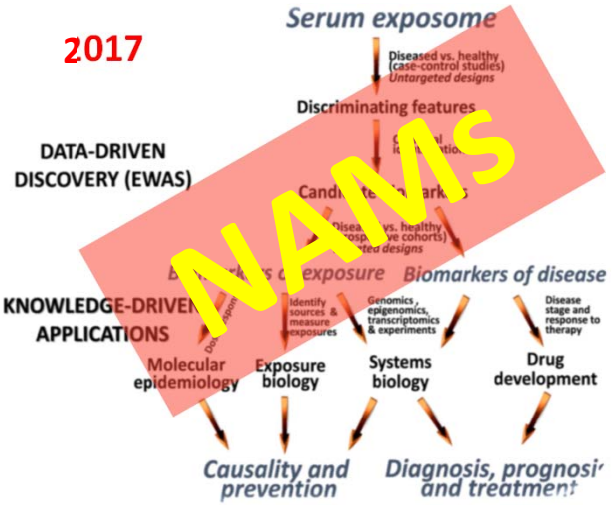
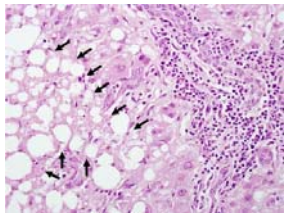

1983
Hazard Identification
Dose-Response Assessment
Response
Dose
Exposure Assessment
Risk Characterization

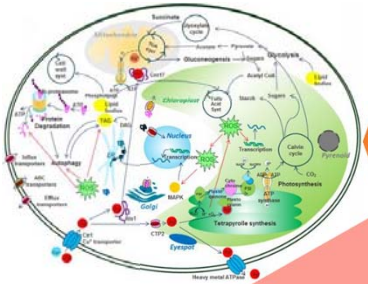

2007
Risk Contexts
Chemical Characterization
Toxicity Testing
Toxicity Pathway-Targeted Testing
Dose-response and Extrapolation Modeling
Population-based and Exposure Data
NAMs


2017
Serum exposome
Diseased vs. healthy (case-control studies)
Untargeted designs
Discriminating features
DATA-DRIVEN DISCOVERY (EWAS)
Biomarkers of disease
KNOWLEDGE-DRIVEN APPLICATIONS
Molecular epidemiology
Exposure biology
Systems biology
Drug development
Causality and prevention
Diagnosis, prognosis and treatment
NAMs

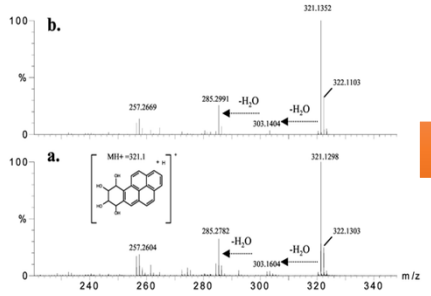



FINE GOLD
999.9


MAYBE
YES
NO




STÄUBLI


b.
a.
321.1352
322.1103
257.2669
285.2991
303.1404
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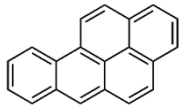
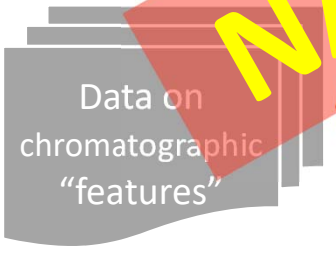
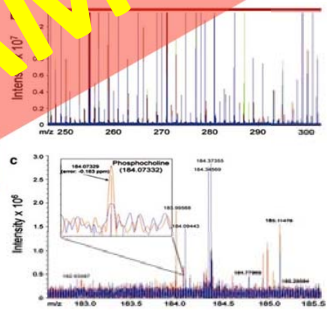
322.1303
285.2782
257.2604
303.1604
240
260
280
300
320
340
m/z

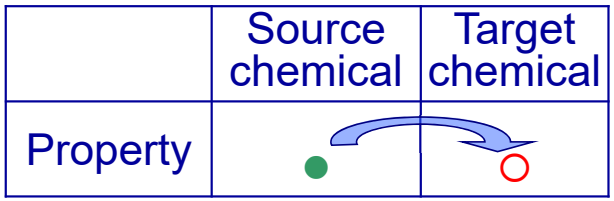



Data on chromatographic "features"


Phosphocholine (184.07332)

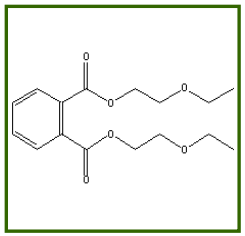
# Definitions: Read-across

- **Read-across** is a method of filling a data gap whereby a chemical with existing data values is used to make a prediction for a '***similar***' chemical
- **Target chemical** is a chemical which has a data gap that needs to be filled i.e. the subject of the read-across
- **Source analogue** is a chemical that has relevant data and has been identified as an appropriate analogue for use in a read-across based on ***similarity*** to the target chemical



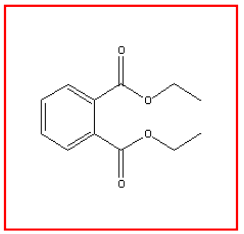

● Reliable data

○ Missing data



Known to be harmful

Acute toxicity?



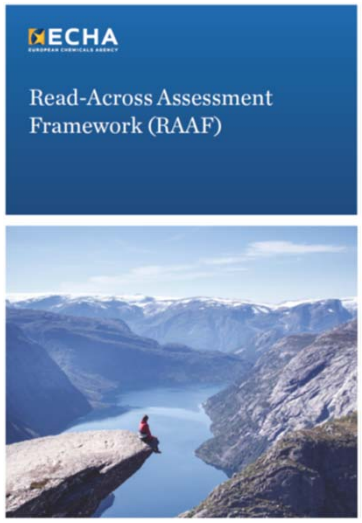
Predicted to be harmful

## Read-across approaches:

- **Analogue** approach (data from a **source** chemical is read across to the **target** chemical)
- **Category** approach (from ***multiple*** source chemicals to the target chemical)

**3 ways to demonstrate "similarity":**

**(i) functional group,**
**(ii) common precursors, and**
**(iii) constant pattern in the changes of potency across the group**




March 2017

## ECHA RAAF read-across scenarios:

1. **Analogue** approach: Common toxicant causing same effect
2. **Analogue** approach: Same effect caused by different toxicants
3. **Category** approach: Common toxicant causing same effect, effect varies (trend) across members
4. **Category** approach: Same effect caused by different toxicants, effect varies (trend) across members
5. **Category** approach: Common toxicant causing same effect, effect does not vary across members
6. **Category** approach: Same effect caused by different toxicants, effect does not vary across members

| Read-Across Scenarios: Characteristics of Anchor and Data-Sparse (DS) Chemicals | Inferring Hazard and Dose-Response Relationships for Data-Sparse (DS) Chemicals from Anchor Chemicals | Examples |
|---|---|---|
| Anchor and DS chemicals are all metabolized to same toxic metabolites. | Hazard: Assume same Dose-Response: Adjust for pk in metabolite formation | Dyes that metabolize to dimethoxybenzidine |
| Anchor and DS chemicals have highly similar metabolic activation. Anchor chemicals show same hazards. | Hazard: Assume same Dose-Response: Adjust for pk and bioactivity of metabolites | Various glycol ethers metabolized to alkoxyacids, sets of nitrosoamines |
| Anchor and DS chemicals have highly similar patterns of upstream biological effect. Anchor chemicals show same hazards. | Hazard: Assume same Dose-Response: Adjust for pk and differences in levels of bioactivity | Dioxin-like compounds (dioxins, furans, co-planar PCBs), PBDEs |
| Anchor and DS chemicals have similar patterns of biological activity. Anchor chemicals show similar and related but not identical hazards | Hazard: Assume hazard based on upstream testing Dose-Response: Adjust for pk and bioactivity after testing | Sets of *ortho*-Phthalates, PAHs |

National Academies Report [2017]: Using 21st Century Science to Improve Risk-Related Evaluations

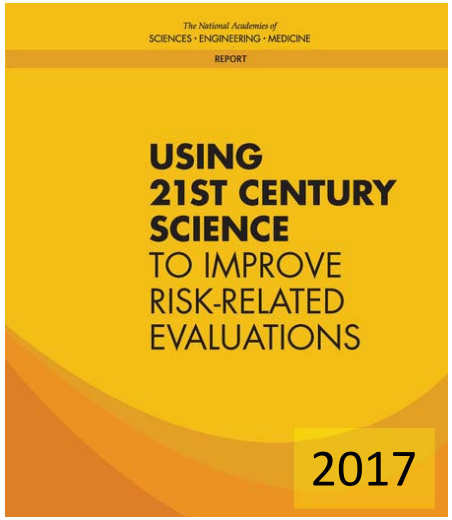
**Tab. 1: Reasons for the rejection of the use of read-across in disseminated compliance check decisions published on the ECHA website by July 31, 2015**

| Reason for rejection | No. of cases |
|---|---|
| Unclear substance identity, not possible to ascertain structural similarity<br>– A significant issue for UVCB substances with a severe impact on large UVCB categories using a combination of read-across and targeted testing | 48 |
| Lack of sufficient evidence to substantiate assumptions made within read-across justifications<br>– Including lack of data on analogues provided in dossier | 43 |
| Read-across to inappropriate data<br>– For example read-across to a reproductive screening study to address higher tier reproductive and developmental study requirements | 5 |
| Lack of scientific plausibility<br>– Disagreement with hypothesis, data not supportive of arguments presented, too much uncertainty<br>– This often combined with the lack of sufficient evidence/information | 20 |

http://dx.doi.org/10.14573/altex.1601251

"Nonetheless, since registrants have made extensive use of alternative methods and adaptation possibilities provided in REACH Annexes VII-XI instead of providing data from experimental studies, verification of the compliance of dossiers in the highest tonnage bands will still require sustained effort over the next years. In particular, ***adaptations based on read-across and weight of evidence are often poorly documented and justified, and are not acceptable***."

Report on the Operation of REACH and CLP 2016




## *Committee Charge:*

- **to provide recommendations on integrating new scientific approaches into risk-based evaluations**

## *Committee Sponsors:*

- US Environmental Protection Agency
- US Food and Drug Administration
- National Institutes of Health (NIEHS and NCATS)

| *TOXICOLOGY* | *EPIDEMIOLOGY* | *EXPOSURE* | *STATISTICS* |
|---|---|---|---|
| George Daston | Jonathan Samet | Melvin Andersen | David Dunson |
| Nigel Greene | Esteban Burchard | Jon Arnot | Fred Wright |
| Heather Patisaul | Beate Ritz | Justin Teeguarden | |
| Kristi Pullen | Paolo Vineis | | |
| Ivan Rusyn | Michelle Williams | | |
| Robert Tanguay | | | |
| James Tiedje | | | |
| Lauren Zeise | | | |

*"Exposure scientists, toxicologists, epidemiologists, and other [subject matter experts] need to collaborate closely to ensure that the full potential of 21st century science is realized."*

http://dels.nas.edu/Report/Using-21st-Century-Science-Improve/24635

# Using 21st Century Science in Decision-Making: Defining the Areas of "Fit for Purpose"

**Priority-setting:** Can be based on hazard, exposure, or risk

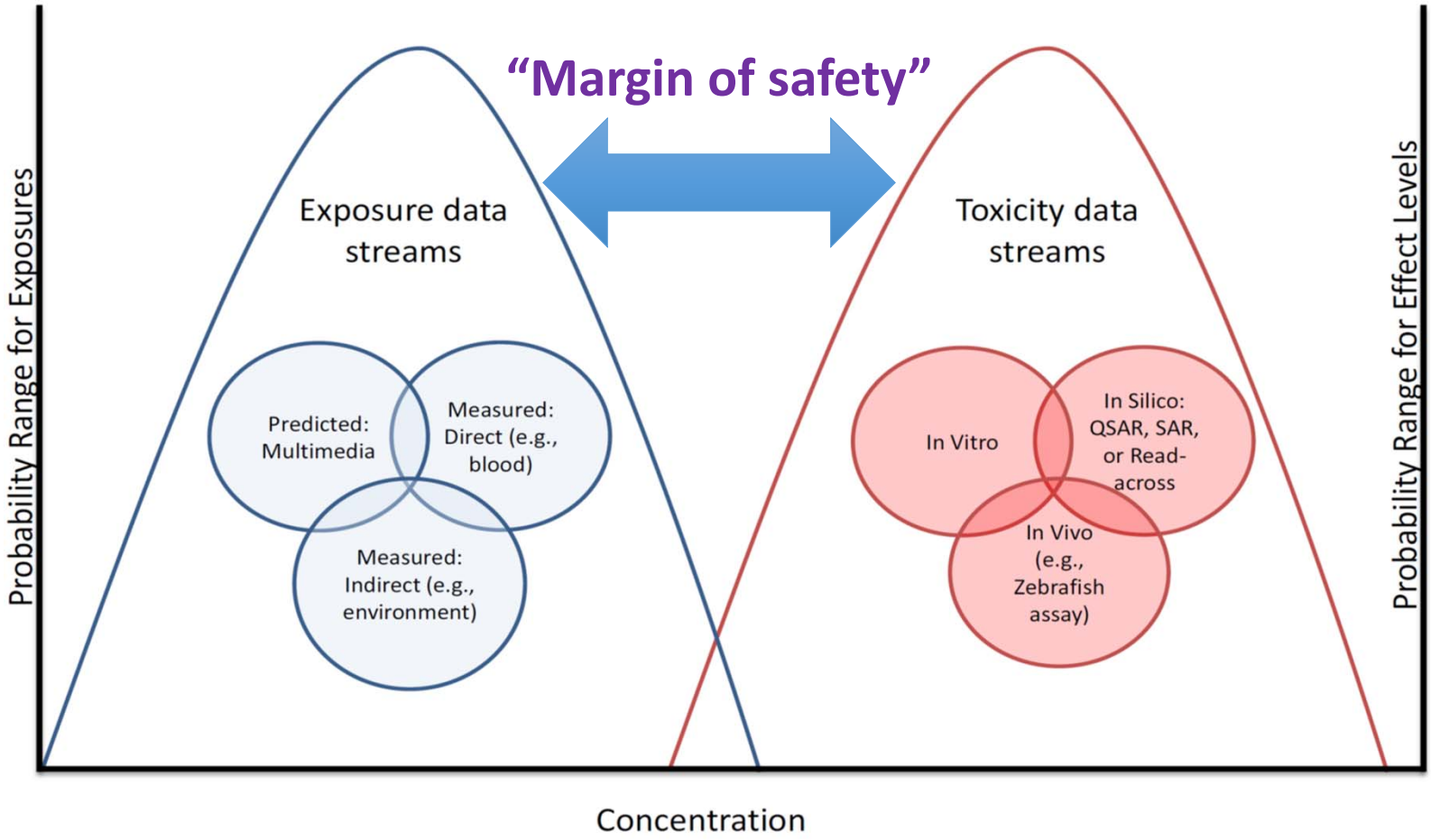
**Assessment of mono-constituent chemicals:** Can be included in traditional chemical hazard and dose-response assessments of various regulated substances, such as pesticides, drugs, and food additives

**"Site-specific" assessments:** Can involve selection of geographic sites or chemicals/mixtures at a contaminated site

**Assessment of new and complex chemistries:** Can involve assessment of green chemistry, new and *complex substances*, and unexpected environmental degradation products of chemicals in commerce

http://dels.nas.edu/Report/Using-21st-Century-Science-Improve/24635

# Priority-setting

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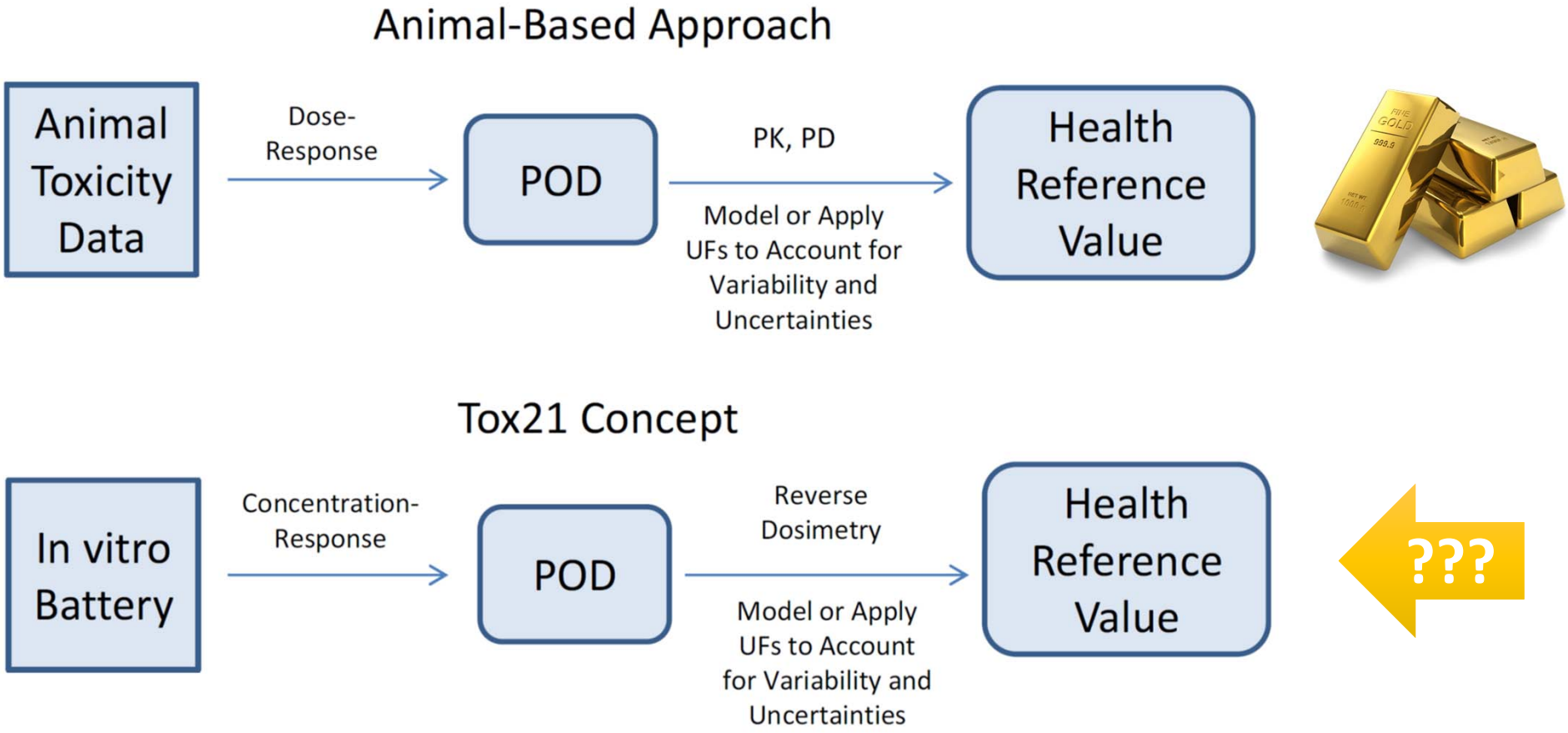
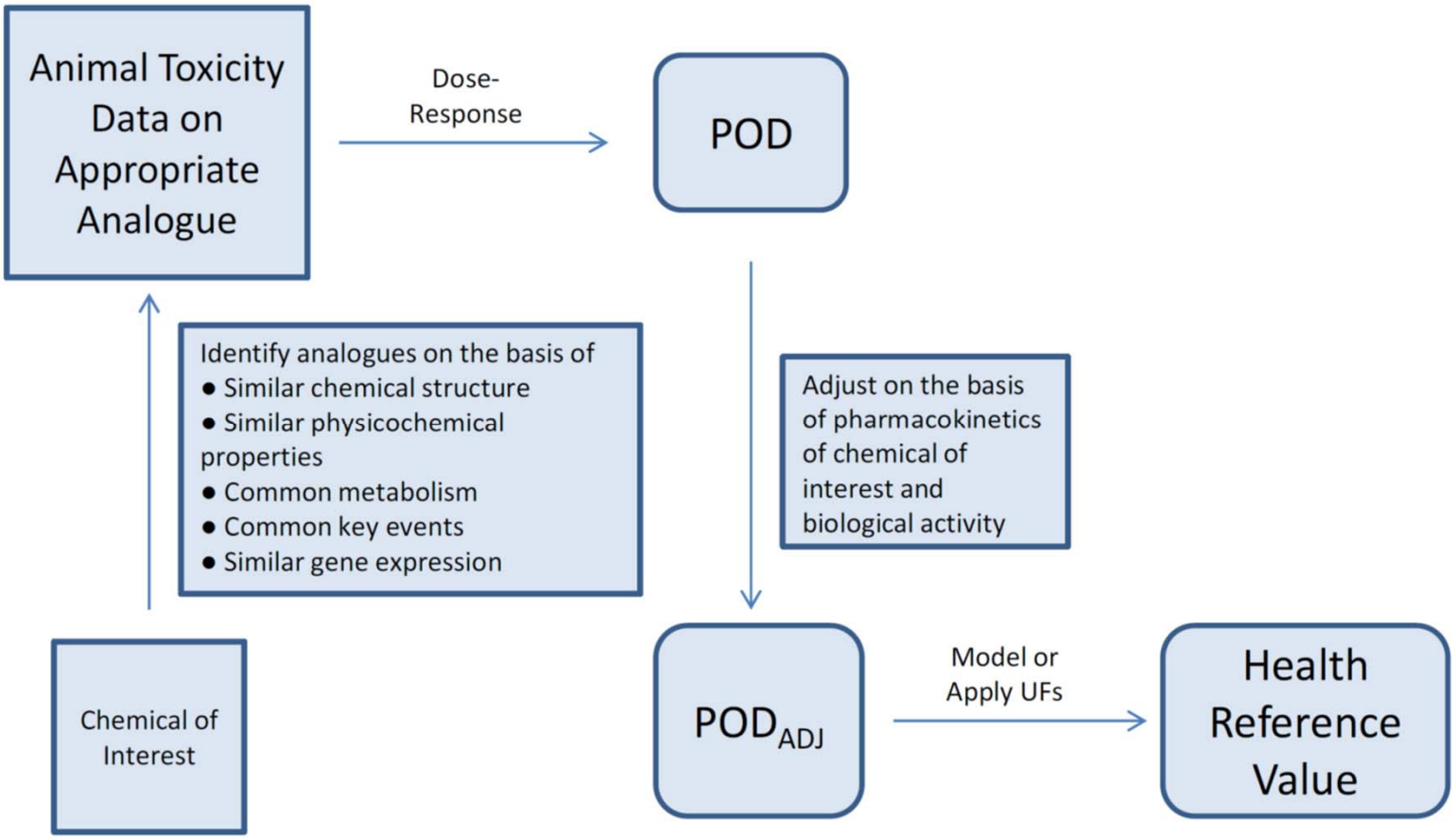
# Assessment of mono-constituent chemicals




http://dels.nas.edu/Report/Using-21st-Century-Science-Improve/24635

# Assessment of mono-constituent chemicals

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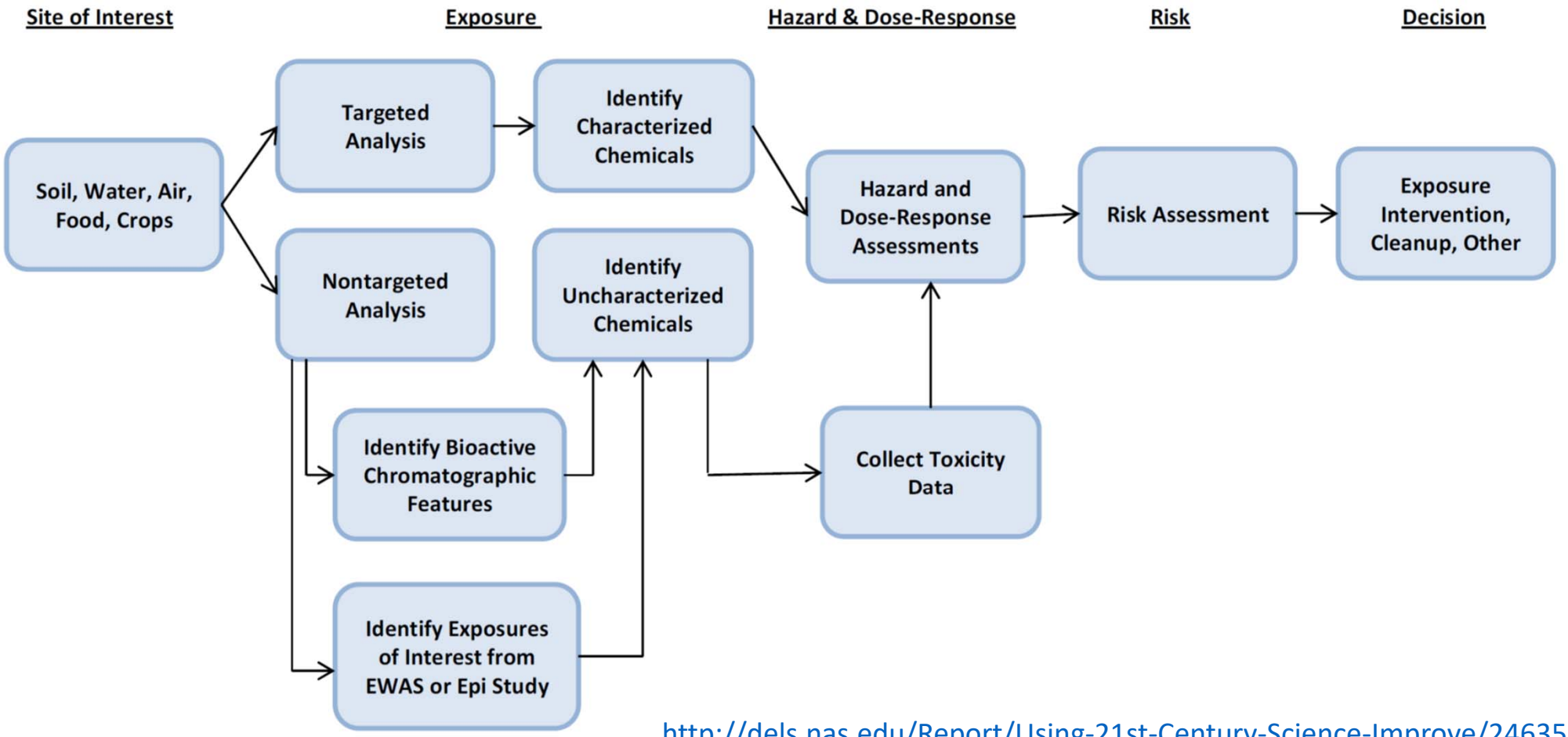
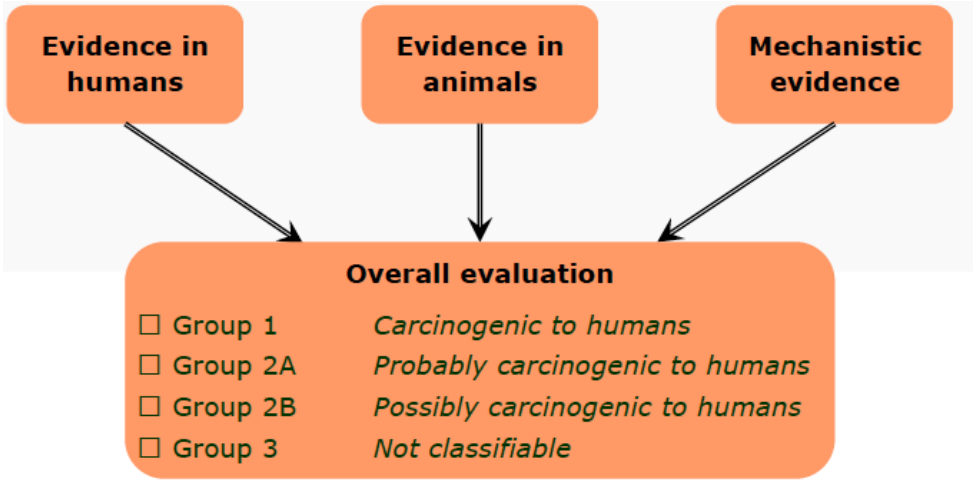
# “Site-specific” assessments




http://dels.nas.edu/Report/Using-21st-Century-Science-Improve/24635

# Use of a "Mechanistic Class" for Cancer Hazard ID

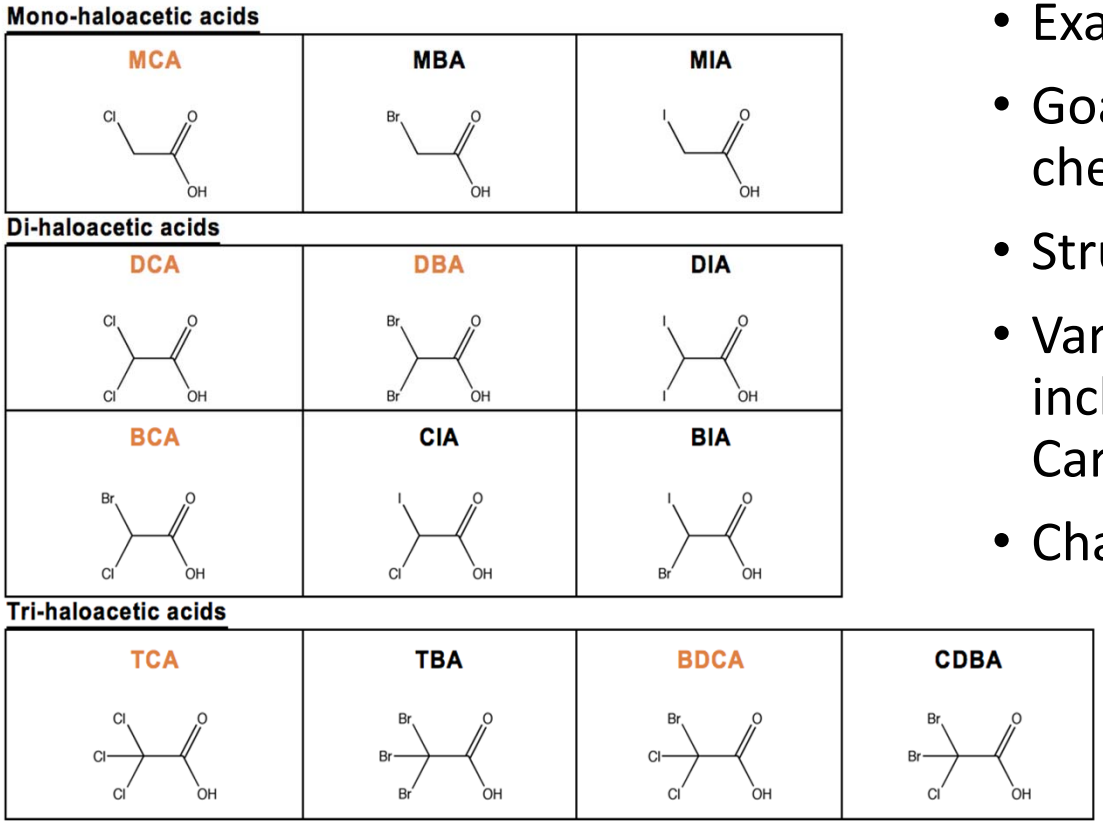
**International Agency for Research on Cancer (IARC)**
Monographs Program evaluates causes of human cancer (hazard identification)




- Classes can be defined by a single common agent
  - Dyes metabolized to benzidine
- Mechanistic class can be defined by similar biological activity
  - Vinyl halides; PCBs; Air pollution
- **Mechanistic data alone can be used as a basis for classification**
  - Using Key Characteristics of Carcinogens as an organizing principle

https://monographs.iarc.fr/cards_page/preamble-monographs/

# “Read-across” of Haloacetic acids for Cancer Hazard ID




- Example from NTP Report on Carcinogens
- Goal: establish carcinogenicity hazard for a chemical class using “new approach data”
- Structural similarity for HAAs is well known
- Variety of *in vivo*, *in vitro*, and *in silico* data, including use of Key Characteristics of Carcinogens to organize mechanistic data
- Challenges:
  - Lack of clear trends, or a common MOAs
  - Conclusions only reached on HAAs metabolized to common moiety that is already “reasonably anticipated to be a human carcinogen”

https://ntp.niehs.nih.gov/ntp/roc/monographs/haafinal_508.pdf

# Read-Across in Risk Assessment by US EPA: A "Tiered Surrogate Approach"

Regulatory Toxicology and Pharmacology 63 (2012) 10–19

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

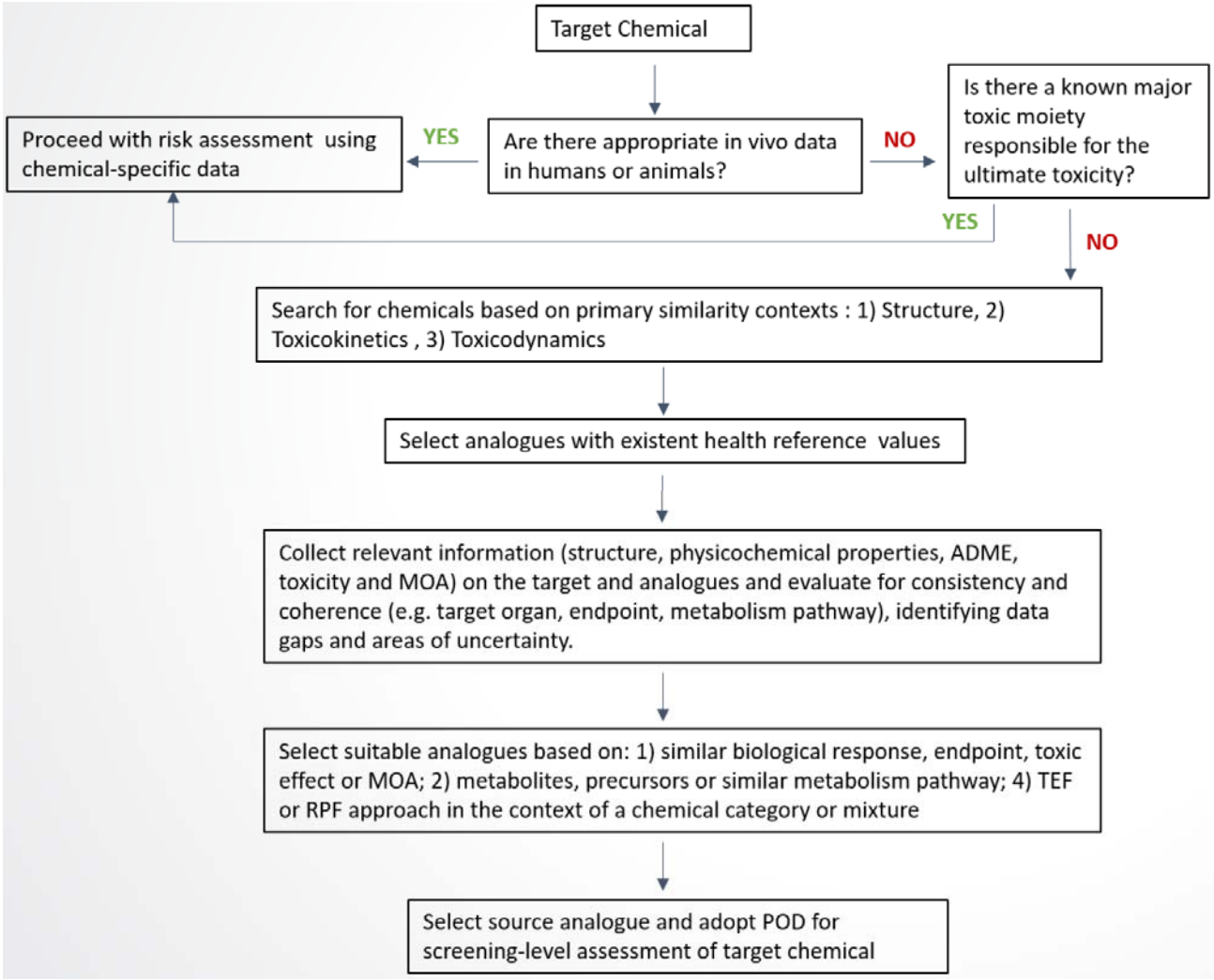
journal homepage: www.elsevier.com/locate/yrtph

Application of computational toxicological approaches in human health risk assessment. I. A tiered surrogate approach

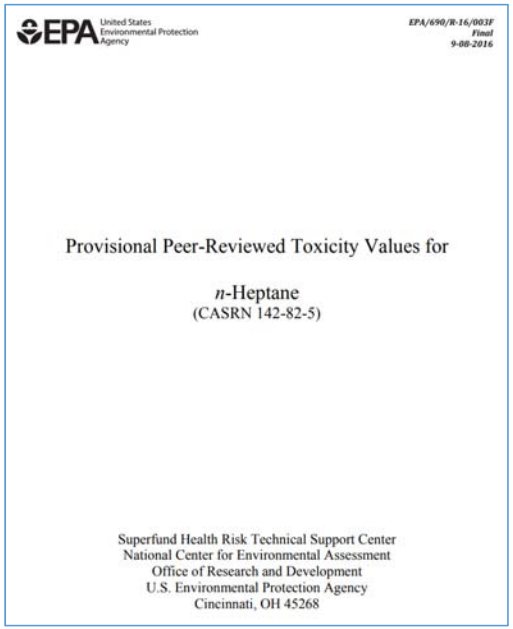
Nina Ching Yi Wang [a,*], Q. Jay Zhao [a], Scott C. Wesselkamper [a], Jason C. Lambert [a], Dan Petersen [a], Janet K. Hess-Wilson [b]

[a] National Center for Environmental Assessment, US Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268, United States
[b] US Air Force Center for Engineering and the Environment, Technical Division, Restoration Branch, 3515 S. General McMullen, San Antonio, TX 78226, United States

"…the Superfund Health Risk Technical Support Center [may use] available information in an **appendix** and develop a "screening value." Appendices **receive the same level of internal and external scientific peer review as the PPRTV** documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that **there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value** than for a value presented in the body of the assessment."



# Read-Across in Action: Case Study of *n*-Heptane (US EPA PPRTV Program, 2016)



EPA United States Environmental Protection Agency

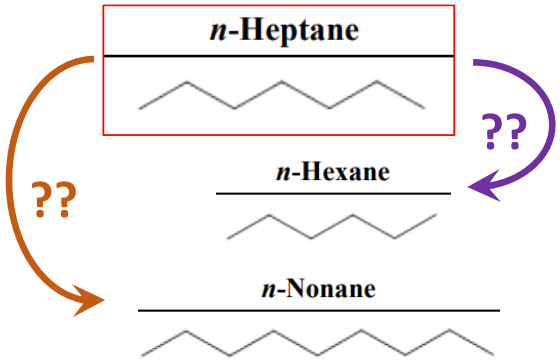
EPA/690/R-16/003F
Final
9-08-2016

Provisional Peer-Reviewed Toxicity Values for

*n*-Heptane
(CASRN 142-82-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

"…the database for continuous exposure to n-Heptane **is inappropriate for the derivation of provisional oral toxicity values**. However, information is available for this chemical, [thus] a "**screening value**" [can be derived]"




**N-Nonane Oral 90 day study**

*Table 5. Incidence of Tissue Lesions*[a]

| Lesion | Dose (mg/kg-day) 0 Mice | 0 Rats | 100 Mice | 100 Rats | 1000 Mice | 1000 Rats | 5000 Mice | 5000 Rats |
|---|---|---|---|---|---|---|---|---|
| *Stomach (nonglandular)—squamous epithelial hyperplasia/hyperkeratosis* | 0/9 | 0/10 | 6/10 | 8/10 | 7/8 | 10/10 | 8/8 | 10/11 |
| *Proximal Duodenum—inflammation (mild)* | 0/7 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 2/10 |
| *Rectum—perianal hyperplasia, hyperkeratosis and inflammation* | 0/9 | 0/10 | 0/10 | 0/10 | 2/10 | 5/10 | 8/10 | 9/11 |
| *Nasal Turbinates—rhinitis* | 0/9 | 0/10 | 0/10 | 1/9 | 0/10 | 7/10 | 4/10 | 9/10 |

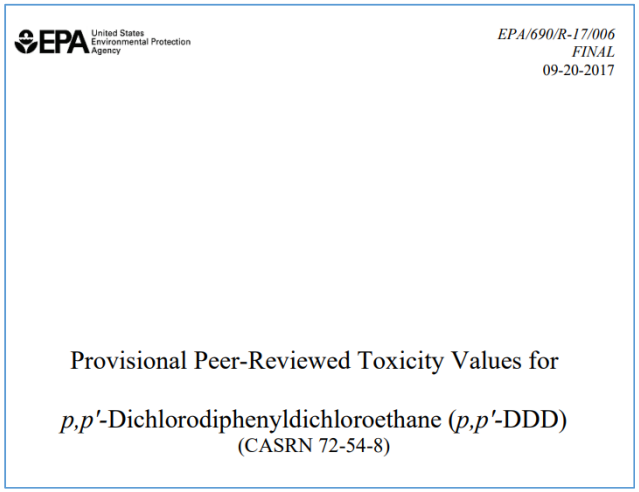
[a]Dodd et al., 2003; C57BL/6 mice; Fischer 344 rats

**Screening Subchronic p-RfD** = Surrogate POD ÷ $UF_C$
= 3.13 mg/kg-day ÷ 1,000
= **$3 \times 10^{-3}$ mg/kg-day**

**(For n-Hexane!)**

- **Similarity Context 1:** n-Hexane and n-Nonane are compounds that have high structural similarity to *n*-Heptane (>84%)
- **Similarity Context 2:** *n*-Nonane is metabolized *in vivo* similarly to *n*-Heptane (higher relative amounts of the 2-and 3-alcohol and g-valerolactone metabolites formed, compared to the neurotoxic g-diketone compounds from *n*-Hexane candidate analogue)
- **Similarity Context 3:** *n*-Nonane-induced proliferative forestomach lesions are similar to the lesions observed after oral *n*-Heptane exposure (as compared to unique n-Hexane induced neurotoxicity)

# Read-Across in Action: Case Study of *p,p'*-DDD (US EPA PPRTV Program, 2017)

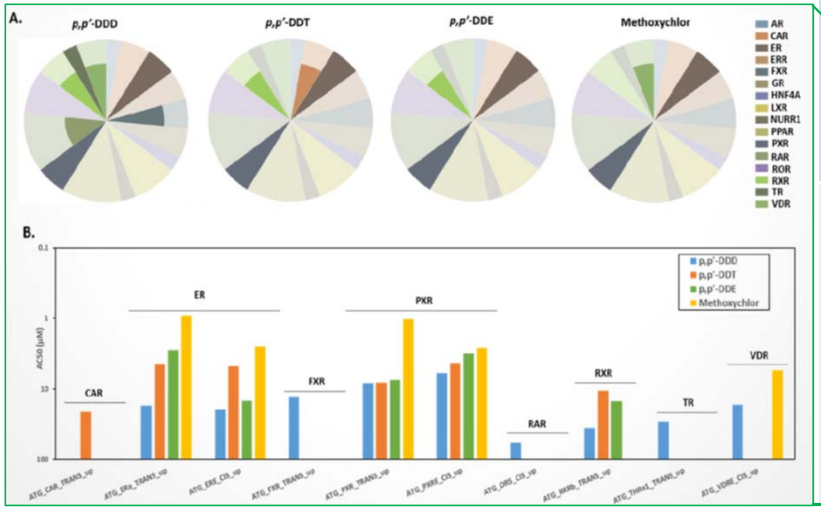


EPA United States Environmental Protection Agency

*EPA/690/R-17/006*
*FINAL*
09-20-2017

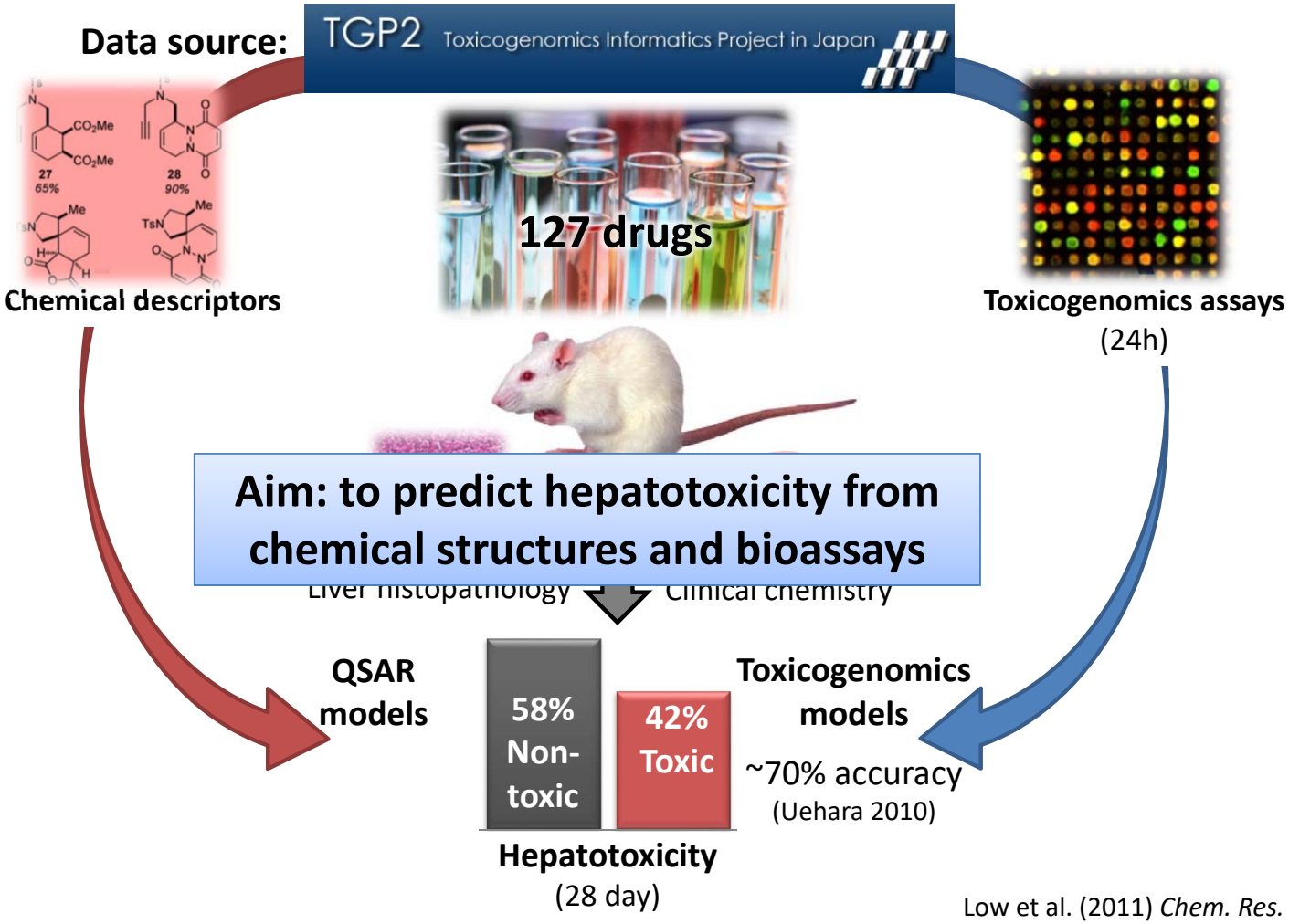
Provisional Peer-Reviewed Toxicity Values for

*p,p'*-Dichlorodiphenyldichloroethane (*p,p'*-DDD)
(CASRN 72-54-8)



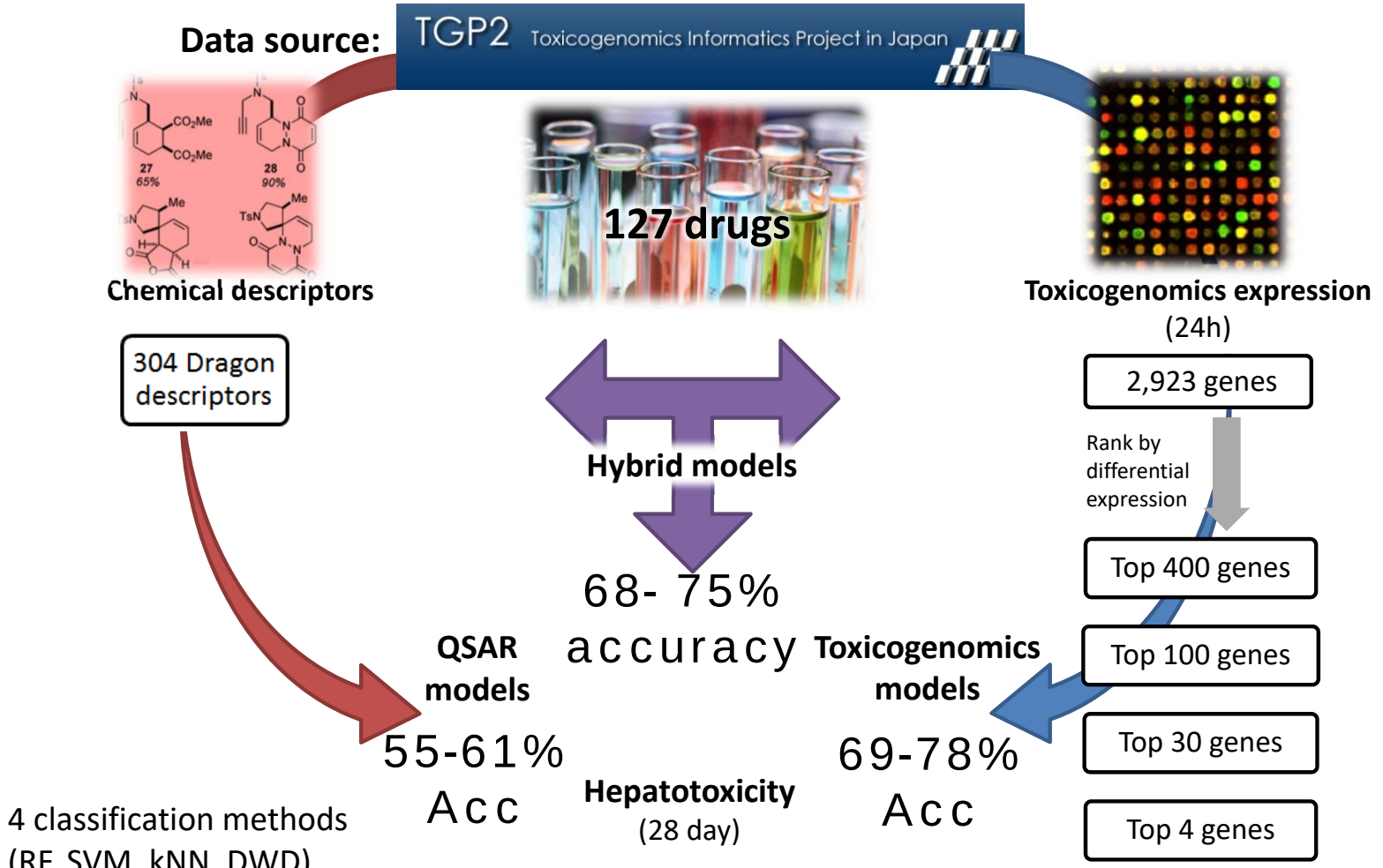

| Similarity Context | Summary of Findings |
|---|---|
| Structure and physicochemical properties | • *p,p'*-DDD and identified analogues (*p,p'*-DDT and *p,p'*-DDE and methoxychlor) demonstrate similarities in basic structural features (chlorinated diphenylalkane structure)<br>• *p,p'*-DDT and *p,p'*-DDE also share key functional groups (*p,p'*-chlorine substituents) and physicochemical properties important for bioavailability (lipophilicity and low BCF values) with *p,p'*-DDD |
| Toxicokinetics | • *p,p'*-DDT is a metabolic precursor of *p,p'*-DDD and both chemicals show similarities in toxicokinetics (Absorption, Distribution and Metabolism [ADME]) in humans and experimental animal models (preferential partitioning into fat, similar metabolism and excretion pathways and prolonged elimination rates)<br>• Other analogues demonstrate differences in ADME in comparison to the target. *p,p'*-DDE is less metabolically active; methoxychlor is metabolized differently and appears to be less bioaccumulative |
| Toxicodynamic | • Consistency and coherence across health effects in experimental animals for non-cancer oral toxicity among the analogues point to putative toxicity targets for *p,p'*-DDD (primarily liver and reproductive toxicity)<br>• Similarities in *in vitro* bioactivity profiles from ToxCast assays between the target and analogues with respect to cell-specific responses and target gene pathways provide mechanistic plausibility for the liver and reproductive effects associated with this group of chemicals |

# Combining chemical descriptors and bioassays



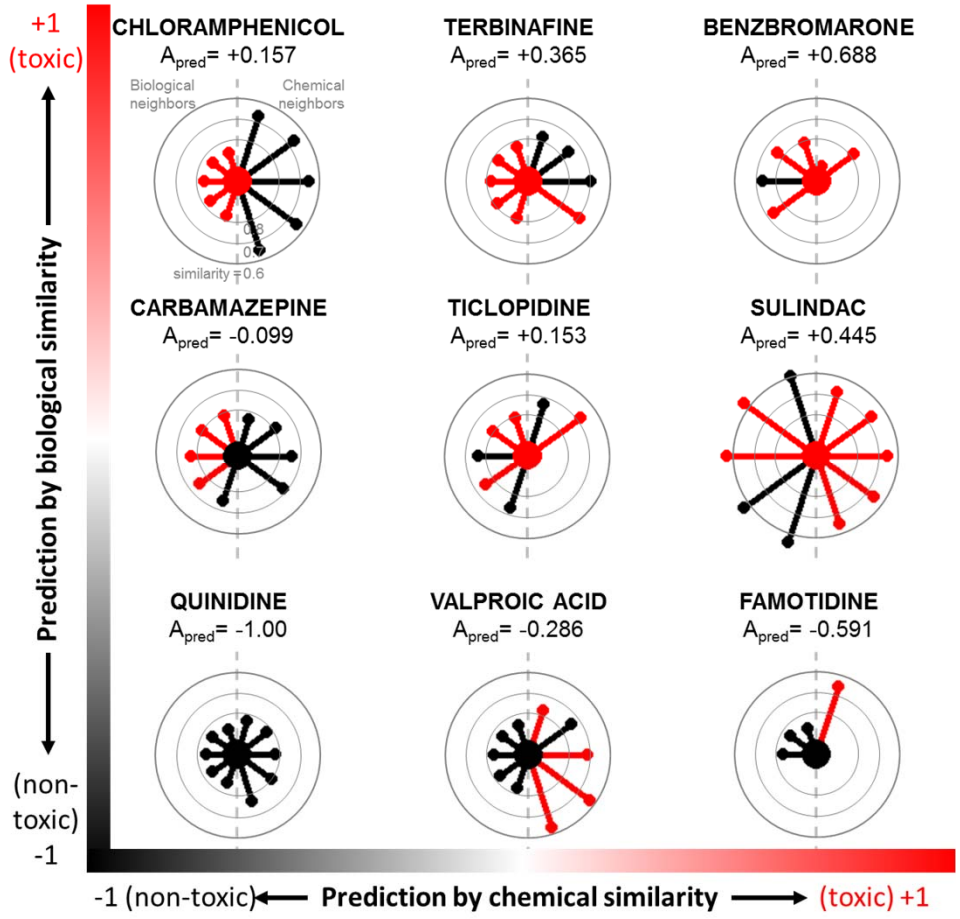

Low et al. (2011) *Chem. Res. Toxicol.* 24, 1251-1262

# Results: QSAR models < Hybrid models < Toxicogenomics models




Low et al. (2011) *Chem. Res. Toxicol.* 24, 1251-1262

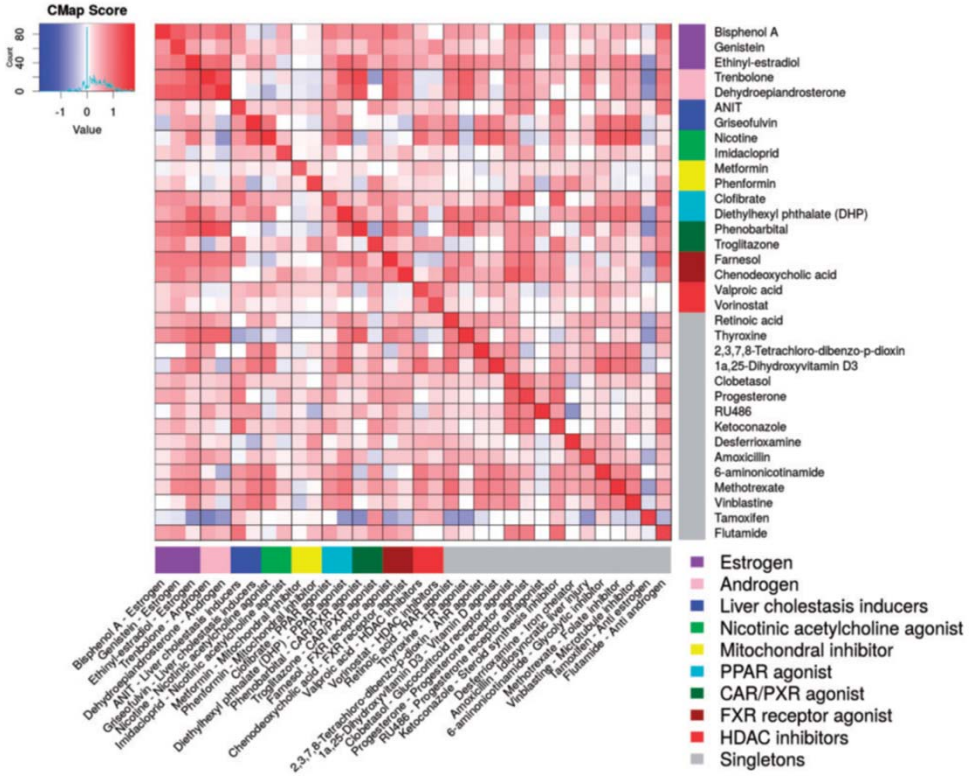
# Chemical-Biological Read-Across (CBRA) allows visual comparison of multiple compounds




Low et al. (2013) *Chem. Res. Toxicol.* 26(8):1199-208.

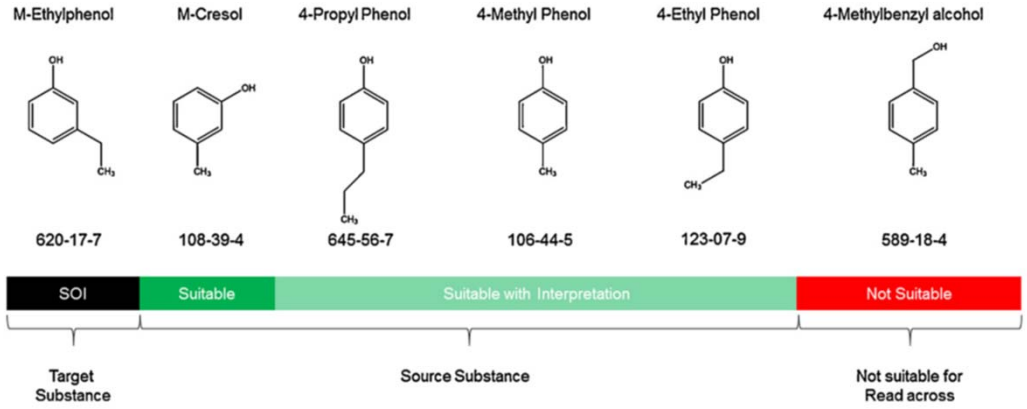
# Use of connectivity mapping and genomics to support read across

- Test 100s of chemicals in many *in vitro* cells
- Collect high-throughput gene expression data
- Find chemicals that are best “analogues”

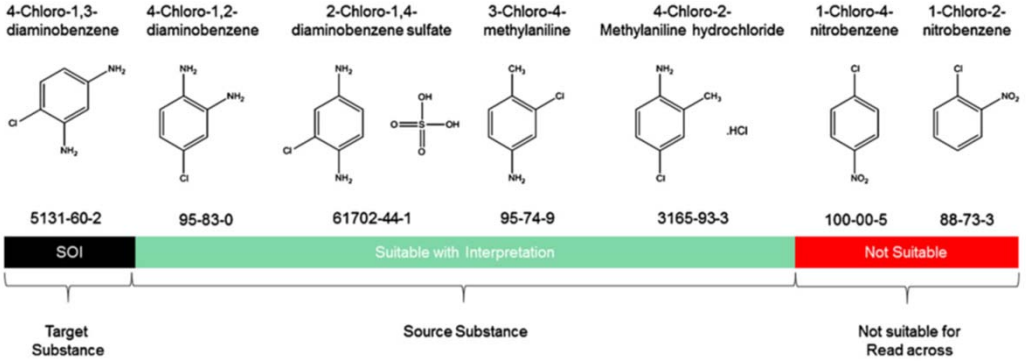



DeAbrew et al Tox Sci 151 (2016) 447–461

## Alkyl Phenol Case Study




## Diaminobenzene Case Study




DeAbrew et al Toxicology 423 (2019) 84–94

# US EPA's GenRA v1 – Approach

**I. Data**
1,778 Chemicals
3,239 Structure descriptors (chm)
820 Bioactivity hitcall (bio)
ToxCast

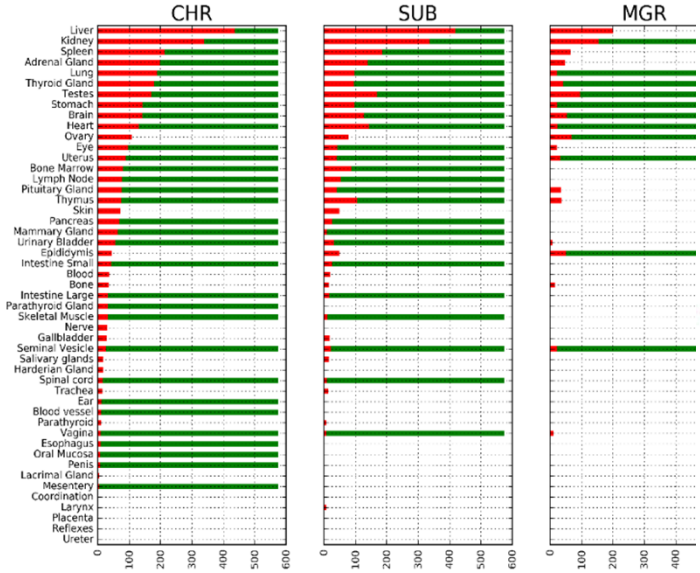
574 toxicity effects (tox) ToxRefDB

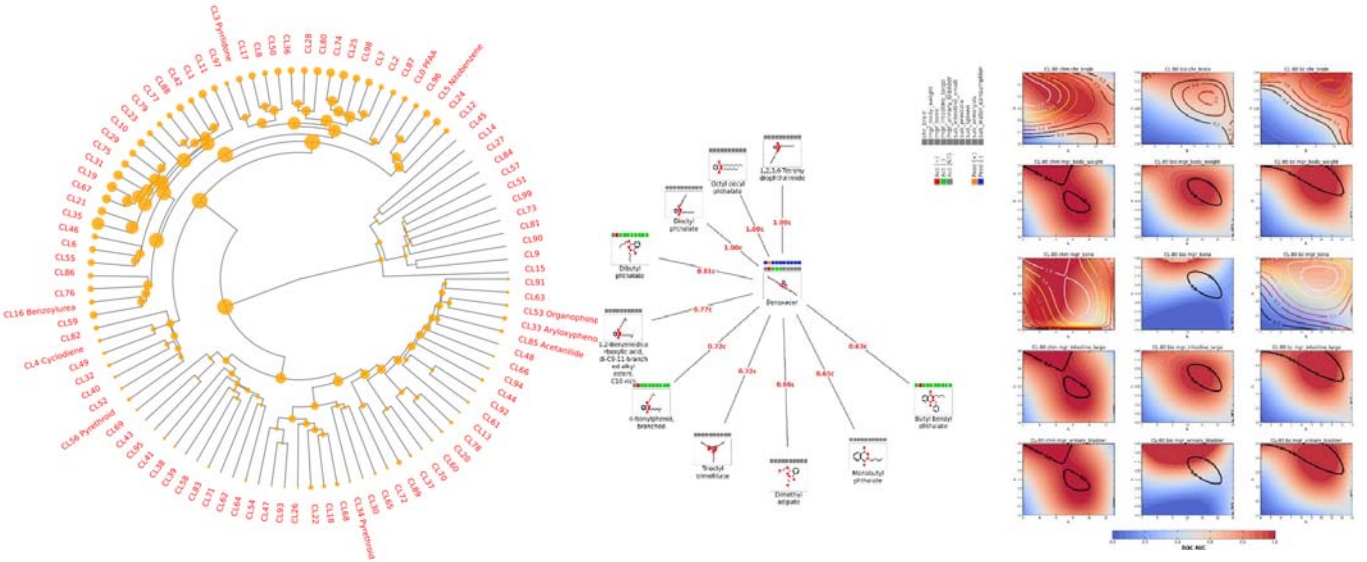
**II. Define Local neighborhoods**

Use K-means analysis to group chemicals by similarity
Use cluster stability analysis
~ 100 local neighborhoods

**III. GenRA**

Use GenRA to predict toxicity effects in local neighborhoods
Evaluate impact of structural and/or bioactivity descriptors on prediction
Quantify uncertainty

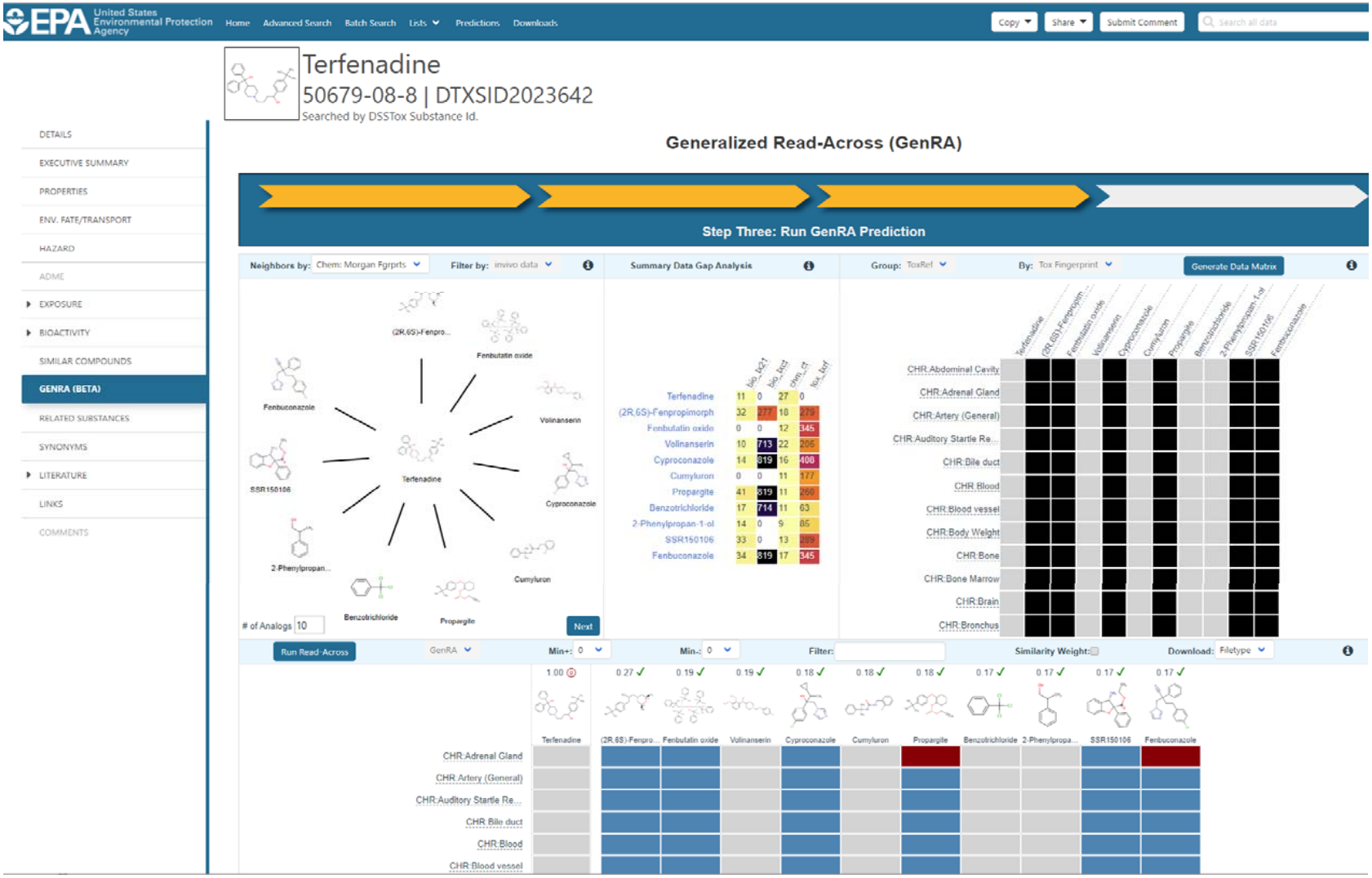


Slide courtesy of Dr. Grace Patlewicz (US EPA)

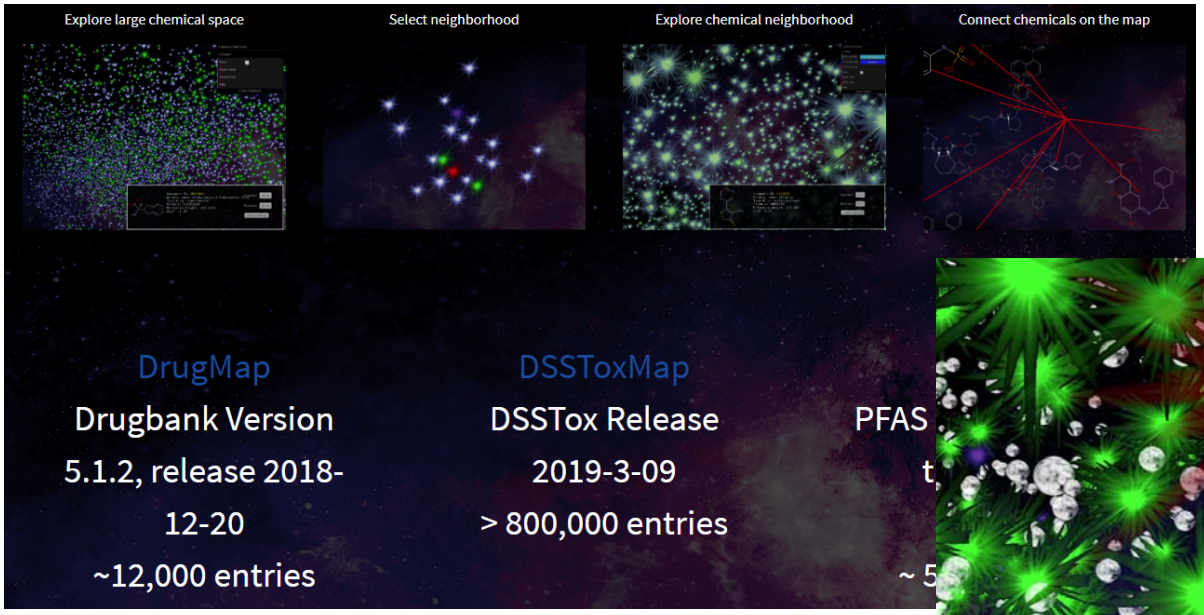
Shah et al. Regul Toxicol Pharmacol. 2016; 79:12-24

**https://comptox.epa.gov/dashboard/**




ALTEX. 2019 Feb 4. doi: 10.14573/altex.1811292. [Epub ahead of print]

# “Exploring drug space with *ChemMaps.com*”




***Chemical space:*** a complex compendium of 1D, 2D and 3D pre-computed molecular descriptors to generate the chemical space in three dimensions

***Web interface:*** an interactive, mouse-based, easy-to-use navigation in any internet browser on mobile or computer platforms

***Navigation options:*** Inspired by Google Maps


**Proposed Applications of ChemMaps:**

- Users can search, mine and explore [the] library of drugs as easily as they would look at a city map.
- [Could] open new perspectives for drug repurposing, e.g. by directly visualizing the proximity and structure similarity between two drugs being very close in the drug space.

Borrel et al *Bioinformatics*, 34(21), 01 November 2018, Pages 3773–3775

# ToxValue.org

## CTV
## Conditional Toxicity Value

An *In Silico* Approach for Generating Toxicity Values for Chemicals

Animal toxicity data

↓

"Toxicity Value" [Regulatory]

↓

Prediction of a Regulatory Value

**Proof of Concept**

**Wignall et al., 2014**

- Collected **880** dose-response datasets for **352** unique chemicals with Toxicity Value(s) (e.g., RfD, OSF)
- ~75% of collected datasets can be modeled with BMDS
- Batch-calculated BMD/Ls available for over 300 chemicals

**Expansion of Methods**

**Pham et al., 2019 (In prep.)**

- BMDS Python Interface and Web Server
- Large public datasets can be efficiently modeled for predictive toxicology
- Python BMDS users can customize BMDS version and model recommendation logic

**Further Application**

**Watford et al., 2019 (In prep.)**

- Extracted additional quantitative dose-response data from ToxRefDB animal studies
- Applied Python BMDS
- More than 28,000 datasets for over 600 chemicals successfully modeled

| Toxicity value type | Toxicity value name | Number of cmpds with a toxicity value |
|---|---|---|
| Oral exposure non-cancer | Reference Dose (RfD) | 671 |
| | No Observed Adverse Effect Level (NOAEL) | 487 |
| | Benchmark Dose (BMD)* | 137 |
| | Benchmark Dose Lower Level (BMDL)* | 137 |
| Oral exposure cancer | Oral Slope Factor (OSF) | 302 |
| | Cancer Potency Value (CPV) | 225 |
| Inhalation exposure (non-cancer and cancer) | Reference Concentration (RfC) | 152 |
| | Inhalation Unit Risk (IUR) | 150 |

Please select a toxicity value of interest.

- Select All
- CTV Reference Dose (RfD) (Chembench models: 67612 and 70526)
- CTV Reference Dose (RfD) NO(A)EL (Chembench models: 67624 and 66226)
- CTV Reference Dose (RfD) BMD (Chembench models: 67570 and 70508)
- CTV Reference Dose (RfD) BMDL (Chembench models: 67582 and 66214)
- CTV Reference Concentration (RfC) (Chembench models: 67600 and 70520)
- CTV Oral Slope Factor (OSF) (Chembench models: 67588 and 70514)
- CTV Cancer Potency Value (CPV) (Chembench models: 67534 and 70490)
- CTV Inhalation Unit Risk (IUR) (Chembench models: 67546 and 70496)

**Step 1:** Enter Compound Information

**Step 2:** Verify Chemical Name and Structure

**Step 3:** Look Up Toxicity Values or Make Predictions

**Step 4:** Export Results (including applicability domain)

Wignall et al. Environ Health Perspect. 2018 126(5):057008

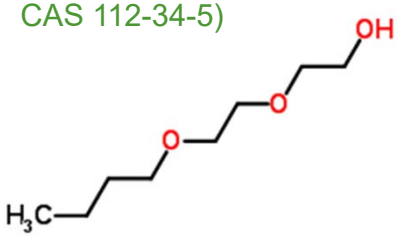
# Read-Across Example Using ToxValue.org

## Diethylene glycol ethers (Di EGEs)

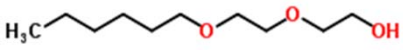
**Chemical**

Diethylene glycol ethyl ether (DGEE, CAS 111-90-0 )

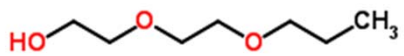

Diethylene glycol monobutyl ether (DEGBE, CAS 112-34-5)




Diethylene glycol hexyl ether (DGHE, CAS No. 112-59-4)




Diethylene glycol propyl ether (DGPE, CAS 6881-94-3)




**Critical No Effect Level**

NOAEL: 167 mg/kg-day based on kidney and liver effects in pigs

| Dose | Incidence |
|---|---|
| 0 | 0/3 |
| 167 | 0/3 |
| 500 | 1/2 |
| 1117 | 1/1 |

NOAEL: 50 mg/kg-day for anemia in rats

| Dose | # | Mean | SD |
|---|---|---|---|
| 0 | 10 | 9.27 | 0.35 |
| 50 | 10 | 9.13 | 0.22 |
| 250 | 10 | 8.94 | 0.34 |
| 1000 | 10 | 8.53 | 0.31 |

**?**

**50 mg/kg-day**

↕

**167 mg/kg-day**

**?**

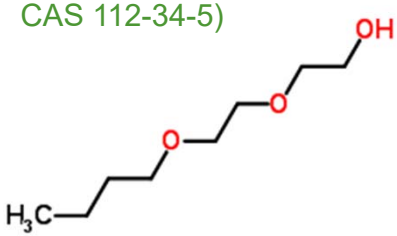
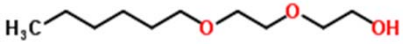
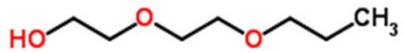
**50 mg/kg-day**

↕

**167 mg/kg-day**

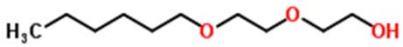
# Read-Across Example Using ToxValue.org

**Diethylene glycol ethers (Di EGEs)**

| Chemical | Diethylene glycol ethyl ether (DGEE, CAS 111-90-0 ) | Diethylene glycol monobutyl ether (DEGBE, CAS 112-34-5) | Diethylene glycol hexyl ether (DGHE, CAS No. 112-59-4) | Diethylene glycol propyl ether (DGPE, CAS 6881-94-3) |
|---|---|---|---|---|
| |  |  |  |  |
| Critical Point of Departure | NOAEL: 167 mg/kg-day based on kidney and liver effects in pigs | NOAEL: 50 mg/kg-day for anemia in rats | ? | ? |
| | BMD 443 mg/kg-day<br>BMDL 45.2 mg/kg-day | BMD 222 mg/kg-day<br>BMDL 81.4 mg/kg-day | **50 mg/kg-day**<br>↕<br>**167 mg/kg-day** | **50 mg/kg-day**<br>↕<br>**167 mg/kg-day** |

# ToxValue.org Output

Diethylene glycol hexyl ether
(DGHE, CAS No. 112-59-4)




| Chemical name | Model Name | Unit | Prediction | Lower 95%* | Upper 95%* | Appl Domain* |
|---|---|---|---|---|---|---|
| C6E2 | CTV Reference Dose (RfD) BMD | -$Log_{10}$Mol/(kg·day) | 3.36 | 1.36 | 5.30 | -0.453 |
| | | mg/(kg·day) | 83.2 | 0.960 | 8.29e+3 | |
| | CTV Reference Dose (RfD) BMDL | -$Log_{10}$Mol/(kg·day) | 3.69 | 1.91 | 5.41 | -0.453 |
| | | mg/(kg·day) | 38.6 | 0.739 | 2.33e+3 | |

**Z-score output:** Distance from **your chemical** to the **nearest chemical** in training set **compared** to the average nearest-neighbor-distances in the training set

- 0 = same distance as average distances in the training set
- >0 = your chemical is at a further distance than average distances in the training set
- <0 = your chemical is at a closer distance than average distances in the training set

Use Z > 1 as a conservative cut-off for applicability, Z > 3 as a less-restrictive cut-off (to define anything < cut-off as within AD of model).

# Read-Across Example Using ToxValue.org

**Diethylene glycol ethers (Di EGEs)**

**Chemical**

**Critical Point of Departure**

Diethylene glycol ethyl ether (DGEE, CAS 111-90-0 )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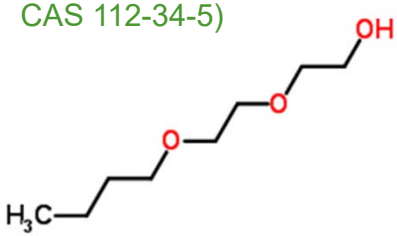


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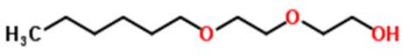


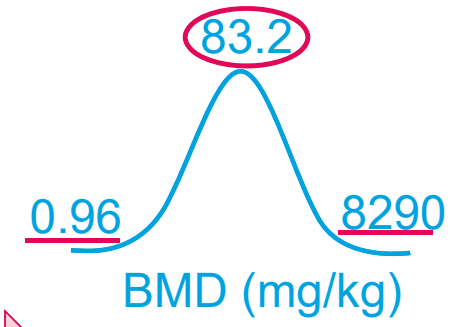


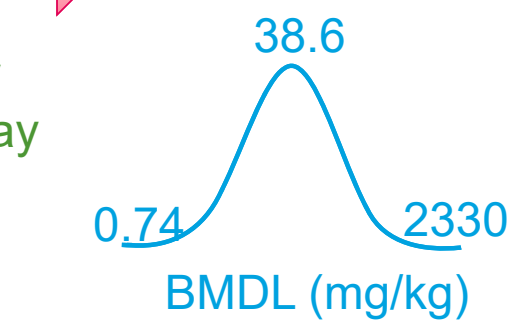


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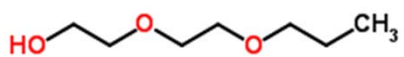


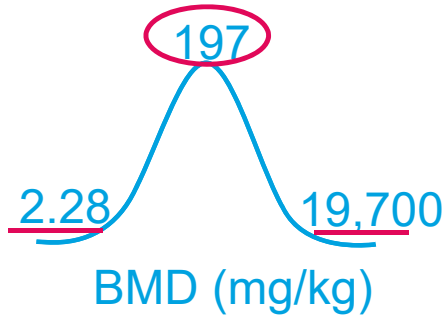


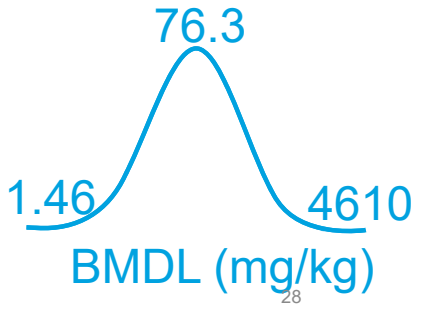

# Reflections on single-chemical read-across

- Metabolism is often easiest way to define a “class”
- Common mechanisms have worked for a few well-established classes (dioxins, PCBs, PAHs, etc.), but may be more difficult to generalize to other “classes” (e.g., HAAs)
- “Key characteristics” approach may be helpful to organize mechanistic data
- Decision-context-specific questions
  - Hazard or dose-response?
  - Do we need an “-icity”?
  - Do we need to bring in other components such as physical-chemical properties, persistence, bioaccumulation?

# ***Sufficient Similarity* Challenge in Read-Across:**

## *From Case Studies to Application*

- Defining “sufficient”: Depends on who (which agency) you ask…
- Defining “similarity”: It is clear that structure-based similarity alone is insufficient, if you ask the regulators (especially in Europe)
- So if one’s “sufficient similarity” argument is not accepted, what then?
- Are “case studies” the way forward? Yes and no, because some regulators are very inpatient and deem “case studies” to be just another “delay tactic” by the industry…
- There are no easy answers but there is no alternative to more work in this area – publication of “case studies” is a path to acceptance