Introduction
Michigan State University
Superfund Research Center

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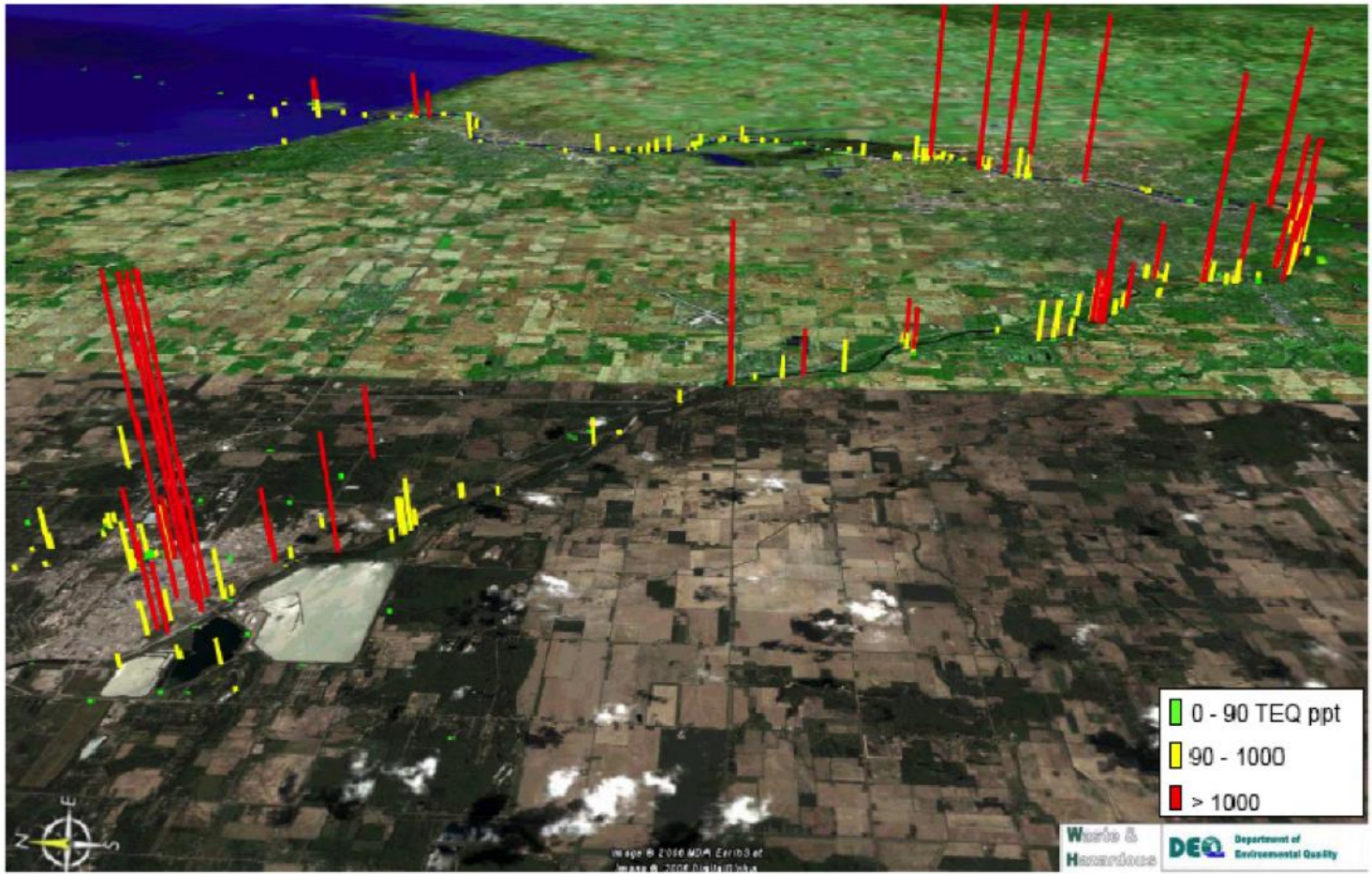
Supported by P42ES004911

Central Overarching Theme

To define environmental, microbial and mammalian biomolecular responses to environmental contaminants that act as aryl hydrocarbon receptor (AHR) agonists.


0 - 90 TEQ ppt
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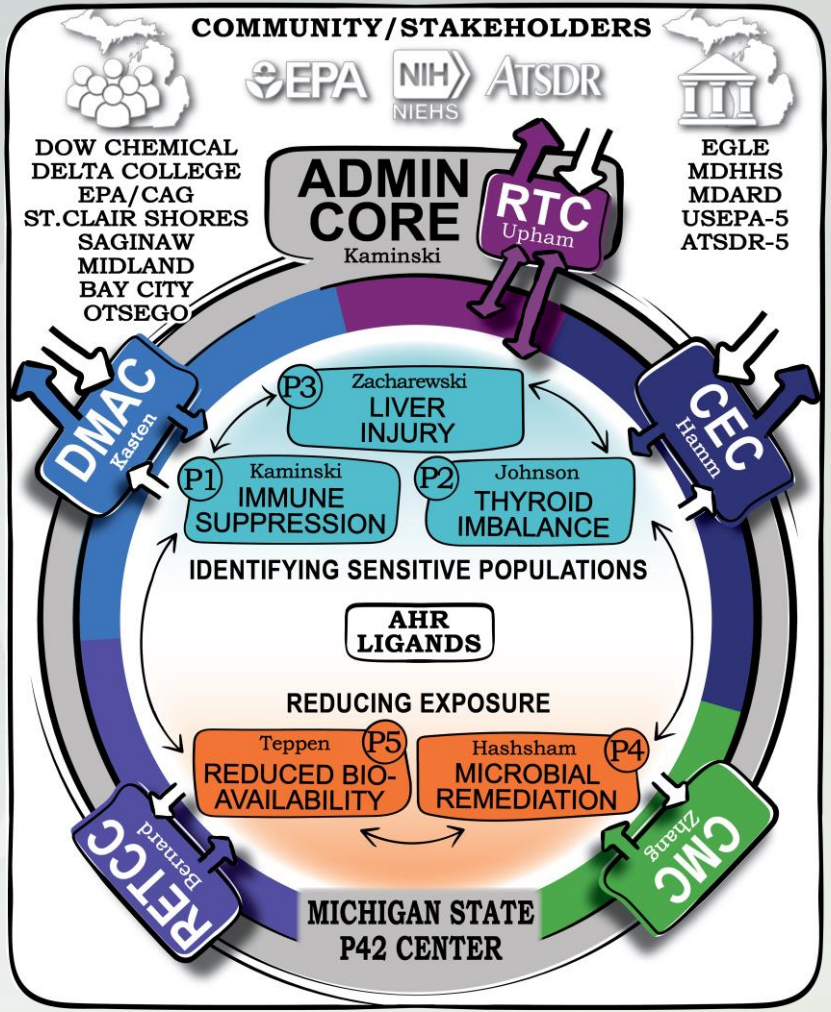
Waste & Hazardous
DEQ Department of Environmental Quality


COMMUNITY/STAKEHOLDERS
EPA
NIH
NIEHS
ATSDR
DOW CHEMICAL
DELTA COLLEGE
EPA/CAG
ST.CLAIR SHORES
SAGINAW
MIDLAND
BAY CITY
OTSEGO
EGLE
MDHHS
MDARD
USEPA-5
ATSDR-5
ADMIN CORE
Kaminski
RTC
Upham
DMAC
Kasten
CEC
Hamm
RETCC
Bernard
CMC
Zhang
P3
Zacharewski
LIVER INJURY
P1
Kaminski
IMMUNE SUPPRESSION
P2
Johnson
THYROID IMBALANCE
IDENTIFYING SENSITIVE POPULATIONS
AHR LIGANDS
REDUCING EXPOSURE
P5
Teppen
REDUCED BIO-AVAILABILITY
P4
Hashsham
MICROBIAL REMEDIATION
MICHIGAN STATE
P42 CENTER

Coupled computational and bioengineered models of thyroid imbalance to support human PCDD/F risk-assessment

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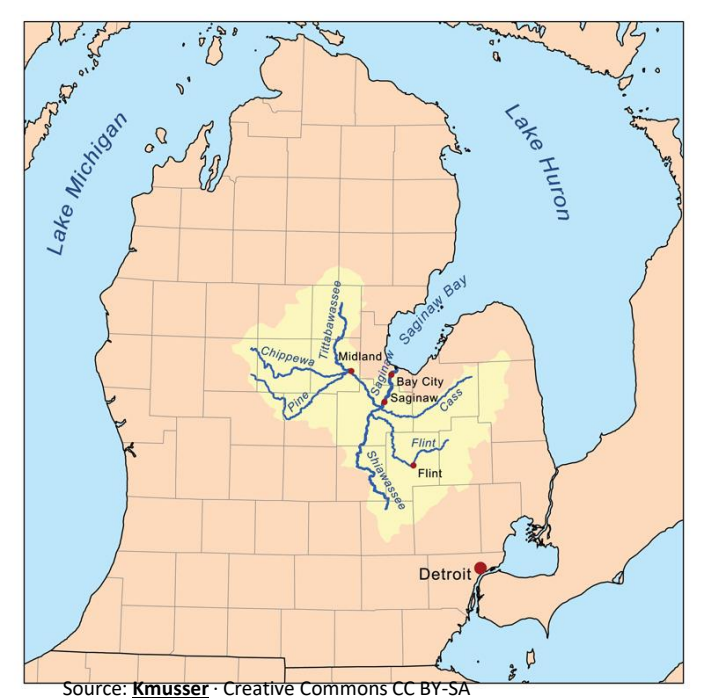
Conflict of Interest Brian Johnson owns equity in Onexio Biosystems LLC. A company that develops solutions for high-throughput toxicity testing, translational medicine and other multi-culture applications.

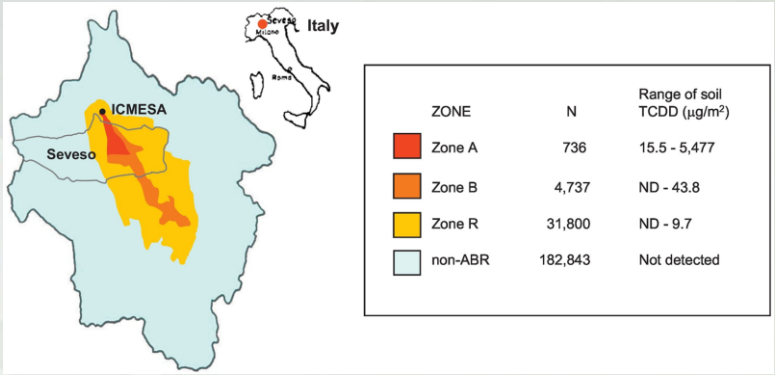
Are dioxin and furan pollutants harming human health? How and at what levels?

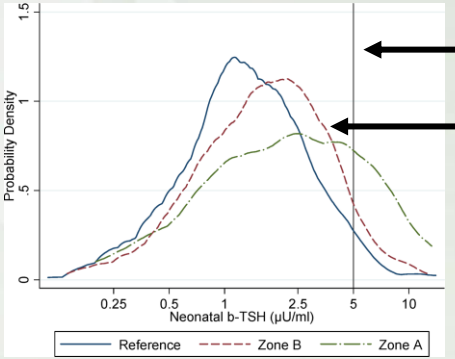


Source: **Kmusser** · Creative Commons CC BY-SA

Thyroid imbalance is one of the most sensitive reported effects of human exposure

- Rodents are thought to be more (overly?) sensitive to dioxins and furans.
- Thyroid hormone effects are seen in humans (Baccarelli et al., 2008) at 30-fold **lower** exposures than for humans (Crofton et al., 2005) .
- Data from other rodent models suggest glucuronidation mechanism may not be correct.
- A human biology based testing system is needed to understand risk of exposures to human populations.

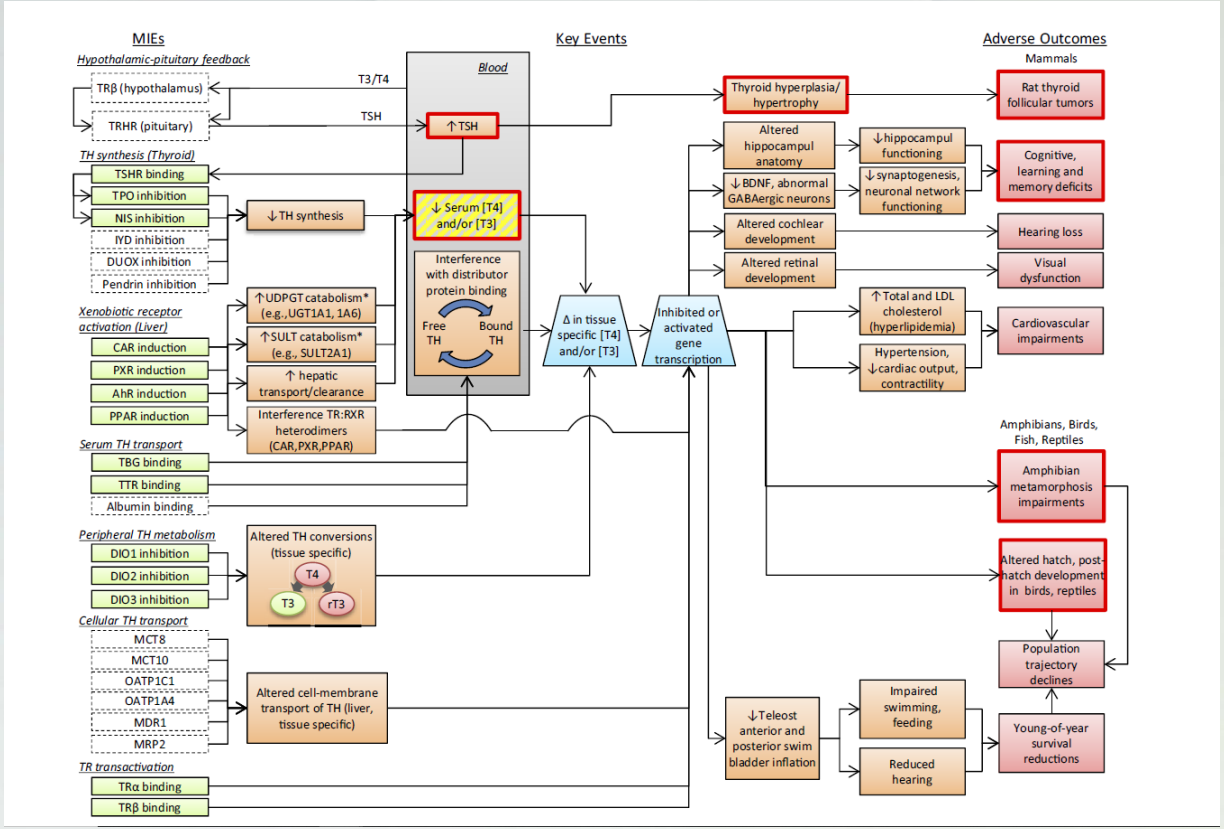




Clinical effects

Sub-clinical effects

Chemical disruption of thyroid signaling is complicated!

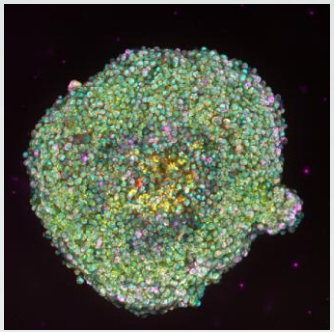


(Noyes et. al., 2019)

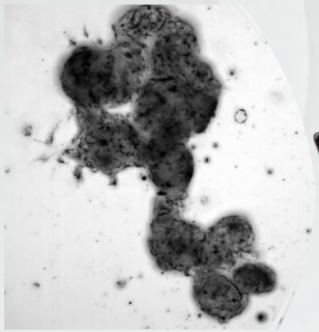
Computational modeling helps define what is important to include in physical model.

- Human computational physiologically based pharmacokinetic model for thyroid hormones with MSU Superfund Computational Modeling Core.

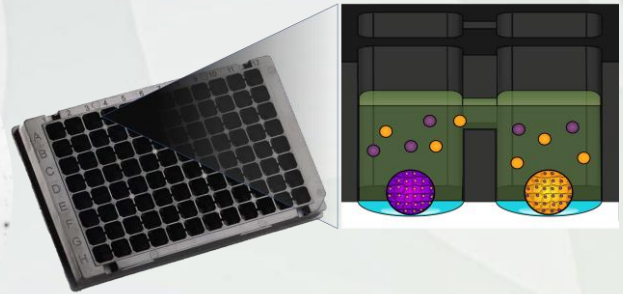
- Human derived, liver and thyroid compartments, generation/testing of metabolites, measure thyroid function, need to run lots of tests.



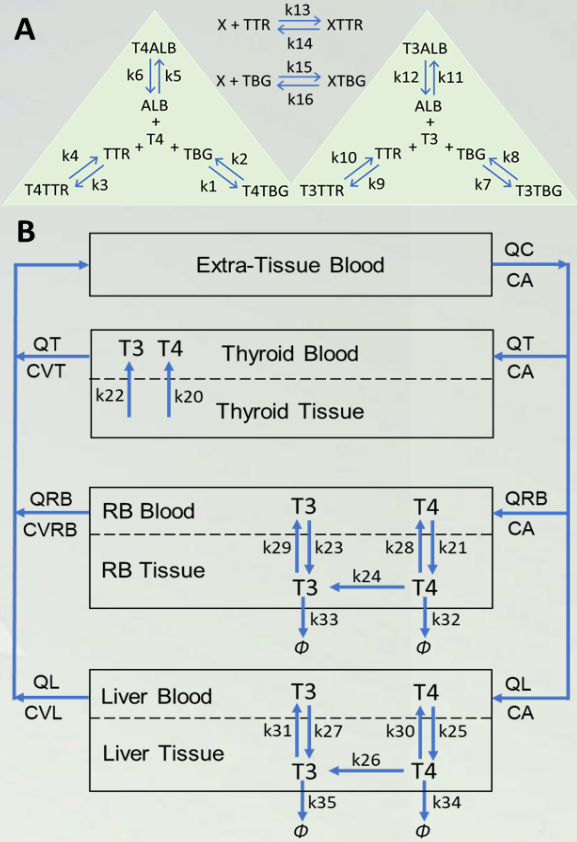
Human Hepatocytes



Thyrocyte Follicles

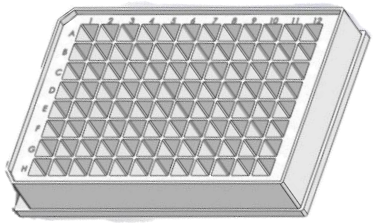


High throughput Coculture System

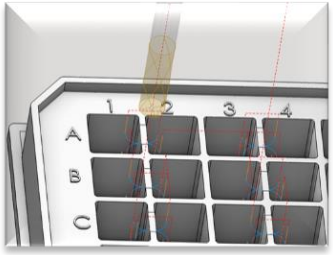


Bagga M, Johnson B, Zhang Q, 2023 (in revision

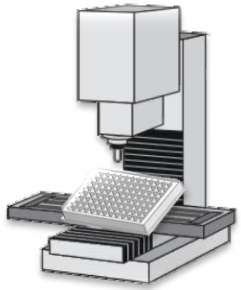
Microplate Micromachining



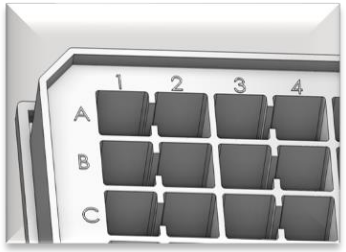
ANSI/SLAS microtiter plate



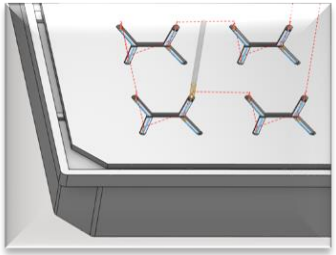
CAD/CAM

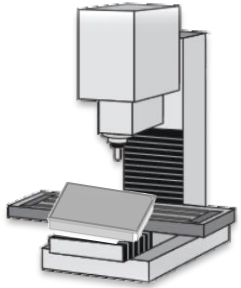


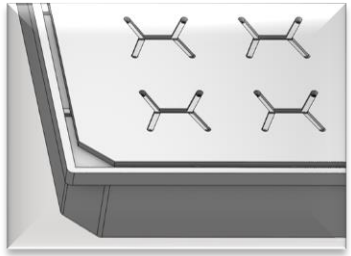
CNC Machining



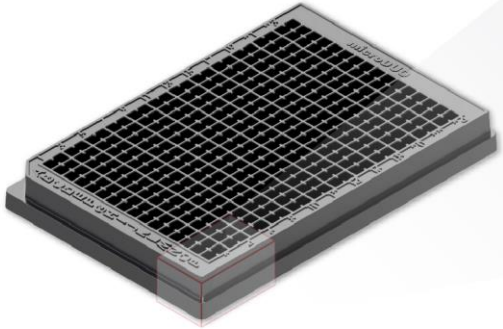
HTS Devices



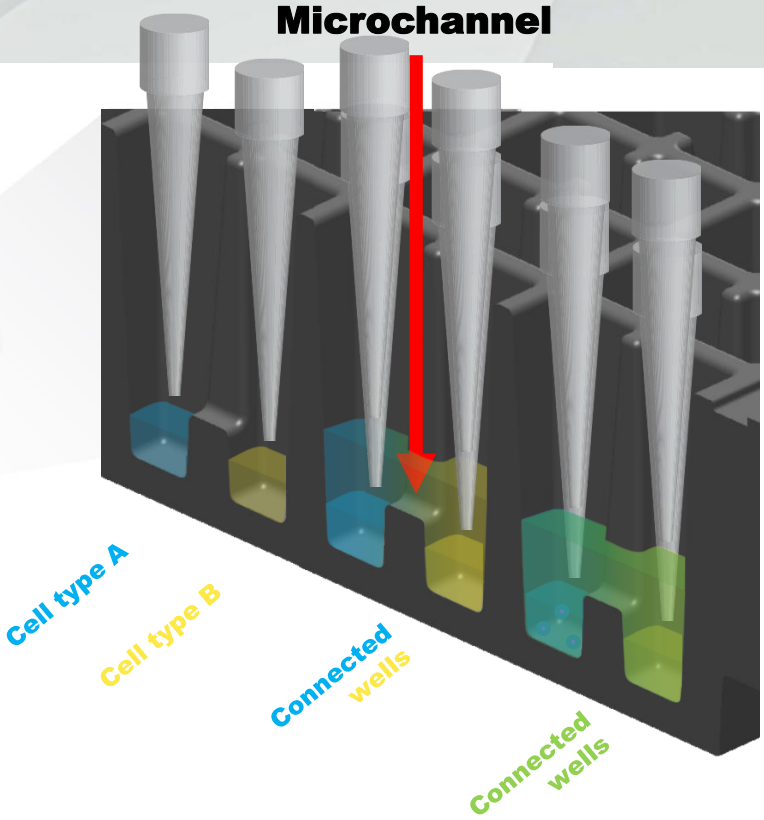




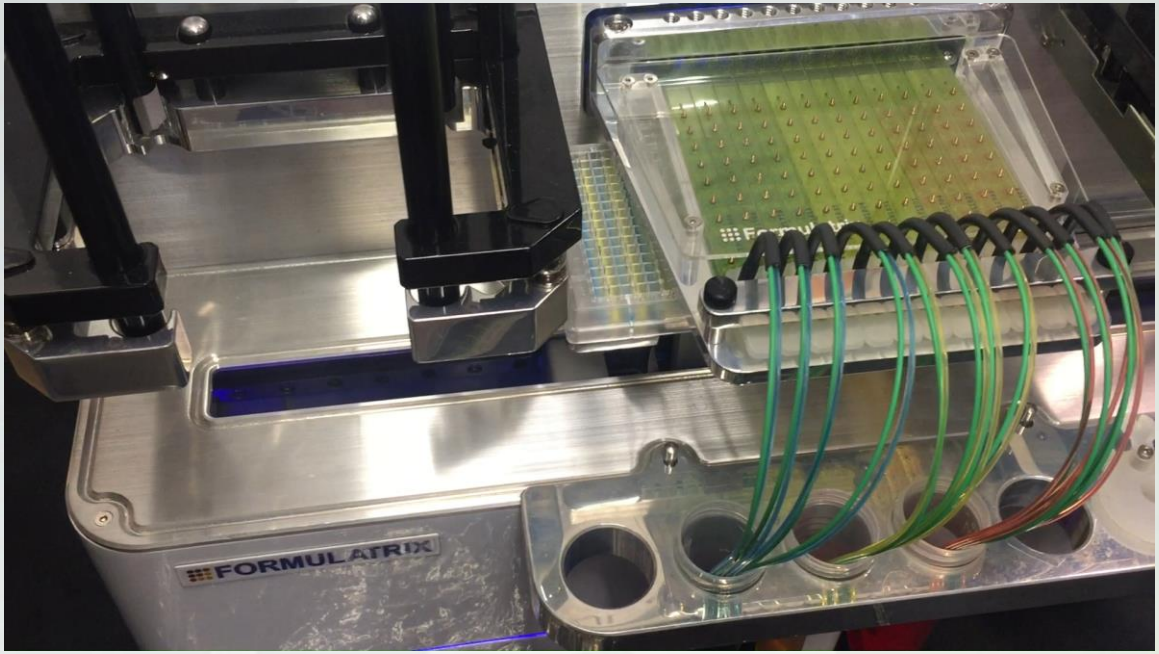
High-throughput coculture



- **Elegantly simple**
- **Fully HTS compatible**
- **Allows co-culture and multi-culture**

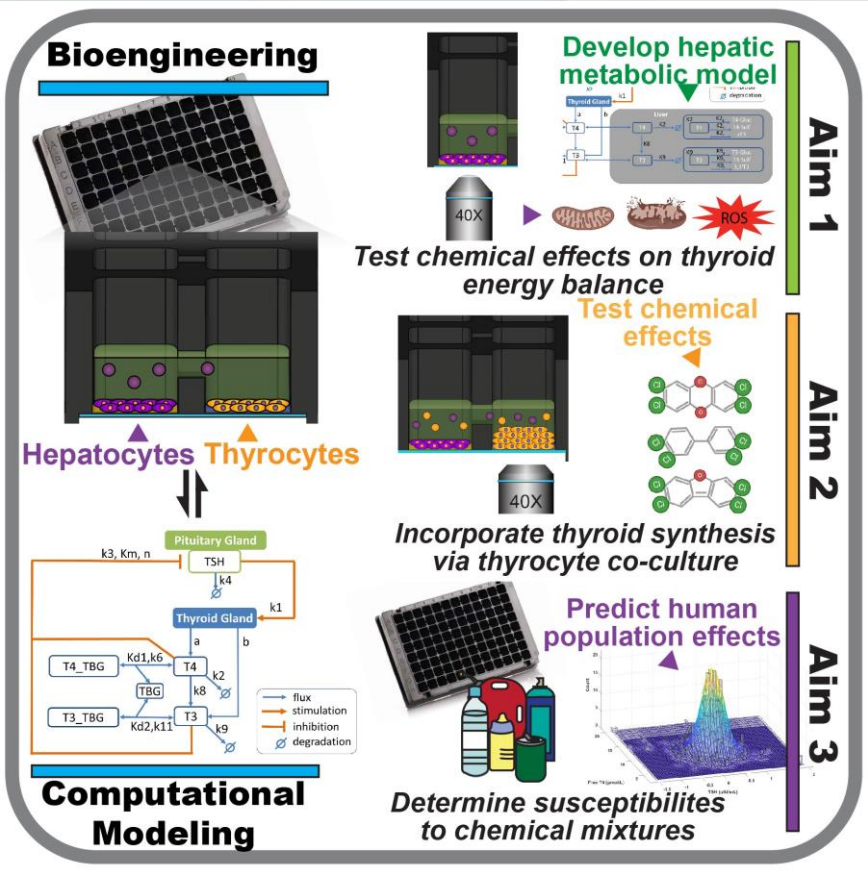


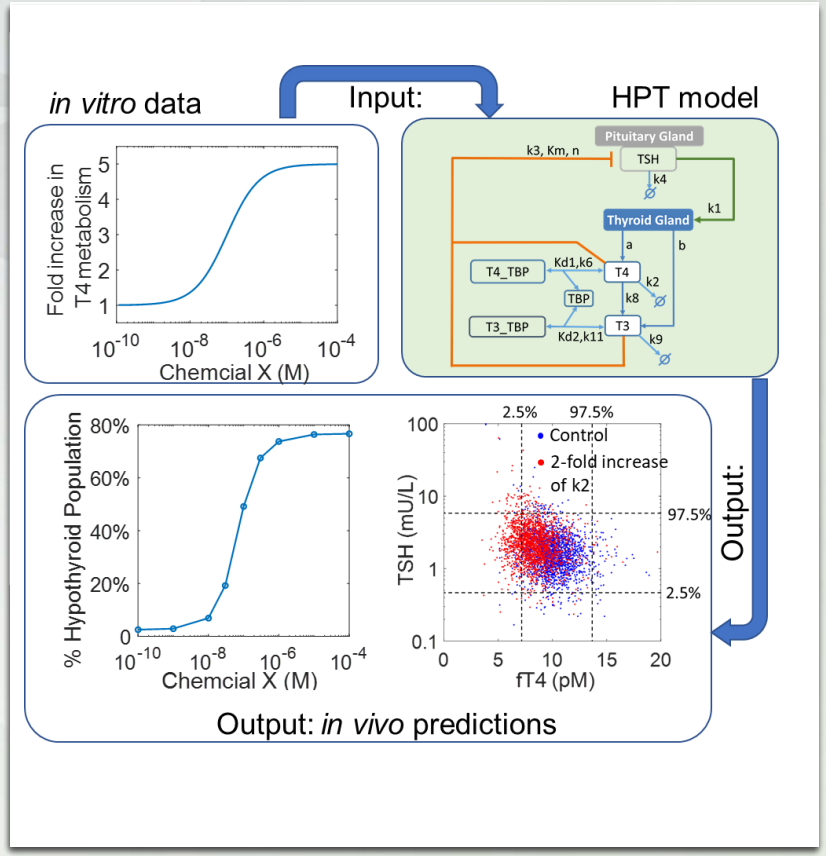
HTS Functionality



Standard HTS handling

Research overview





Questions answered

- ***What is the mechanism*** *of PCDD/F induced TH imbalance?*
- *Can background PCDD/F exposure cause hepatic TH imbalance w/o affecting serum TH?*
- ***How do in vitro findings translate to human effects*** *of PCDD/Fs?*
- *Is the TEQ approach valid in determining risk of chemicals that disrupt thyroid signaling?*
- *Does integration of computational modeling correctly predict molecular pathway sensitivities?*
- *Can intercellular models identify synergism in chemical mixtures?*
- ***What populations are most susceptible to PCDD/Fs?***

Acknowledgments

- Johnson Lab @ MSU
  - Jacob Reynolds (BME), Leah Terrian, Meredith Adams (MD 3), Keri Gardner and future Postdocs like you?!?
- Zhang Lab @ Emory
  - Qiang Zhang and Max Bagga
- Chad Deisenroth and Steve Fergusson
- MSU P42 Center
  - especially Norb Kaminski, Amy Swagart, John LaPres
- Funding

  P42ES004911-27A1

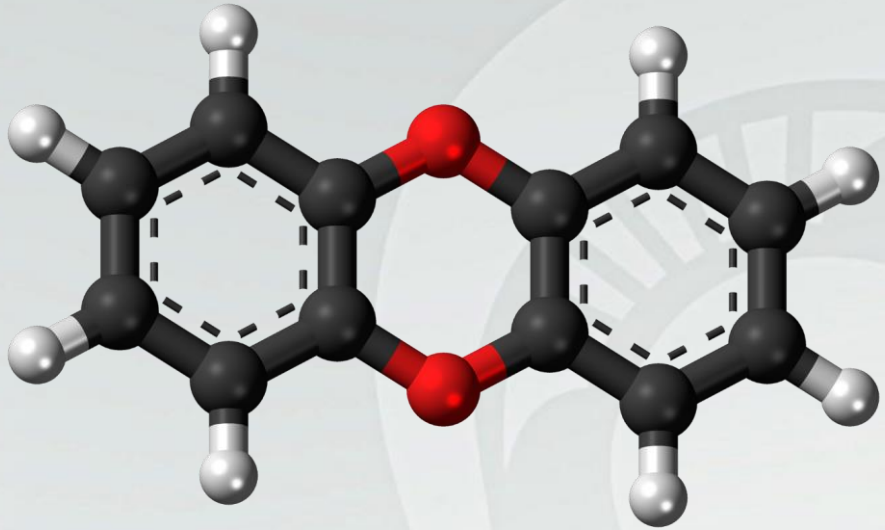
MSU Project 5: **Bioavailability as a central concept in determining remediation goals and strategies for PCDD/F-contaminated Superfund sites**

Brian J. Teppen, Cliff T. Johnston, Hui Li, and Stephen A. Boyd

A) NIEHS SRP Mandate #4: Develop and test “methods to reduce the amount and toxicity of hazardous substances.”

B) NIEHS SRP Mandate #2: Develop methods to “assess the risks to human health presented by hazardous substances.”

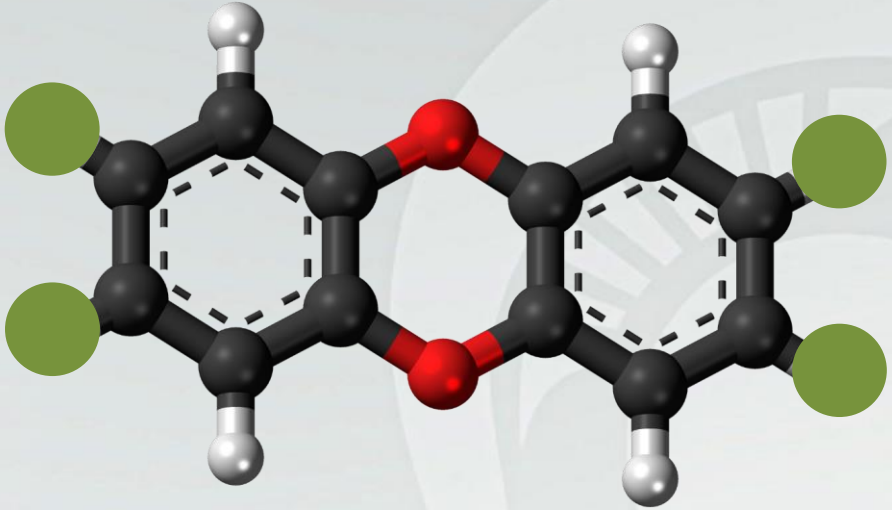
What does PCDD/F mean in our title?



Gray atoms = carbon
Red atoms = oxygen
White atoms = hydrogen

This represents dibenzo-*p*-dioxin, DD; if any of the white H atoms are replaced by chlorine atoms, then the molecule is a (poly)chlorinated DD, or PCDD. Similar jargon refers to the closely related dibenzofurans (DFs).

What does PCDD mean in our title?

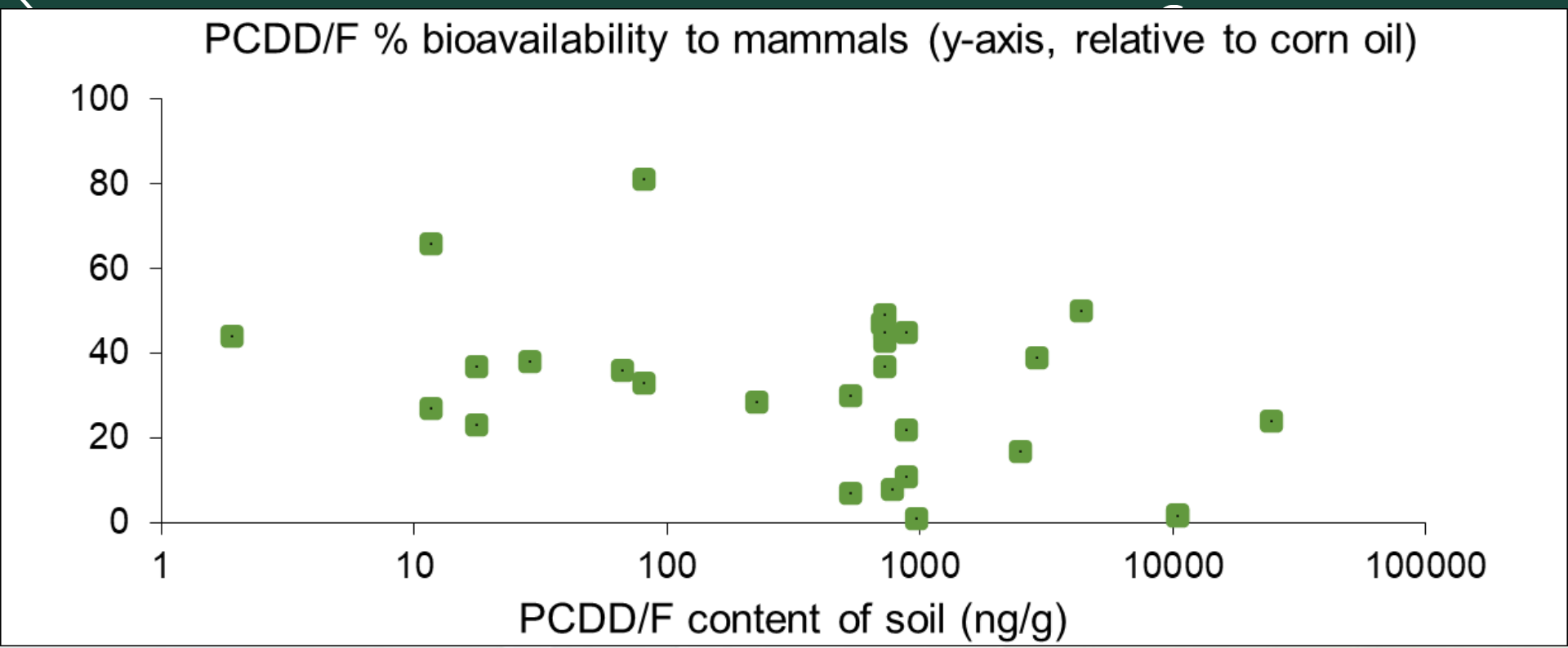


Gray atoms = carbon
Red atoms = oxygen
White atoms = hydrogen
Green atoms = chlorine

This represents 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD; this is the most toxic of the PCDD/Fs and the standard to which all others are compared. The solubility of TCDD in water is only 19 ng TCDD/L water, so essentially all TCDD is found on particles in soils and sediments.

What does “bioavailability” mean in our title?

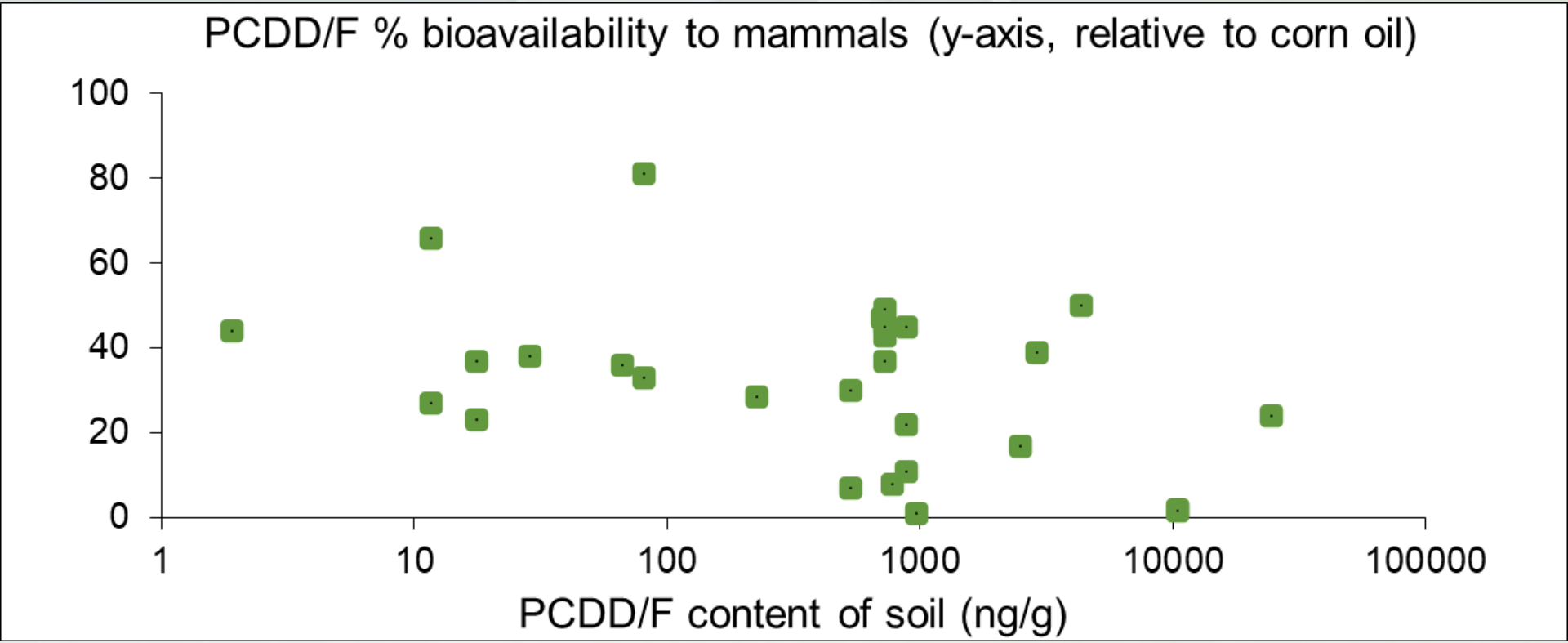
- Ability of a toxin to cause toxic effects in organisms (usually means ability of toxin to cross some critical biological membrane of the organism)
- The main route by which people and other animals are exposed to PCDD/Fs is by eating (PCDD/Fs in food, soil, etc.)
- What does bioavailability look like when PCDD/Fs are in soil that is eaten?



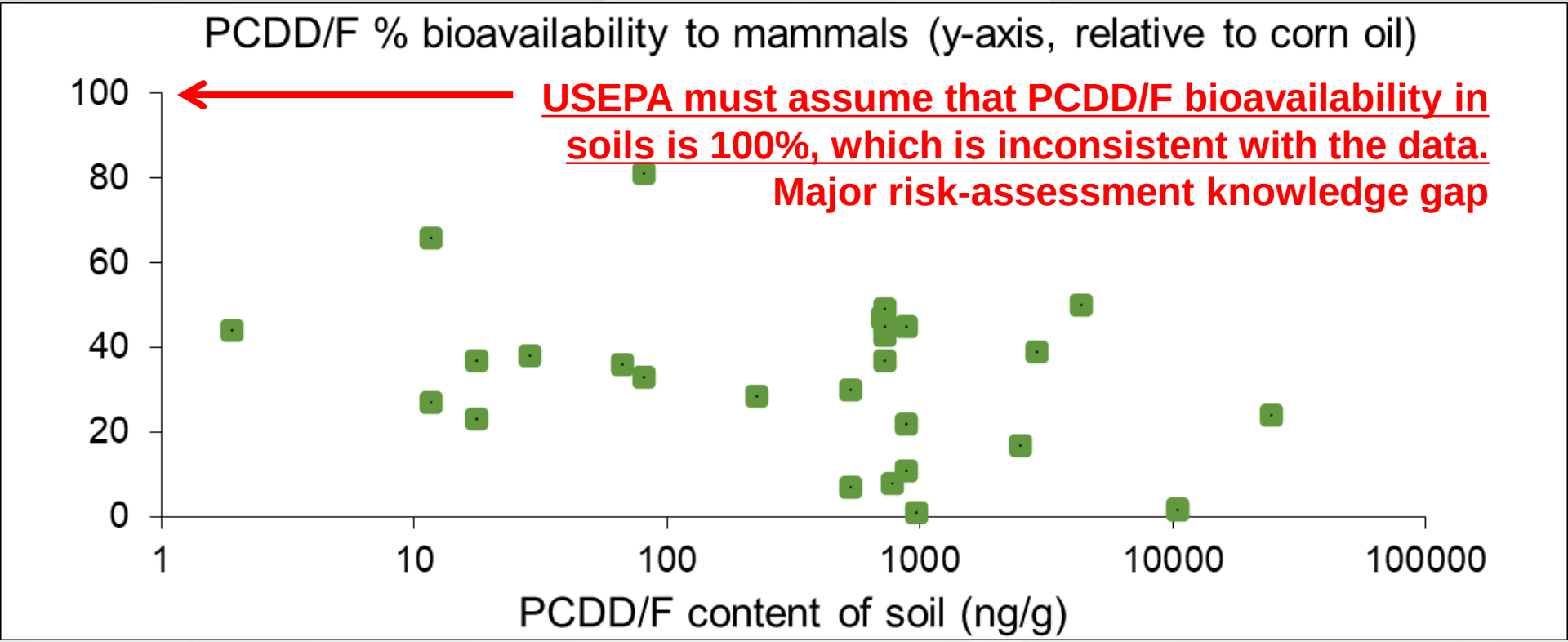
This graph is a literature review of all previous controlled studies that measured bioavailabilities of PCDD/Fs in whole soils to mammals (swine, rats, guinea pigs)

Kimbrough, R.D., C.A. Krouskas, M.L. Carson, T.F. Long, C. Bevan and R.G. Tardiff. 2010. Human uptake of persistent chemicals from contaminated soil: PCDD/Fs and PCBs. *Regul. Toxicol. Pharmacol*. 57: 43-54; USEPA Office of Superfund Remediation and Technology Innovation. 2010. *Final report: Bioavailability of dioxins and dioxin-like compounds in soil*. 53 p.

Unfortunately, these data provide no risk-management hypotheses because almost none of these soils were well characterized.



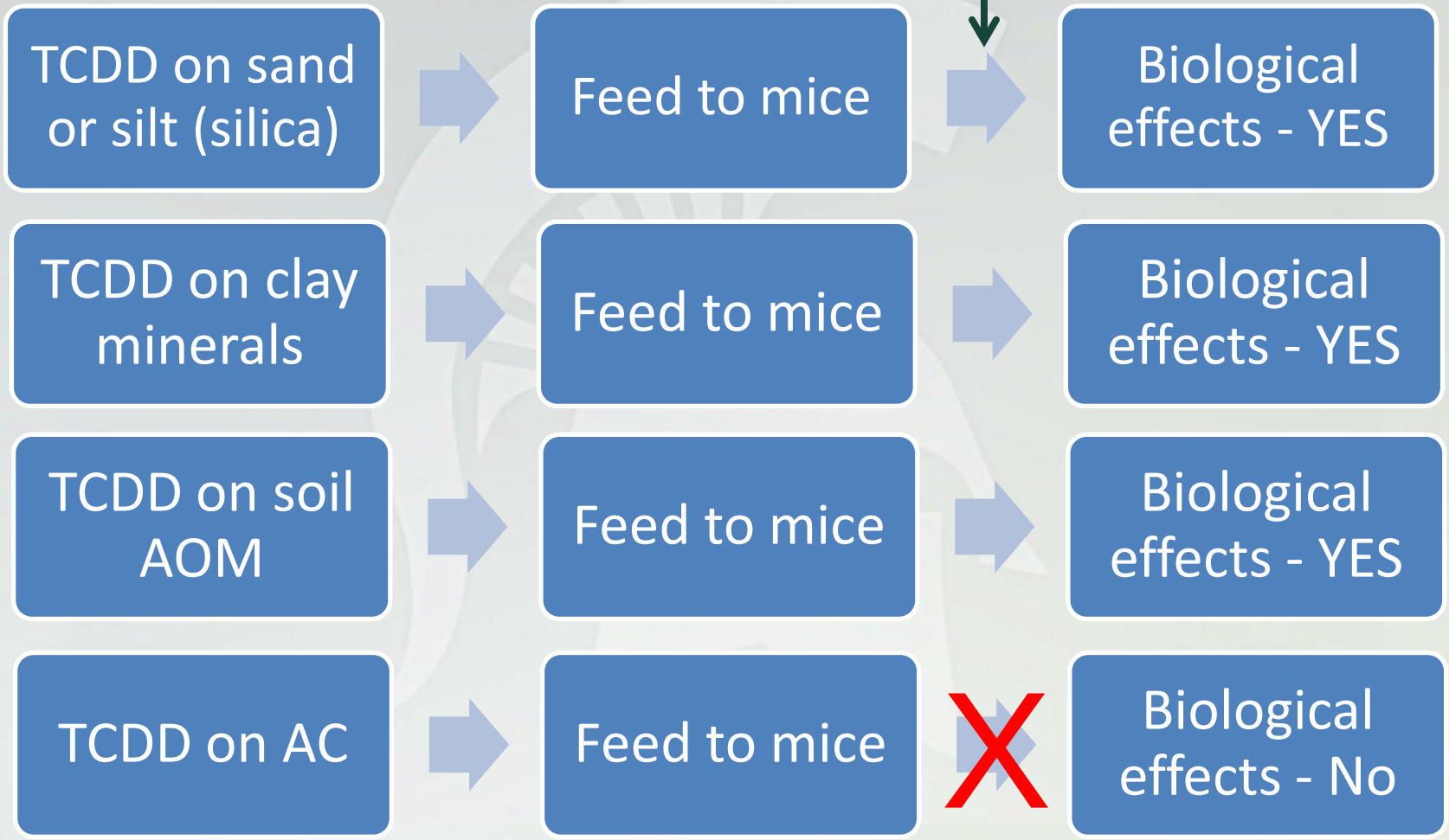
As a result of no strong risk-management hypotheses…



What are the building blocks of soil particles?

1) Clay minerals – tiny layers that can move independently and often hold toxins between the layers
2) Other minerals (typically non-layered, but may be porous) – the most common by far is silica (SiO_2) that makes up most silt and sand (medium and large soil particles)
3) “Amorphous” organic matter (AOM) that is the result of partial microbial degradation of plant/animal material in soil or water
4) Pyrogenic (fire-derived) carbonaceous material (PCM) that results from burning plant/animal material (e.g., grass fires, forest fires). An extreme form of PCM is activated carbon (AC)

We have been addressing the PCDD/F-soil **bioavailability** knowledge gap

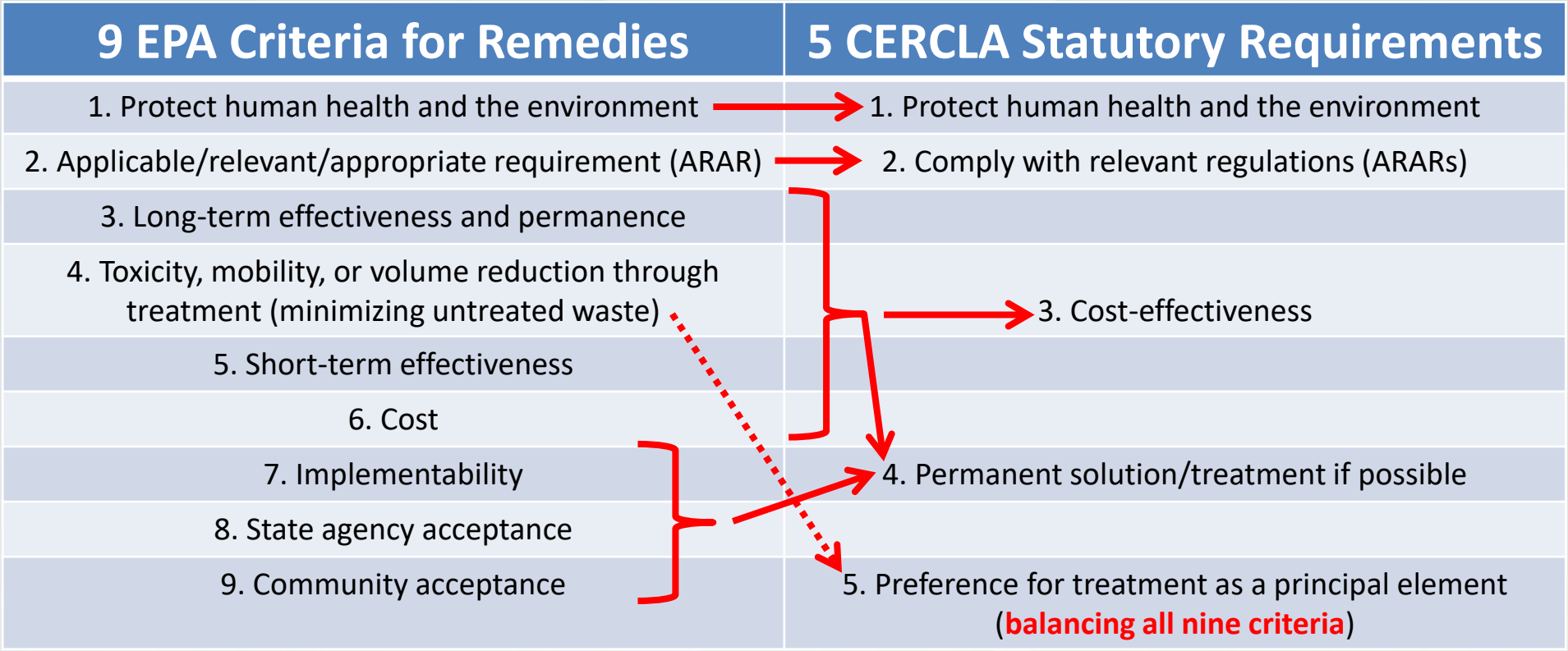


Overall goal: To test the efficacy of activated carbon (AC) as a potentially effective, low-cost and low-impact remediation remedy for PCDD/F-contaminated soils

- What does it mean to be a good remediation remedy?

Rules of thumb for Superfund remedy selection

(EPA 540-R-97-013; OSWER 9355.0-69; PB97-963301), August 1997



Red arrows indicate how EPA says it maps its criteria onto the statutory requirements

Rules of thumb for Superfund remedy selection

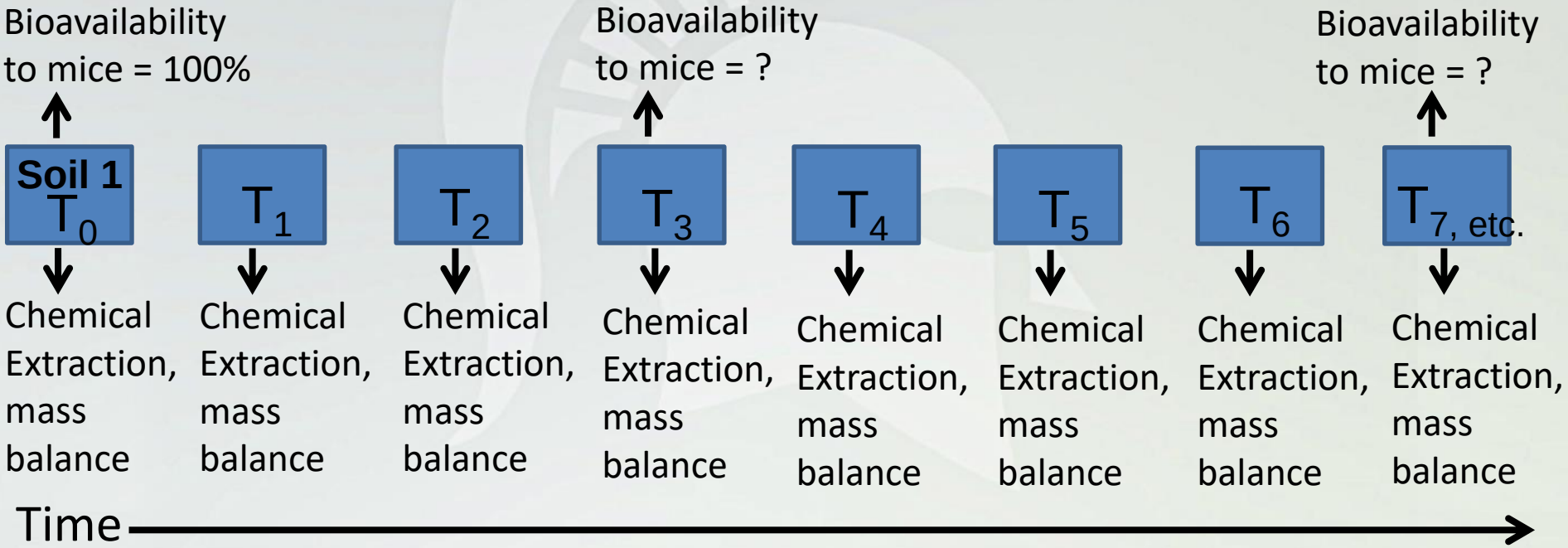
(EPA 540-R-97-013; OSWER 9355.0-69; PB97-963301), August 1997

9 EPA Criteria for Remedies	5 CERCLA Statutory Requirements
SA3 1. Protect human health and the environment	1. Protect human health and the environment SA3
2. Comply with relevant regulations (ARARs)	2. Applicable/relevant/appropriate requirement (ARAR)
SA2b,3b 3. Long-term effectiveness and permanence	
SA2,3 4. Toxicity, mobility, or volume reduction through treatment (minimizing untreated waste)	3. Cost-effectiveness SA2,3
SA2a,3a 5. Short-term effectiveness	
6. Cost	
7. Implementability	4. Permanent solution/treatment if possible SA2,3
8. State agency acceptance - **Work with RTC (Admin. Core, Upham) to share our bioavailability data.**	
9. Community acceptance - **Work with CEC (Hamm) to determine, using their annual surveys.**	5. Preference for treatment as a principal element (SA2,3)

Soils will be constructed of the same building blocks, with particle size small enough for reproducible mouse feeding

1) Clay minerals – 10% by weight
2) Silica (SiO_2), silt-sized (approx. 0.05 mm diameter) – about 80%
3) “Amorphous” organic matter (AOM) – Zero to 5% by weight
4) Activated carbon – Zero to 5%

Specific Aims 2a and 3a: Initially (T_0), TCDD is sorbed to clay minerals, then AC is added. Measure the kinetics of TCDD sorption by AC and the kinetics of bioavailability.



Specific Aims 2b and 3b: Initially (T_0), all TCDD is sorbed to AC, then age the soil for years to test the long-term stabilities of TCDD-AC complexes and of bioavailability reduction.