USING THE RISK21 FRAMEWORK AS A TIERED APPROACH FOR CHEMICAL RISK ASSESSMENT: A PROOF OF CONCEPT

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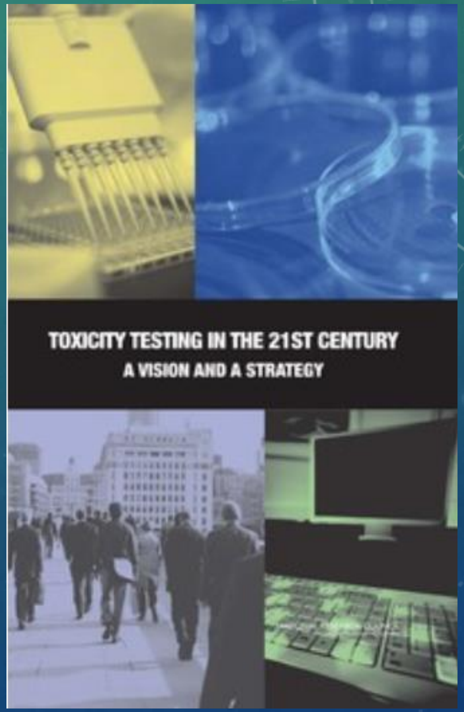
SOT 2020

May 19, 2020

HESI®

CHEMICAL RISK EVALUATION

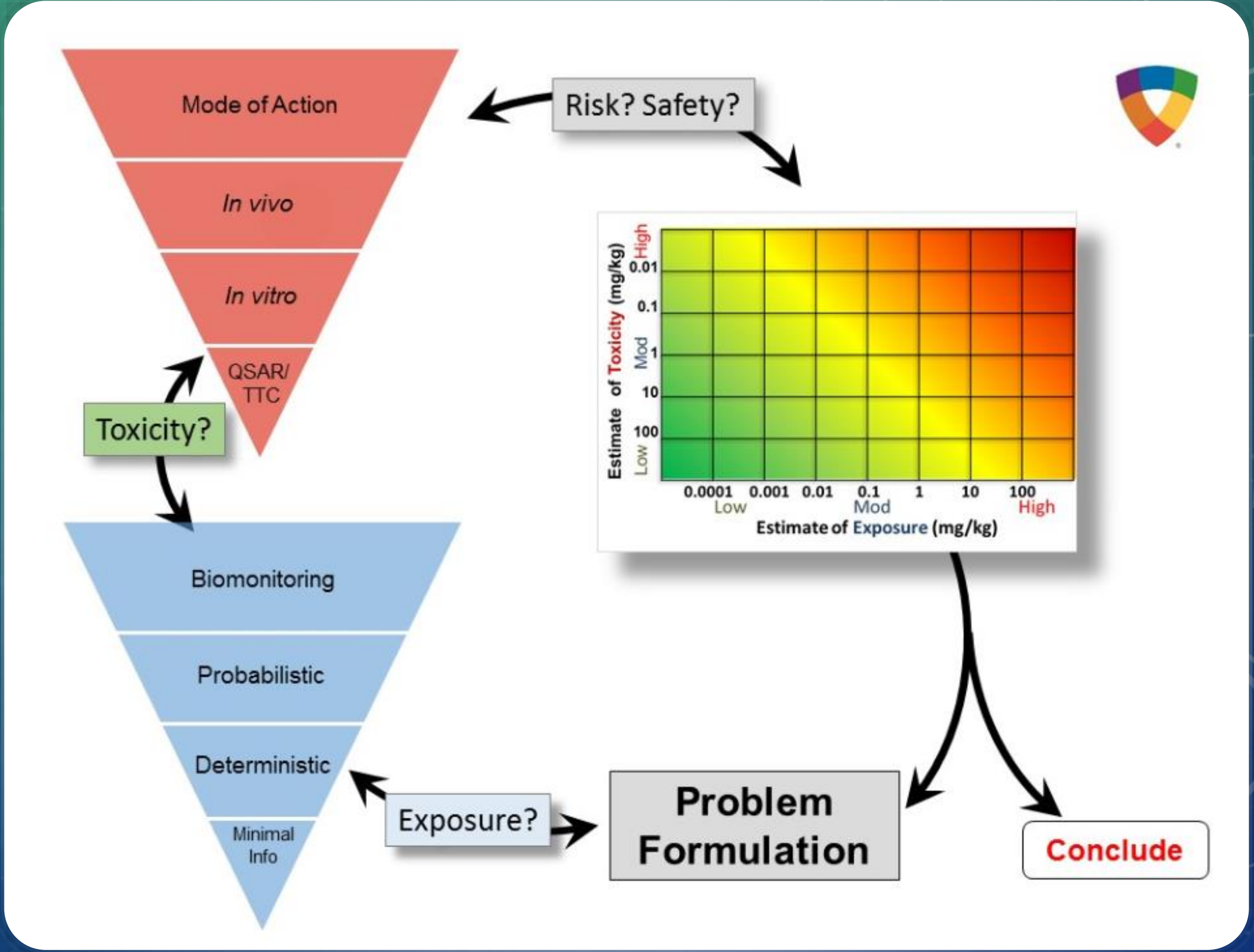
- How evaluate the risk associated with
  - A large number of chemicals,
  - Often with limited data,
  - Within a reasonable amount of time?



Screen, prioritize, and spend time and resources where most needed

GOAL OF THE EXERCISE

Show how a tiered approach like RISK21 can be used to inform prioritization of chemical toxicity testing



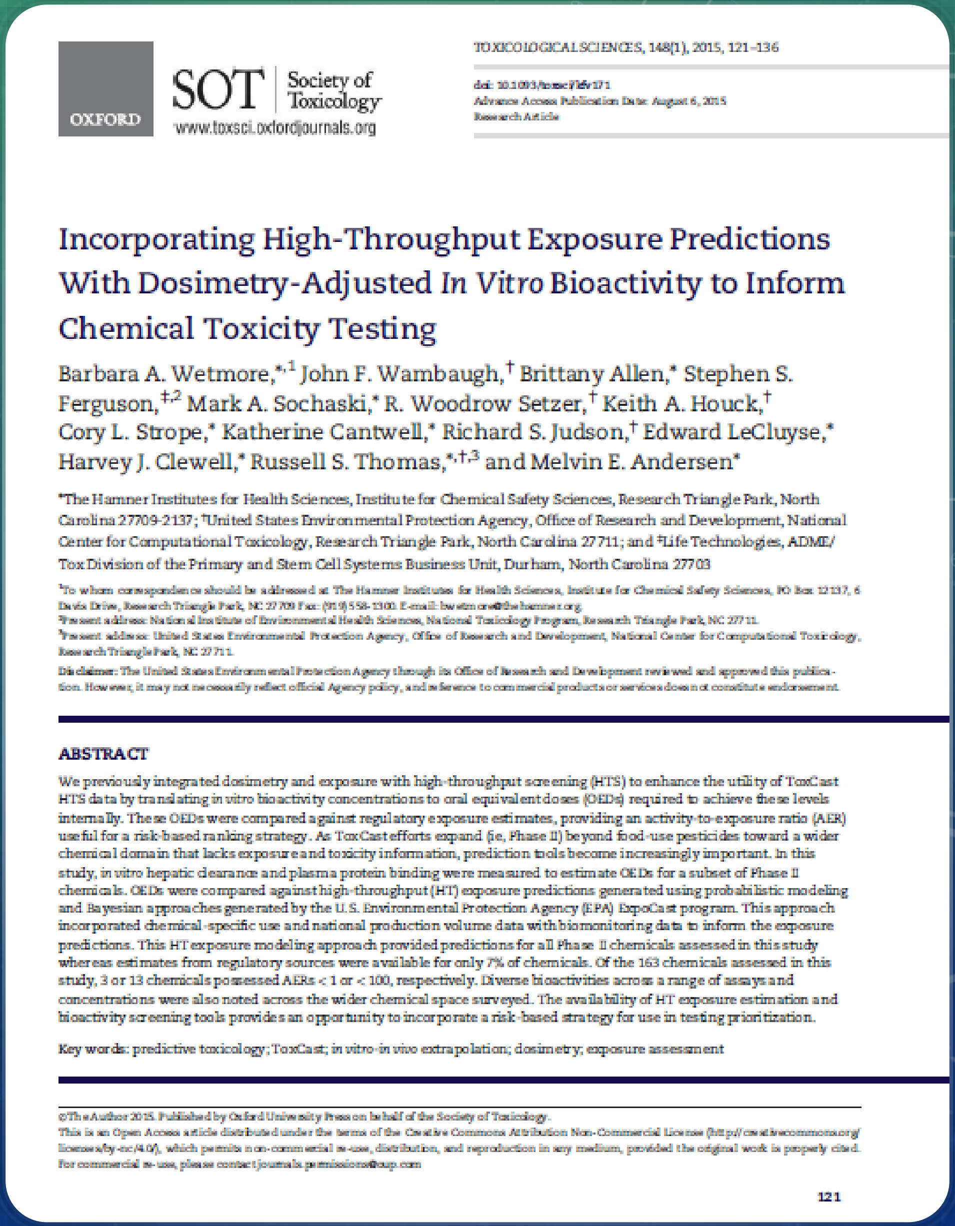
WETMORE ET AL. (2015)

USING HIGH-THROUGH-PUT EXPOSURE AND EXPOCAST FOR CHEMICAL PRIORITIZATION

WETMORE ET AL. 2015

Overview

- 163 ToxCast Phase II chemicals which have
  - An analytical chemistry detection method
  - Human exposure data
  - Chemical assay hits without data quality alert flags (> 4,500 hits)
- Evaluated the risk associated with 163 chemicals based on
  - High-throughput exposure predictions (HTEs)
  - Oral equivalent doses (OEDs) derived from dosimetry-adjusted *in vitro* bioactivity data from ToxCast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SOT Society of Toxicology
www.toxsci.oxfordjournals.org
TOXICOLOGICAL SCIENCES, 148(1), 2015, 121–136
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Research Article

Incorporating High-Throughput Exposure Predictions With Dosimetry-Adjusted *In Vitro* Bioactivity to Inform Chemical Toxicity Testing

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Disclaimer: The United States Environmental Protection Agency through its Office of Research and Development reviewed and approved this publication. However, it may not necessarily reflect official Agency policy, and reference to commercial products or services does not constitute endorsement.

ABSTRACT

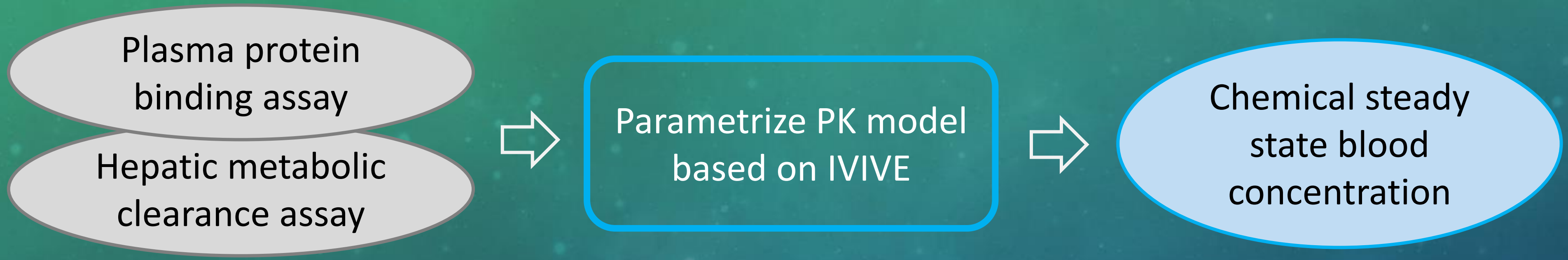
We previously integrated dosimetry and exposure with high-throughput screening (HTS) to enhance the utility of ToxCast HTS data by translating in vitro bioactivity concentrations to oral equivalent doses (OEDs) required to achieve these levels internally. These OEDs were compared against regulatory exposure estimates, providing an activity-to-exposure ratio (AER) useful for a risk-based ranking strategy. As ToxCast efforts expand (ie, Phase II) beyond food-use pesticides toward a wider chemical domain that lacks exposure and toxicity information, prediction tools become increasingly important. In this study, in vitro hepatic clearance and plasma protein binding were measured to estimate OEDs for a subset of Phase II chemicals. OEDs were compared against high-throughput (HT) exposure predictions generated using probabilistic modeling and Bayesian approaches generated by the U.S. Environmental Protection Agency (EPA) ExpoCast program. This approach incorporated chemical-specific use and national production volume data with biomonitoring data to inform the exposure predictions. This HT exposure modeling approach provided predictions for all Phase II chemicals assessed in this study whereas estimates from regulatory sources were available for only 7% of chemicals. Of the 163 chemicals assessed in this study, 3 or 13 chemicals possessed AERs < 1 or < 100, respectively. Diverse bioactivities across a range of assays and concentrations were also noted across the wider chemical space surveyed. The availability of HT exposure estimation and bioactivity screening tools provides an opportunity to incorporate a risk-based strategy for use in testing prioritization.

Key words: predictive toxicology; ToxCast; in vitro-in vivo extrapolation; dosimetry; exposure assessment

Risk-based determination of chemical testing priorities

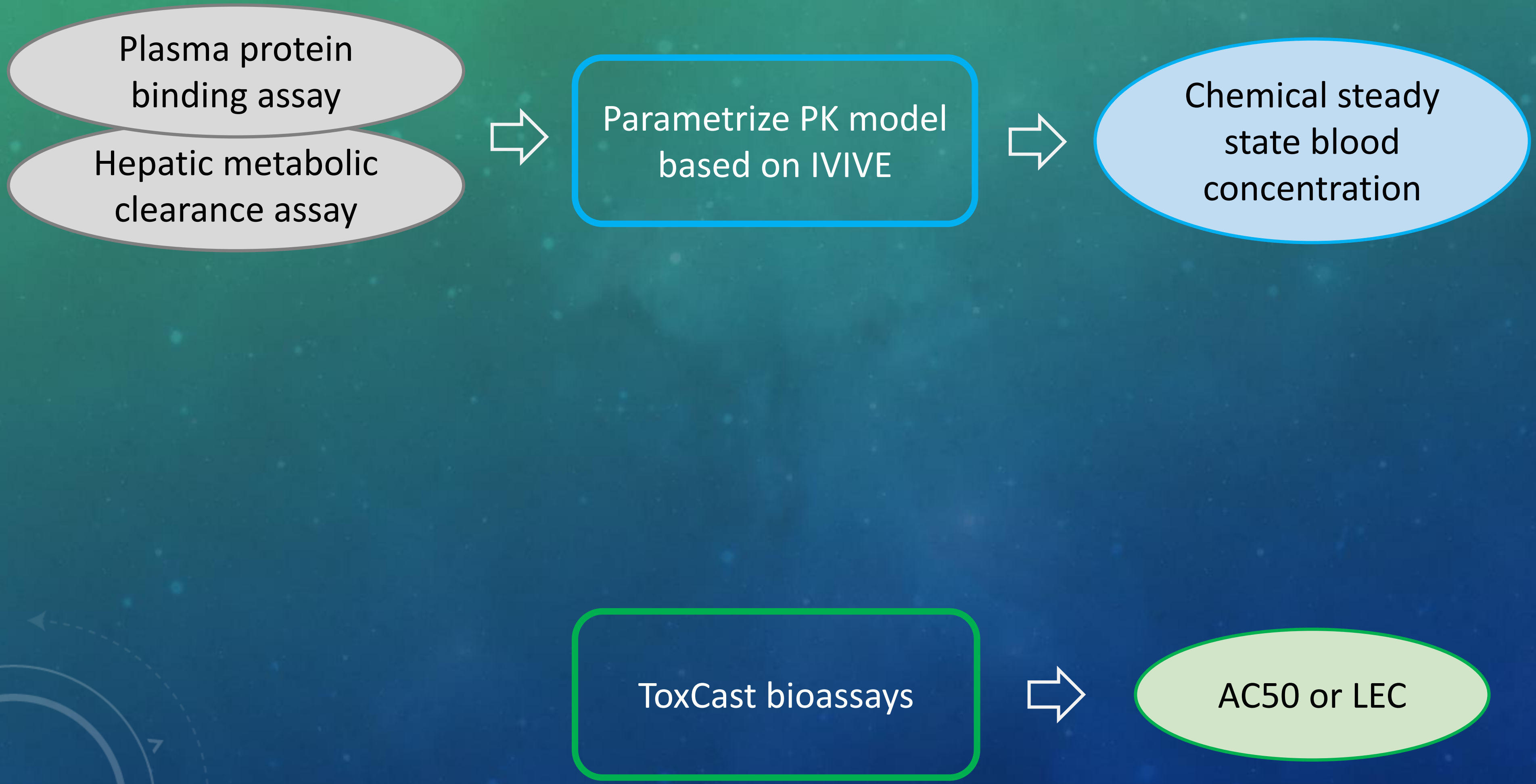
WETMORE ET AL. 2015

Toxicity Assessment and Oral Equivalent Dose



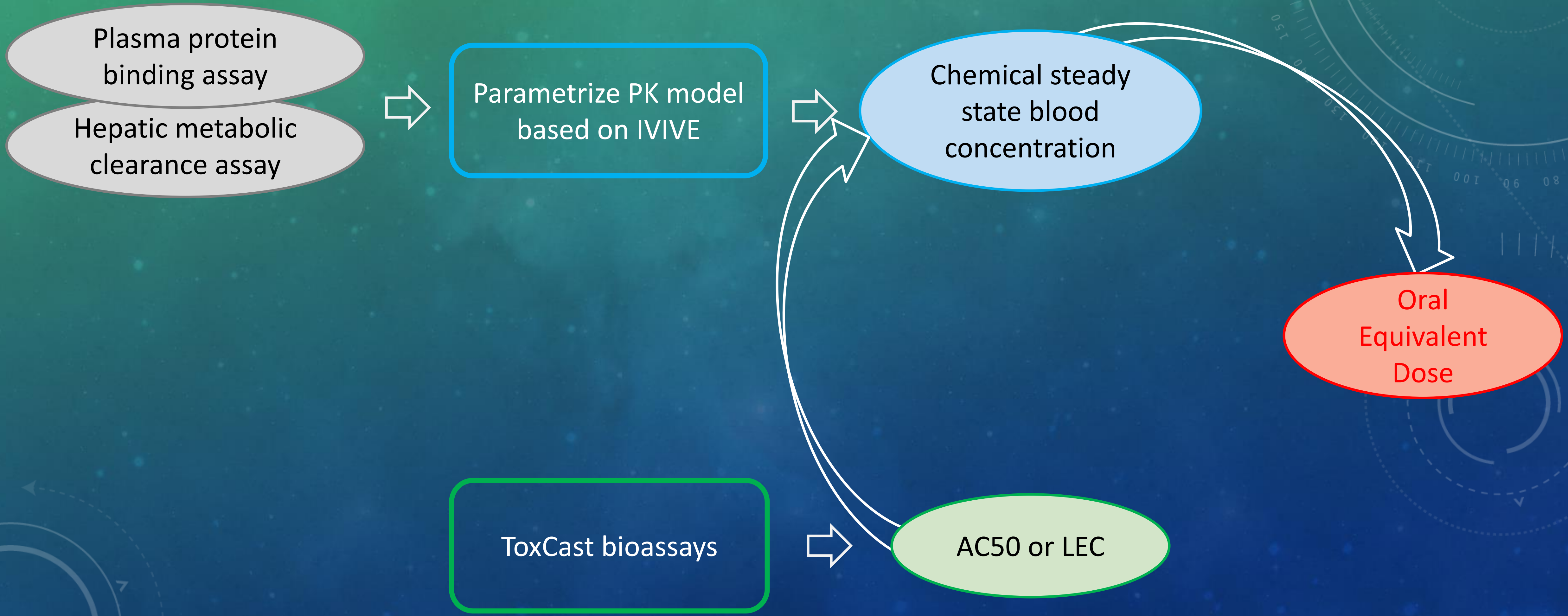
WETMORE ET AL. 2015

Toxicity Assessment and Oral Equivalent Dose



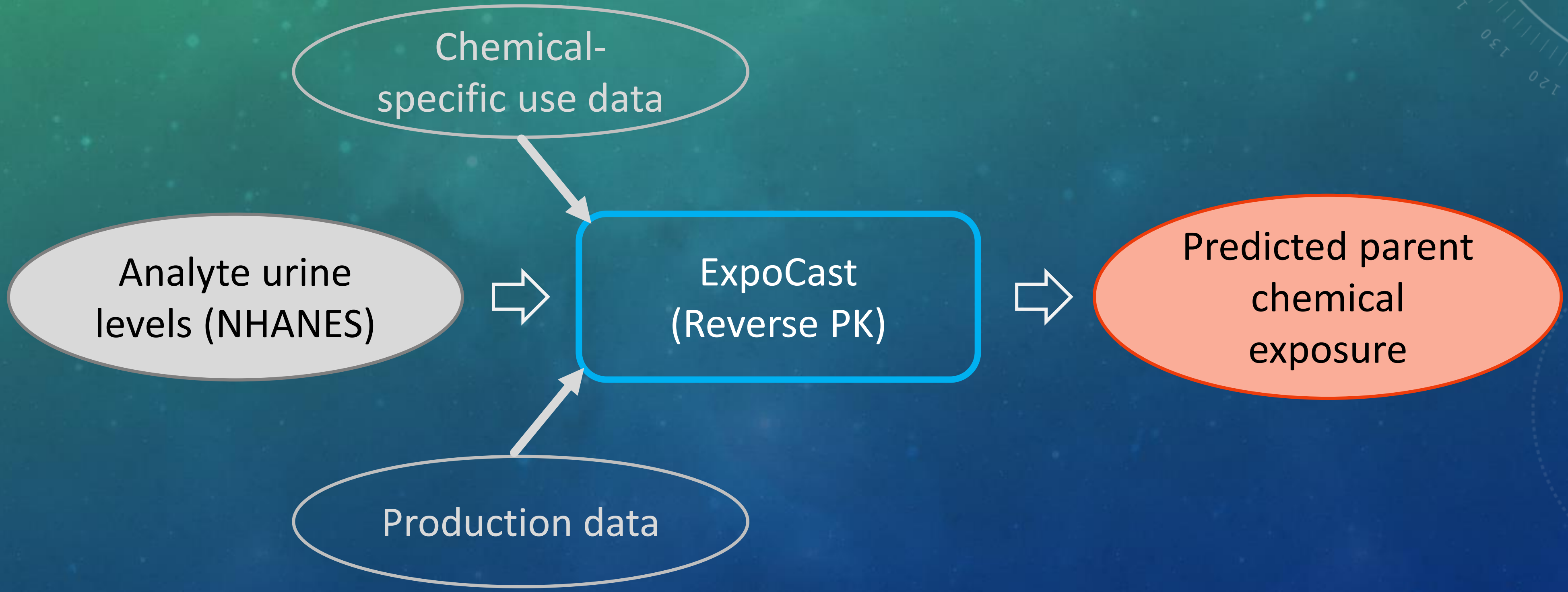
WETMORE ET AL. 2015

Toxicity Assessment and Oral Equivalent Dose



WETMORE ET AL. 2015

Exposure Assessment



WETMORE ET AL. 2015

Activity Exposure Ratio

Oral Equivalent Dose

Predicted parent chemical exposure

WETMORE ET AL. 2015

Activity Exposure Ratio

$$AER = \frac{\text{Oral Equivalent Dose}}{\text{Predicted parent chemical exposure}}$$

If AER < x with x a chosen risk threshold >1,
then the chemical of concern is of potential risk

RESULTS

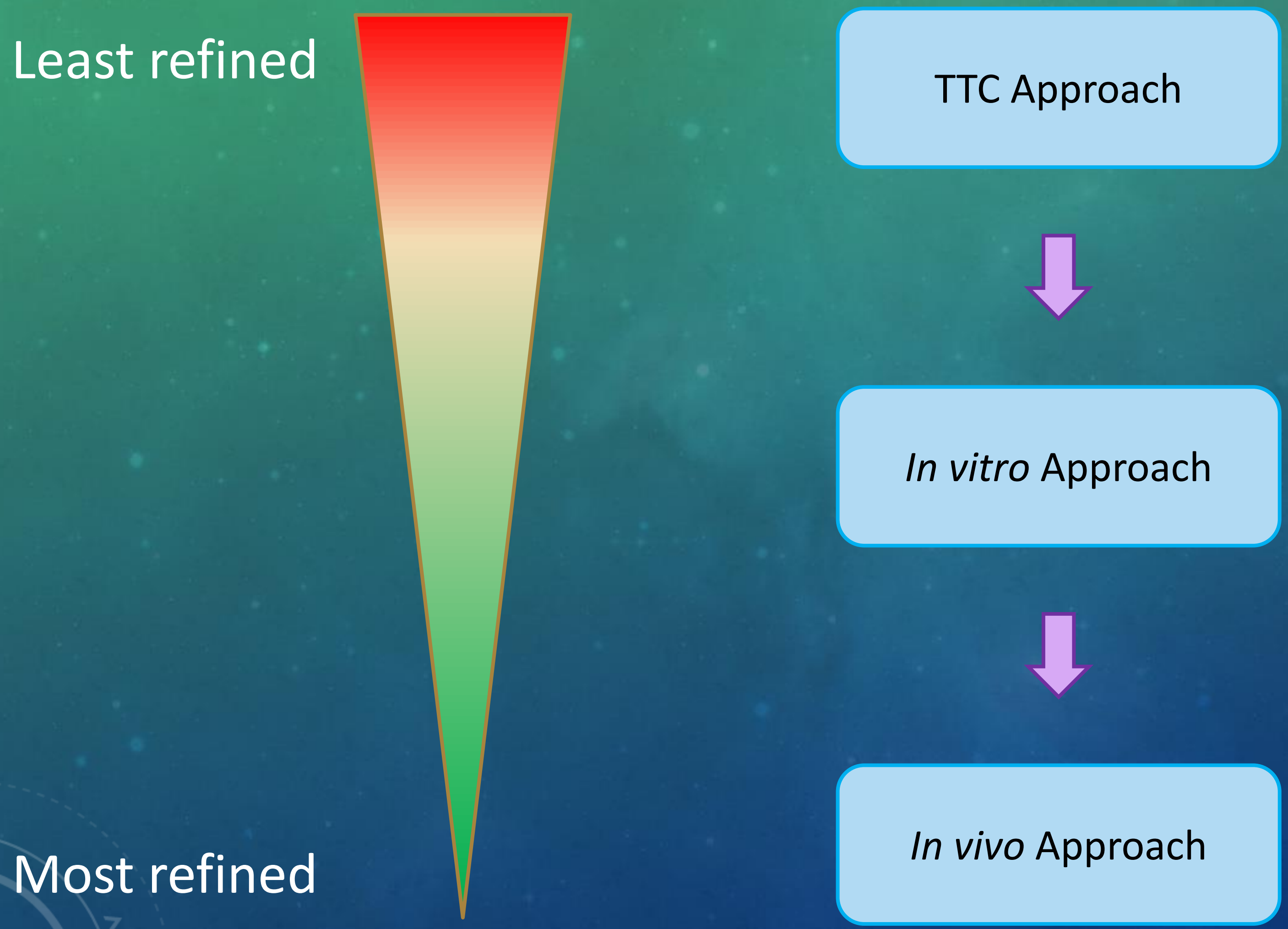
- 163 chemicals assessed
- When considering maximum exposure
  - 5 had an AER <1
  - 18 had an AER <100

Chemical	Description/Use	No. Assay Hits Where MHE[a] AER[b] < 100	AC_{50} (μM)[c]	Oral Equivalent[c] (mg/kg/day)	Exposure Total (MHE) (mg/kg/day)	AER (MHE AER)
Tannic acid	Plant polyphenol; food, drug uses; mordant during dyeing process	5	0.0002	5.83E-04	1.35E-02 (3.36E-02)	0.043 (0.02)
Triphenyl phosphate	Plasticizer; fire retardant	3	0.0006	7.66E-04	6.57E-03 (1.41E-02)	0.117 (0.054)
Heptadecafluorooctanesulfonic acid potassium salt	Organofluorine	12	0.013	5.99E-05	3.21E-04 (8.72E-04)	0.187 (0.069)
Mirex	Banned organochlorine insecticide	3	0.01144	1.61E-04	1.55E-04 (3.13E-04)	1.040 (0.516)
Ammonium perfluorooctanoate	Organofluorine	9	0.20182	7.48E-04	3.24E-04 (1.09E-03)	2.310 (0.684)
Tributyl phosphate	Solvent; plasticizer	3	1.28	2.04E-02	4.03E-03 (6.60E-03)	5.05 (3.09)
Potassium perfluorohexanesulfonate	Organofluorine	2	0.0825	3.09E-04	3.09E-05 (7.27E-05)	10.02 (4.26)
Dioctyl phthalate	plasticizer	6	4.88	7.62E-02	7.49E-03 (1.34E-02)	10.18 (5.68)
DES	Nonsteroidal estrogen	6	0.000074	1.61E-04	1.49E-05 (2.84E-05)	10.82 (5.68)
Diphenhydramine hydrochloride	Antihistamine drug	2	0.0238	4.91E-03	1.95E-04 (4.27E-04)	25.21 (11.51)
Dinoseb	Herbicide	6	0.35	7.20E-04	1.76E-05 (2.87E-05)	40.81 (25.12)
Oxytetracycline hydrochloride	antibiotic	1	0.004	3.17E-03	7.11E-05 (1.06E-04)	44.64 (29.92)
1,2-Benzisothiazolin-3-one	Microbicide; fungicide	4	0.424	5.89E-02	7.78E-04 (2.00E-03)	75.69 (29.48)

RISK21

A TIERED APPROACH TO CHEMICAL PRIORITIZATION

PRINCIPLES OF A TIERED APPROACH

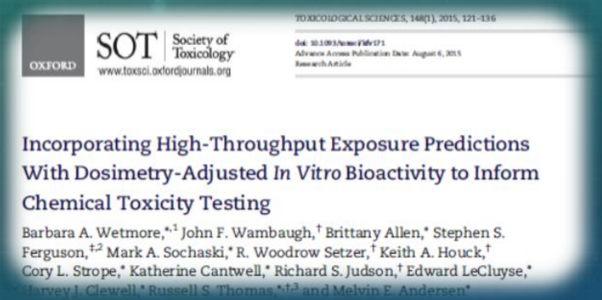


Limitations

- Not applicable to all chemicals
  - ✓ Bioaccumulative
  - ✓ Inorganic
  - ✓ Radioactive
  - ✓ High potency genotoxic
  - ✓ …
- HT Toxicity assessment based on the most potent assay hit
  - ✓ MOA or downstream effects not evaluated
- Costly
- Animal welfare issues
- High labor, time, space requirements…

APPROACH OVERVIEW

Exposure data from Wetmore et al. for 163 chemicals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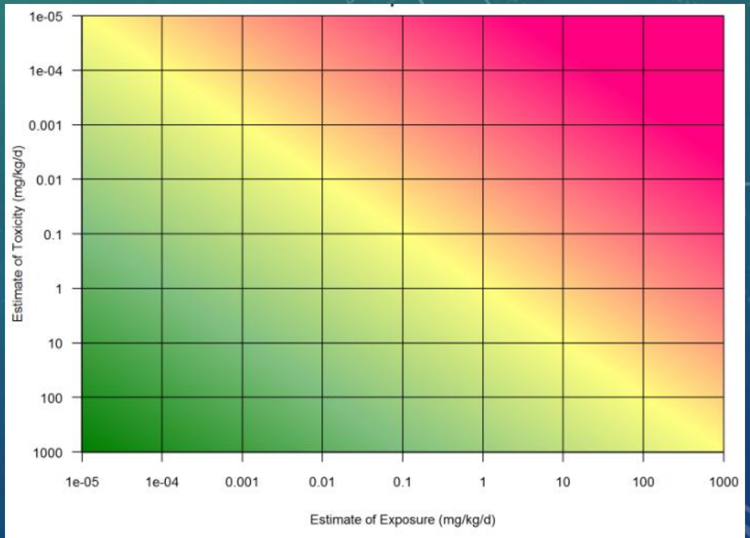
Tiered tox data:

In vivo

In vitro

TTC



RISK21

QUESTION

What chemicals should be prioritized for toxicity testing according to the RISK21 approach?

TTC APPROACH

TIER 0

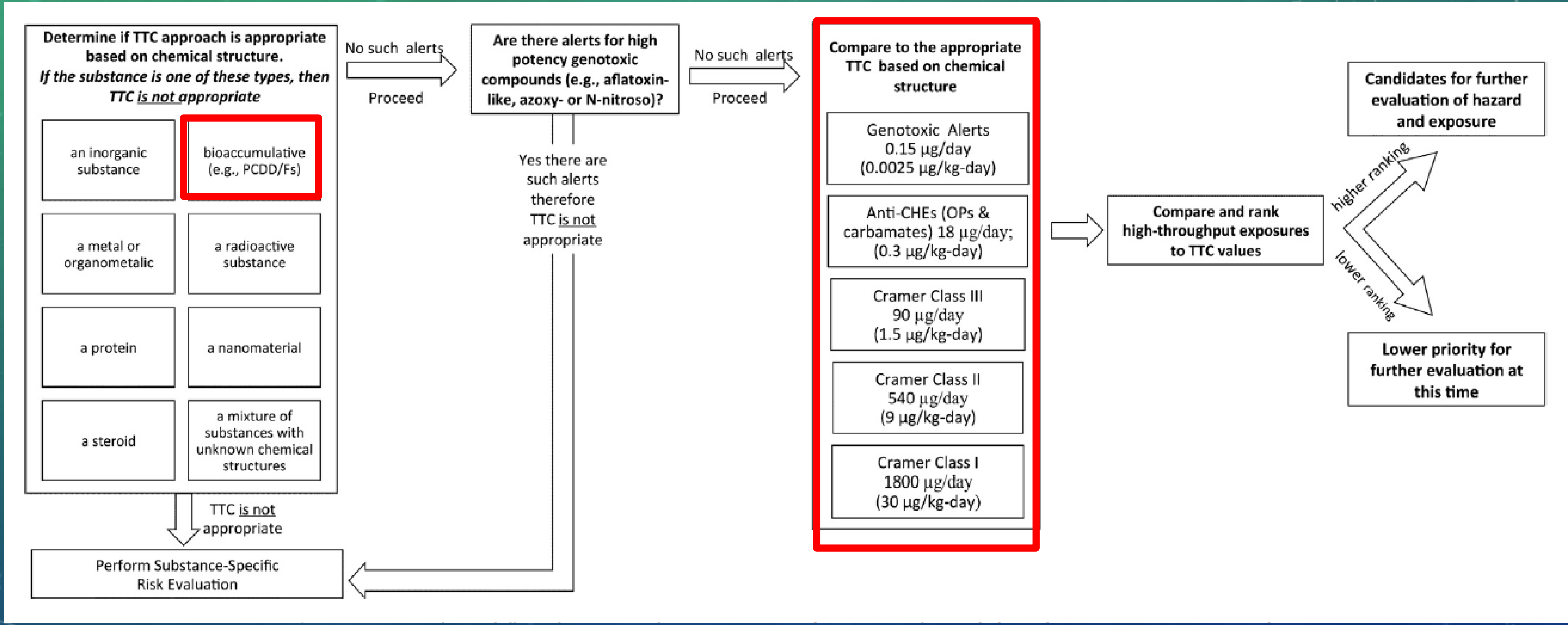
THRESHOLD OF TOXICOLOGICAL CONCERN APPROACH

Premise
For most chemicals, including those of unknown toxicity, there exist
a level of exposure below which there is no appreciable risk to human health.

- This low level of exposure only depends on chemical structure
- Structure leads to 3 classes: the Cramer classification
  - Cramer Class I: 30 µg/kg/d
  - Cramer Class II: 9 µg/kg/d
  - Cramer Class III: 1.5 µg/kg/d

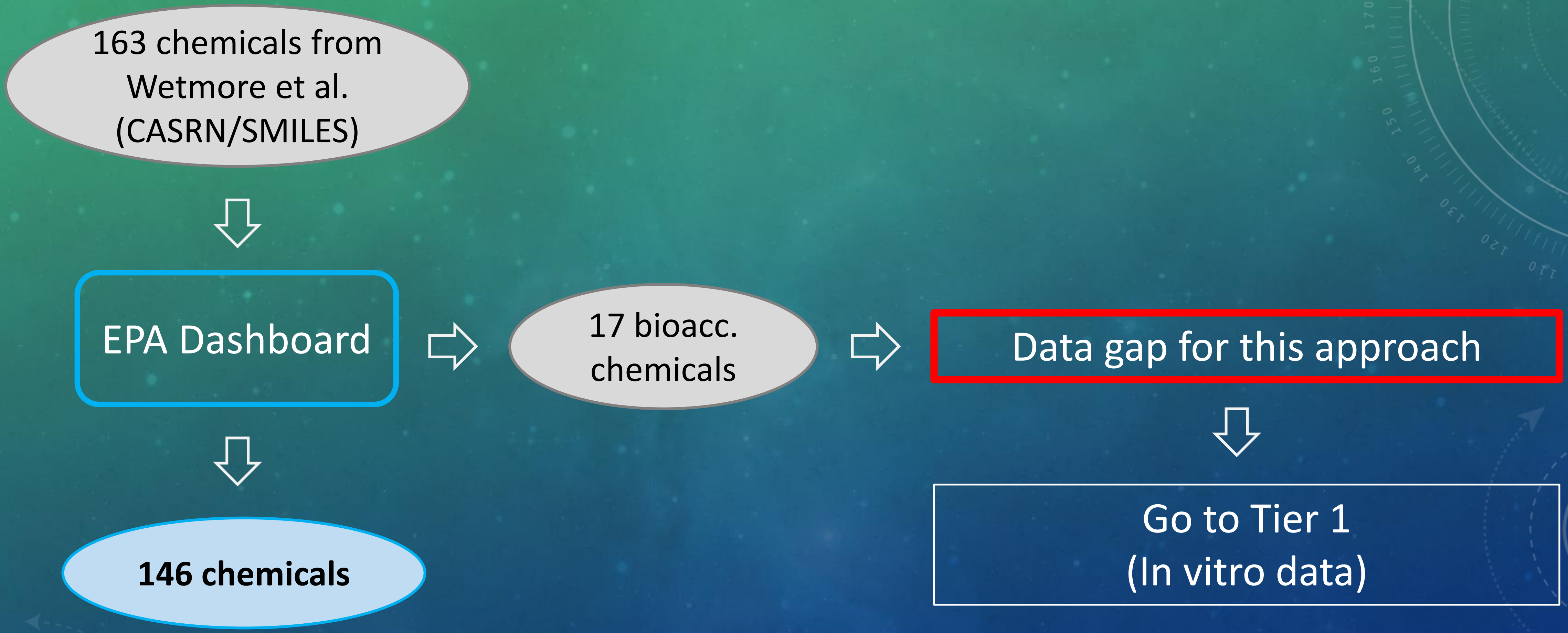
Cramer, G. M., Ford, R. A., and Hall, R. L. (1978). Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16, 255–276.

LIMITATIONS TO THE TTC APPROACH



Patlewicz, Grace, et al. "Utilizing Threshold of Toxicological Concern (TTC) with high throughput exposure predictions (HTE) as a risk-based prioritization approach for thousands of chemicals." Computational Toxicology 7 (2018): 58-67.

THRESHOLD OF TOXICOLOGICAL CONCERN APPROACH



THRESHOLD OF TOXICOLOGICAL CONCERN APPROACH

163 chemicals from Wetmore et al. (CASRN/SMILES)

⇩

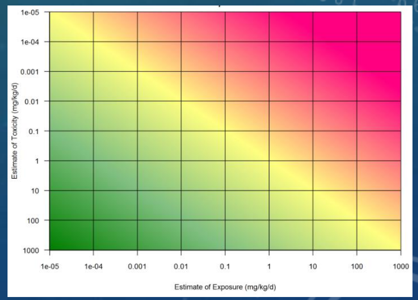
EPA Dashboard

⇩

146 chemicals ⇨ Toxtree ⇨ Toxicity estimates (TTC values)

Exposure to parent compound (Wetmore et al. 2015)

Highest exposure estimate



Patlewicz G, Jeliazkova N, Safford RJ, Worth AP, Aleksiev B. (2008) An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. SAR QSAR Environ Res. ;19(5-6):495-524.

QUESTION

163 Chemicals

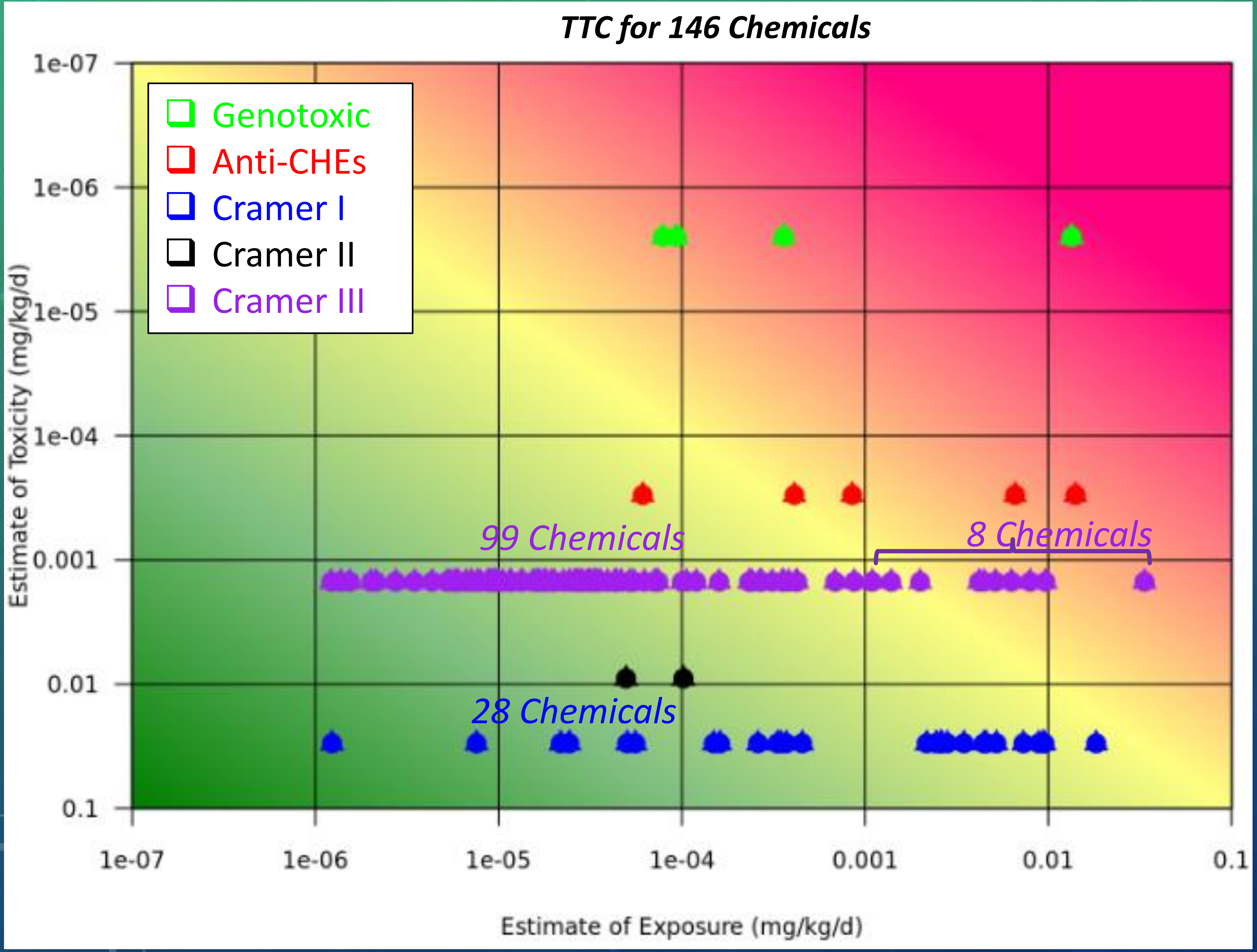
Tier 0 – TTC Approach

146 Chemicals

17 Bioaccumualtive Chemicals

What chemicals should undergo a Tier 1 evaluation?

TTC APPROACH FOR 146 CHEMICALS – MOE = 1



16 Chemicals with TTC MOE ≤1

Name	Alt MOE
Dioctyl phthalate (bis(n-octyl) phthalate)	0.00020
3,3'-Dimethylbenzidine	0.01
Triphenyl phosphate	0.02
Didecyl dimethyl ammonium chloride	0.03
Benzo(b)fluoranthene	0.03
Tannic acid	0.04
Tributyl phosphate	0.05
Naphthalene	0.16
2-Hydroxy-4-octyloxybenzophenone	0.19
Propanol, 1(or 2)-(2-methoxymethylethoxy)-	0.24
Benzophenone	0.29
Nitrobenzene	0.34
Methyl 1H-benzimidazol-2-ylcarbamate	0.35
Caffeine	0.36
Carbamazepine	0.73
1,2-Benzisothiazolin-3-one	0.75
4,4'-Diaminodiphenyl ether	1.08

COMPARISON OF TTC MOES AND MODELED AERS

Name	Alt MOE
Dioctyl phthalate (bis(n-octyl) phthalate)	0.00020
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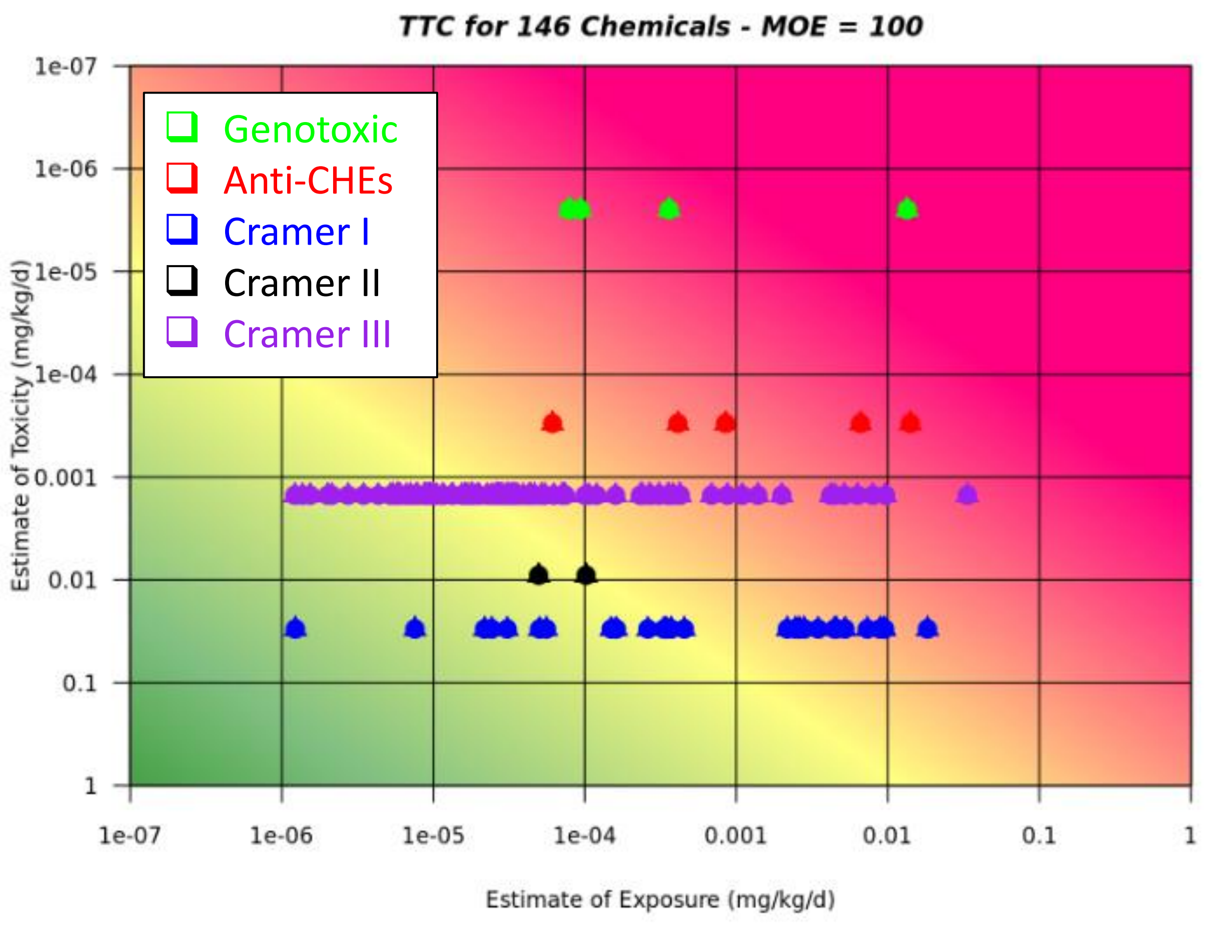
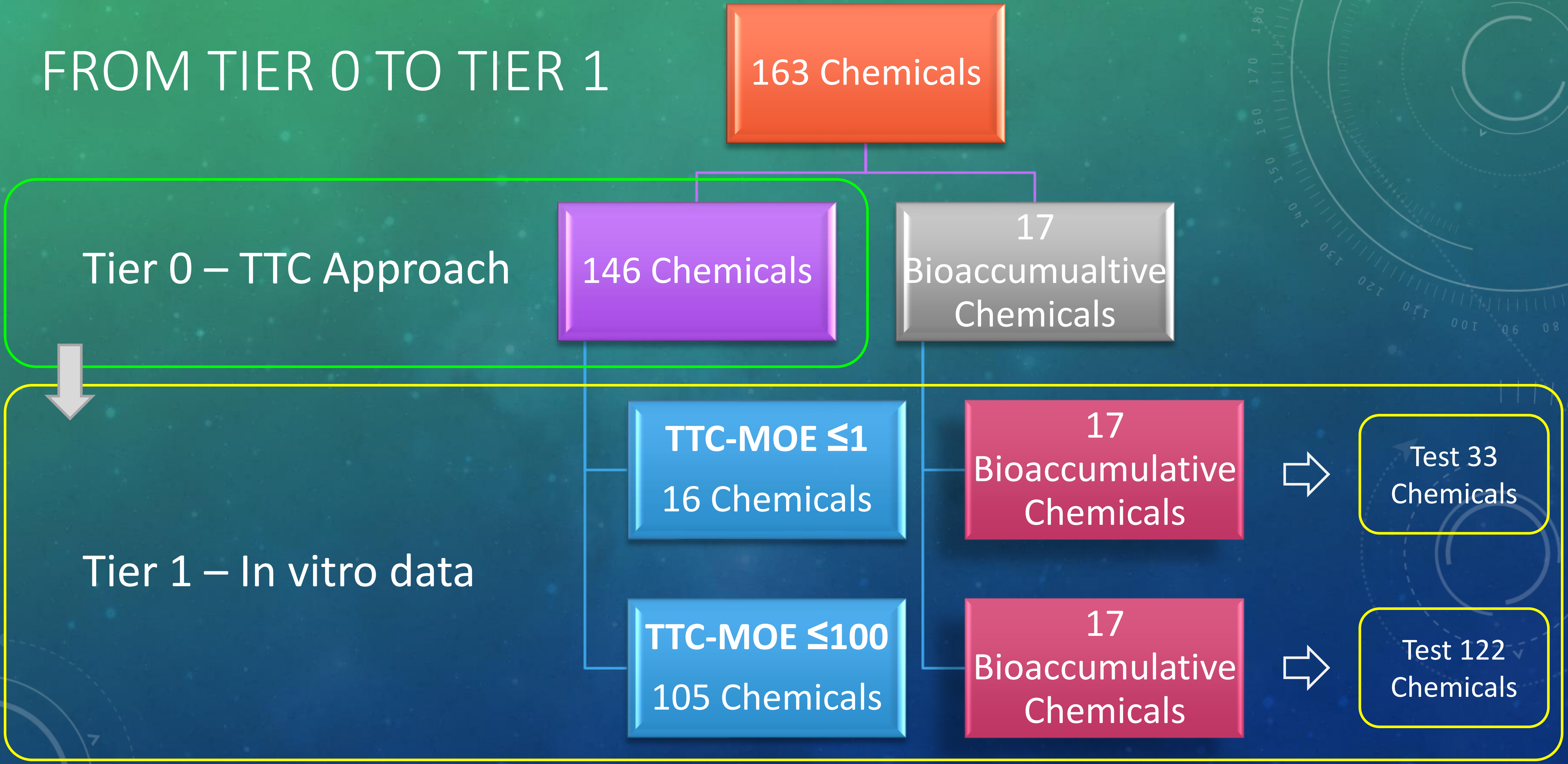
TTC APPROACH FOR 146 CHEMICALS – MOE = 100



- More conservative approach
- 105 chemicals have an MOE ≤100
- All chemicals screened out by Wetmore et al. 2015 are included in the list

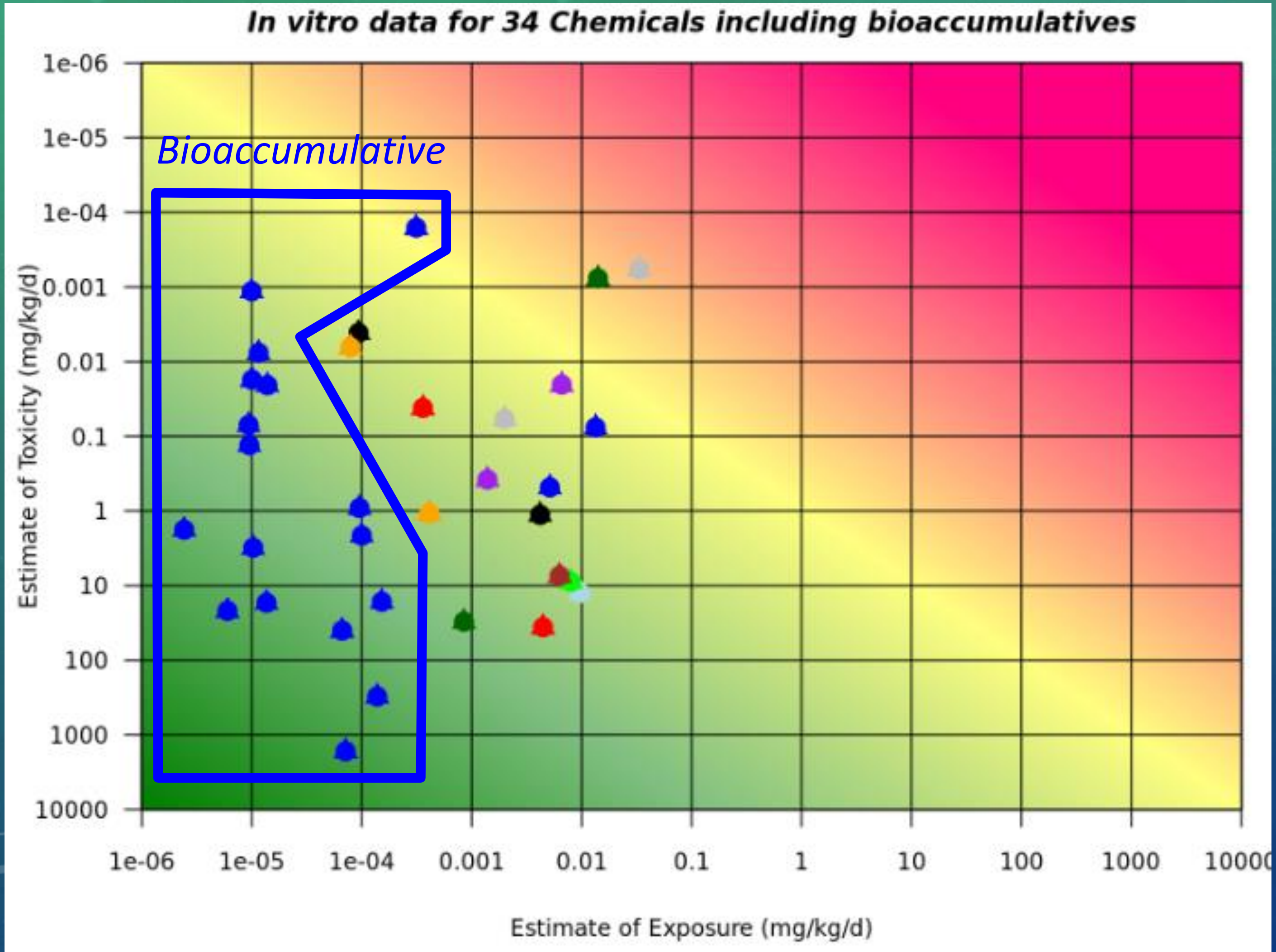
FROM TIER 0 TO TIER 1



IN VITRO APPROACH

TIER 1 - TOXICITY DATA FROM WETMORE ET AL. 2015

IN VITRO DATA FOR 16 CHEMICALS WITH TTC-MOE ≤1 AND 17 BIOACCUMULATIVE CHEMICALS



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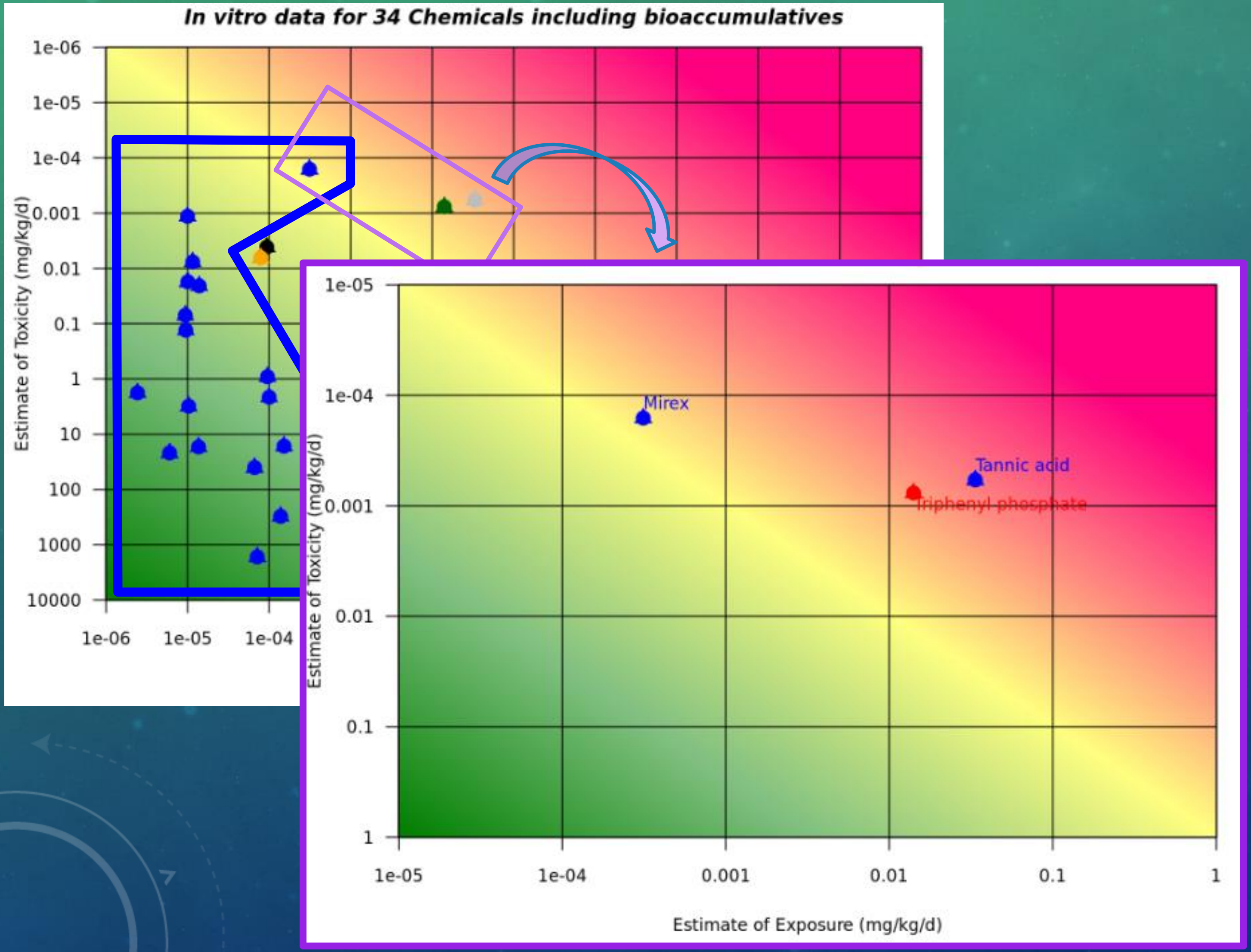
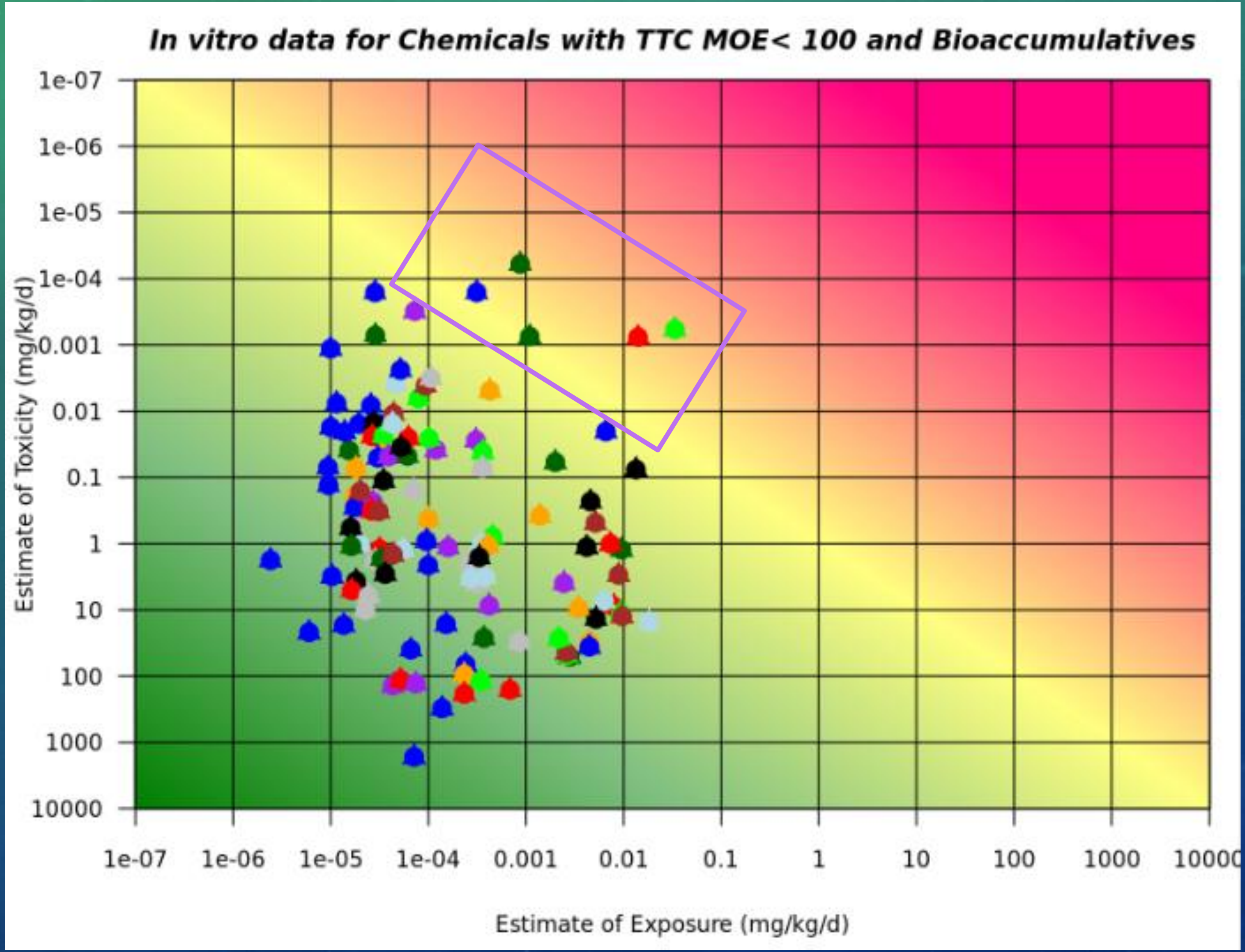
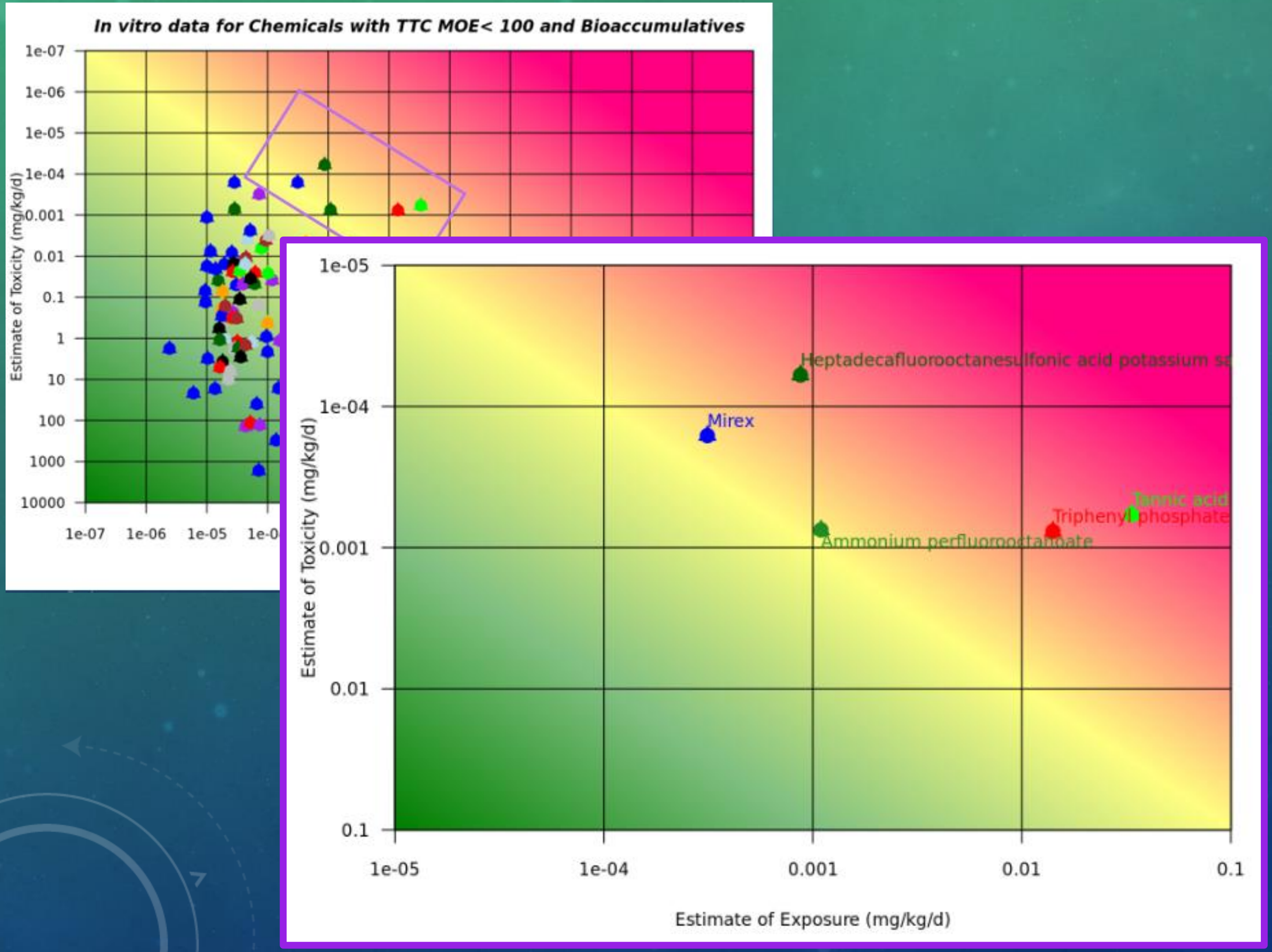


Chemical	MOE
Tannic acid	0.02
Triphenyl phosphate	0.05
Mirex	0.51

IN VITRO DATA FOR 105 CHEMICALS WITH TTC-MOE ≤100 AND 17 BIOACCUMULATIVE CHEMICALS

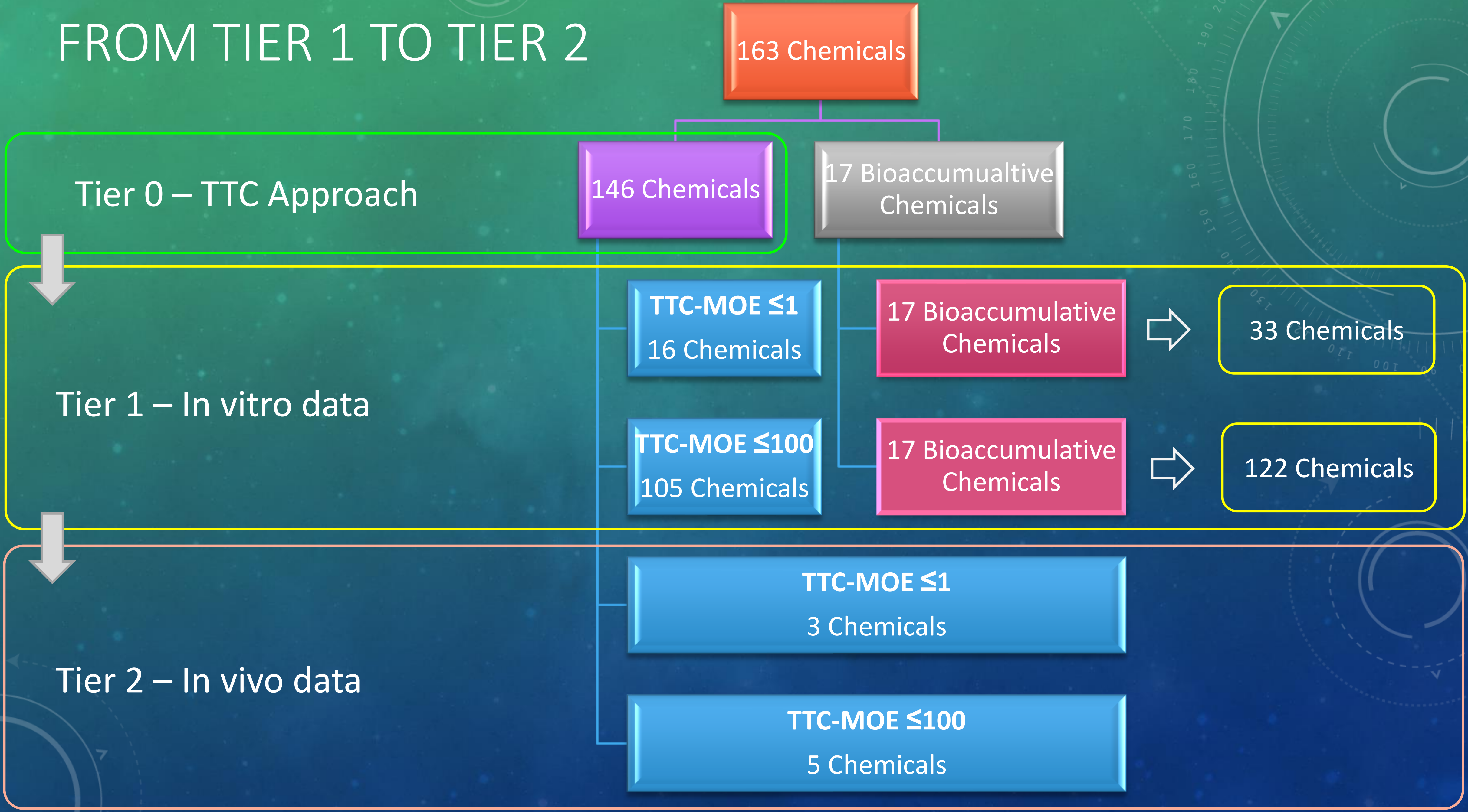


IN VITRO DATA FOR 105 CHEMICALS WITH TTC-MOE ≤100 AND 17 BIOACCUMULATIVE CHEMICALS



Chemical	MOE
Tannic acid	0.02
Triphenyl phosphate	0.05
Heptadecafluorooctanesulfonic acid potassium salt	0.07
Mirex	0.51
Ammonium perfluorooctanoate	0.68

FROM TIER 1 TO TIER 2

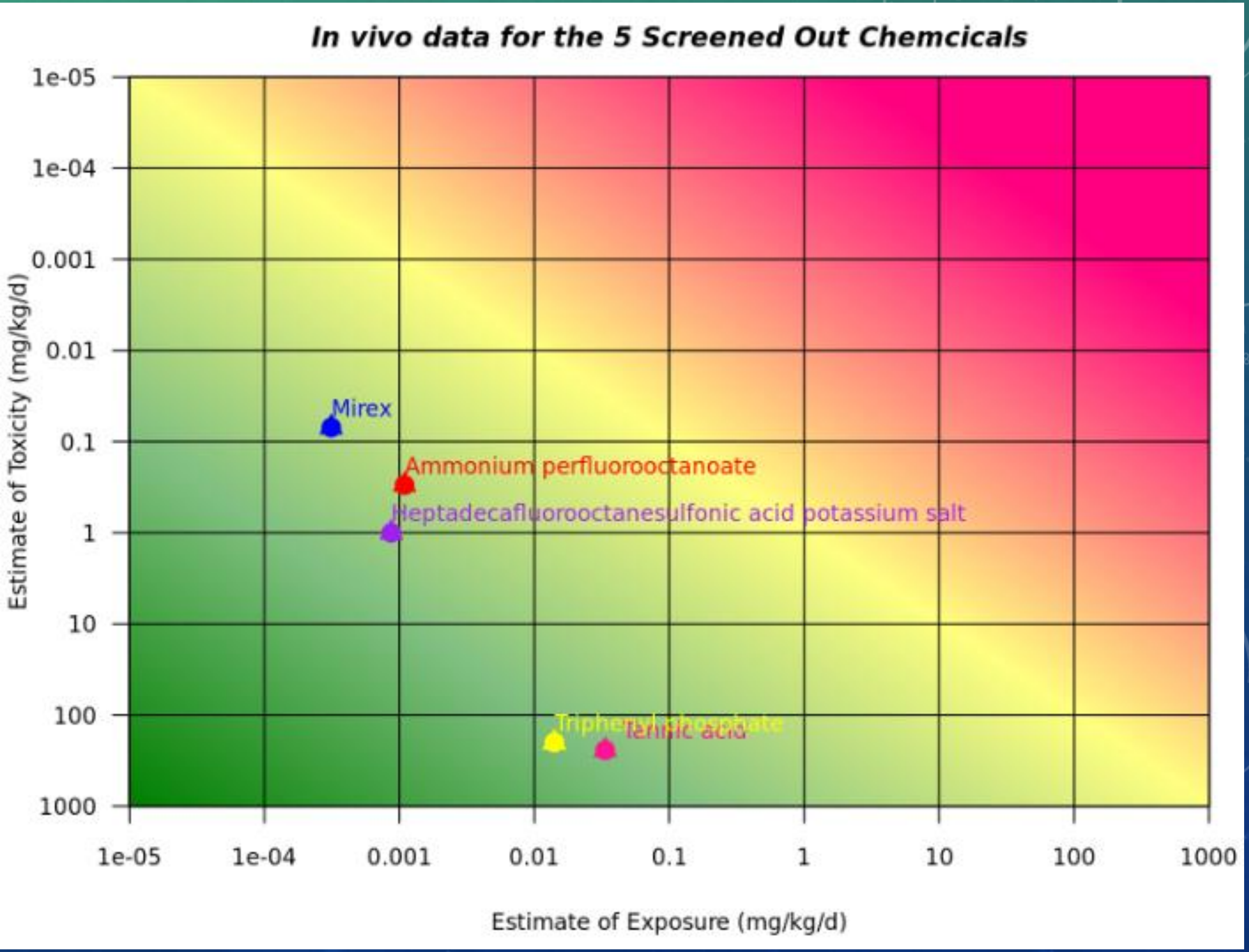


IN VIVO DATA

TIER 3

IN VIVO DATA FOR THE 5 SCREENED-OUT CHEMICALS

- NOAELs were obtained from
  - The USEPA Chemistry Dashboard
  - Other sources (TOXNET, IRIS, CPSC, OLIPA…etc.)
- The most conservative NOAEL was typically used



No major concern posed by those five chemicals

CONCLUSION

RISK21: A CONVENIENT RISK PRIORITIZATION APPROACH

- The RISK21 approach
  - Maximize the use of existing information to decrease the amount of data generated
  - Is risk-based
  - Is fit-for-purpose
  - Is visual

RISK21 provides a transparent risk-based strategy to prioritize chemical testing

THANK YOU!

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