SOT SAN DIEGO 65th Annual Meeting & ToxExpo MARCH 22-25, 2026

Use of Next Generation Risk Assessment to Evaluate the Human Safety of Sunscreen Active Ingredients

This session is an Exhibitor-Hosted Session. Although not an official part of the SOT Annual Meeting scientific program, its presentation is permitted by the Society.

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Ab Initio Case Study: Oxybenzone NGRA

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Principles of Next Generation Risk Assessment (NGRA)

"...an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing"

Dent et al 2018. Computational Toxicology, Volume 7, Pages 20-26

Main overriding principles:

- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

Principles describe how a NGRA should be conducted:

- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

Principles for documenting NGRA:

- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparent and documented

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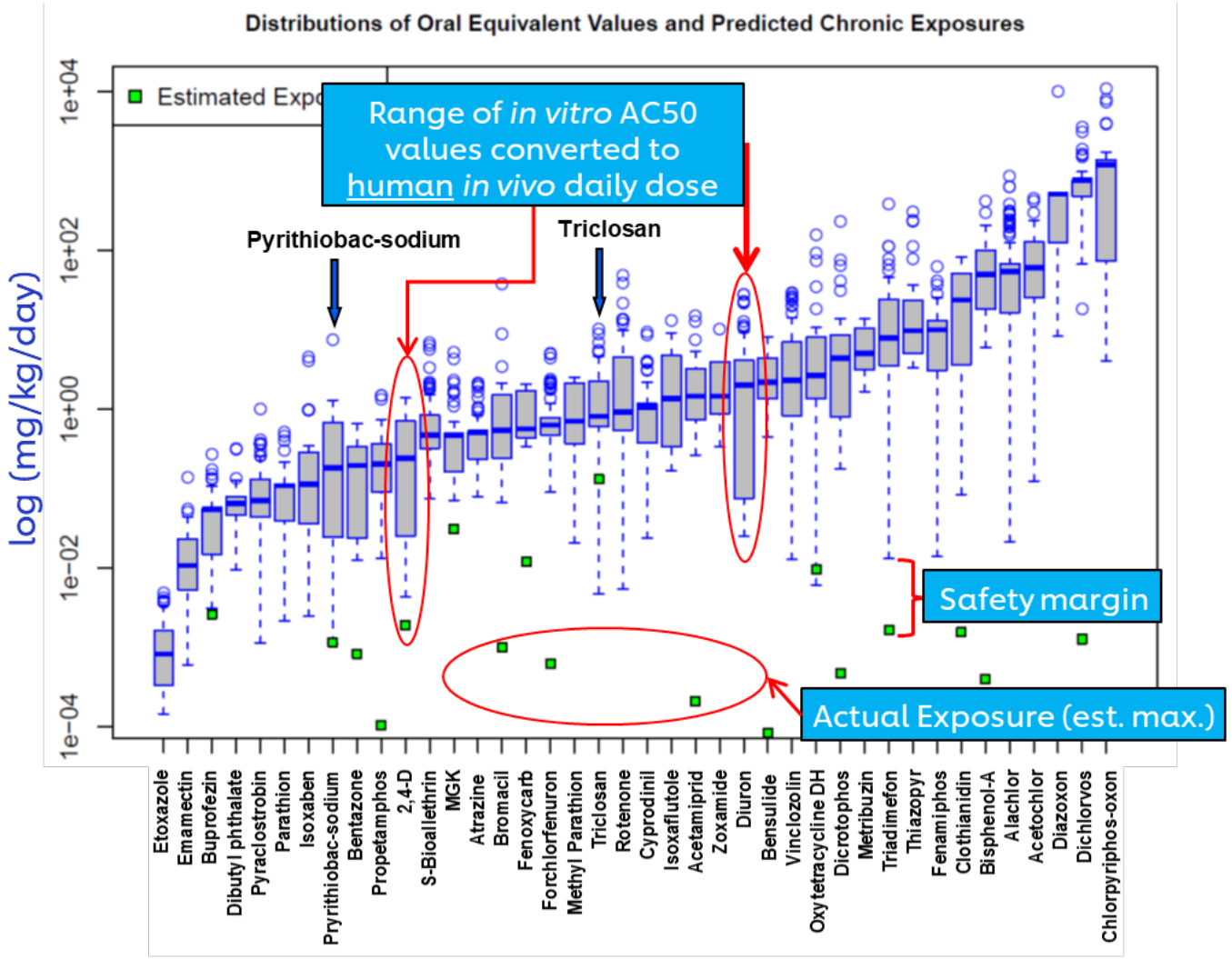
International Cooperation on Cosmetics Regulation

Protection and prediction – This NGRA strategy



- If there is **no** bioactivity observed at consumer-relevant concentrations, there can be no adverse health effects.
- If there **is** bioactivity observed at consumer-relevant concentrations, follow up testing is required to establish if that could result in an adverse effect.
- At no point does NGRA attempt to **predict** the results of high dose toxicology studies in animals.

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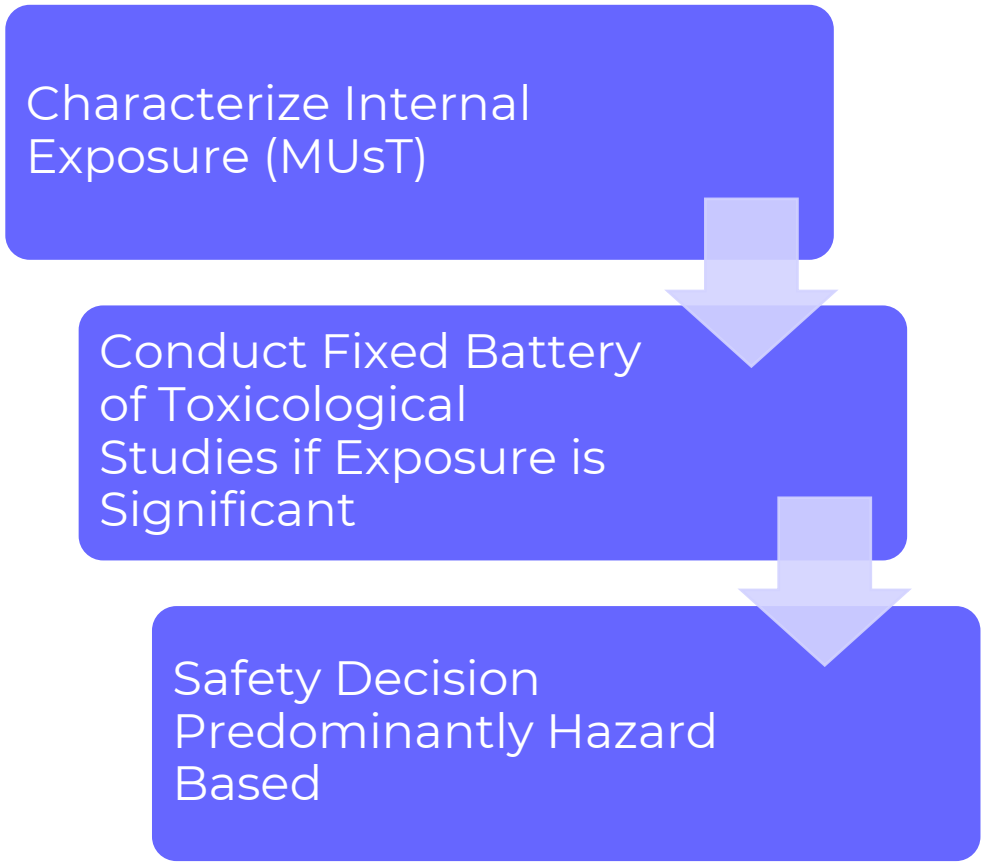
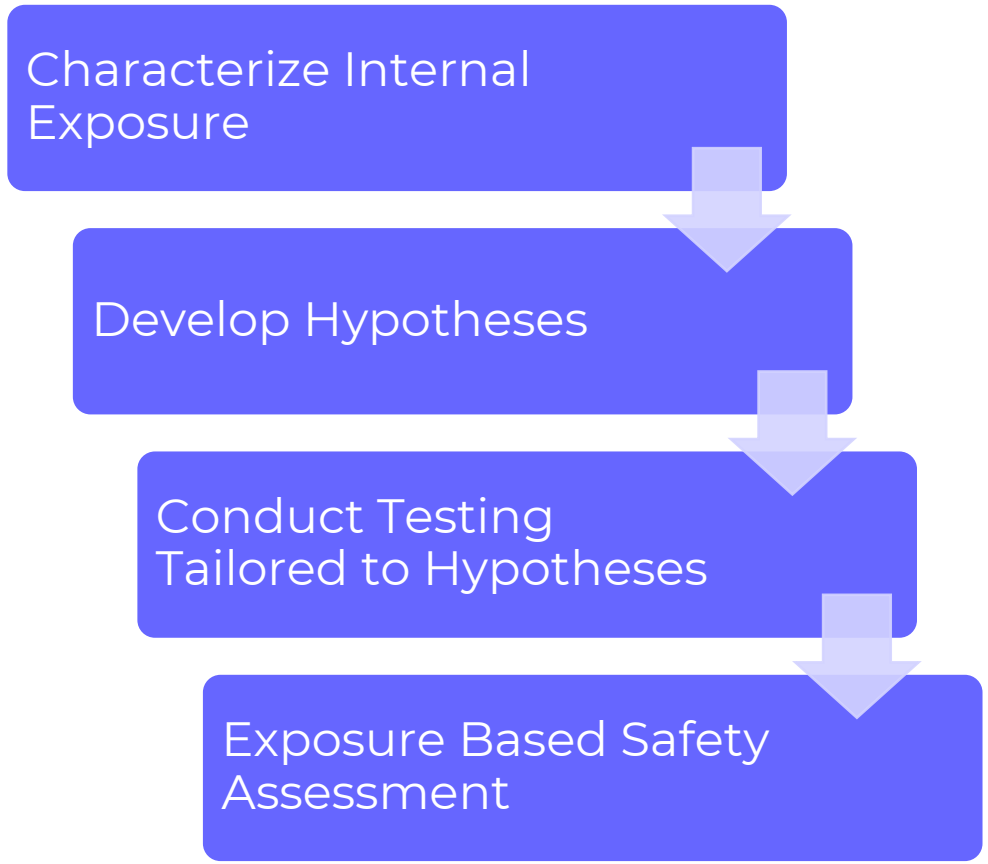
Graph from Rusty Thomas, with thanks. Rotroff et al., (2010) Toxicol Sci 117:348-358

Traditional approach compared with NGRA

Traditional Approach



Next Generation Risk Assessment



OXYBENZONE CASE STUDY

Oxybenzone: Objectives and Approach

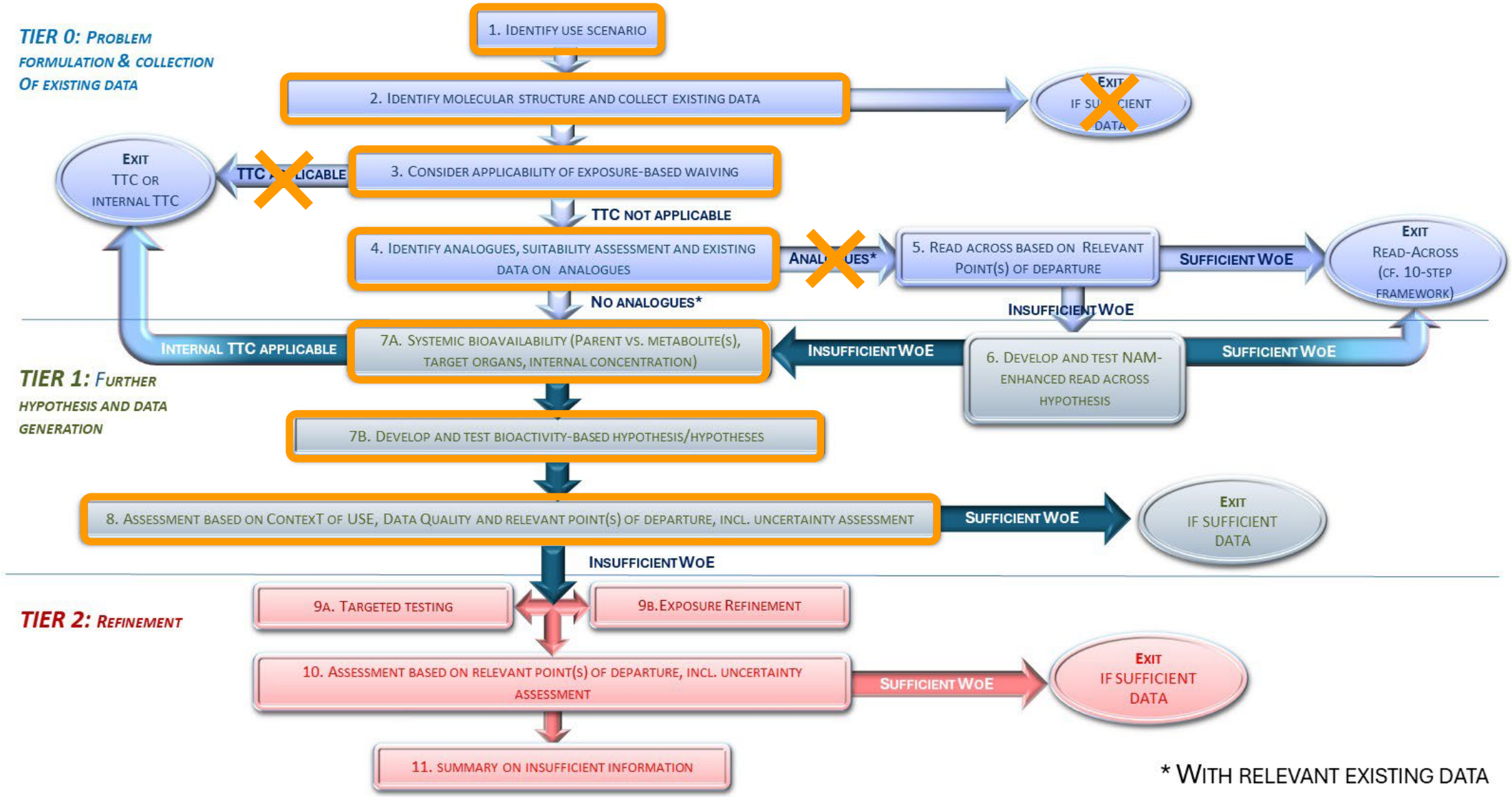
To illustrate the overall structure of an exposure-led, tiered NGRA approach to assess the safety of an active ingredient under regulatory scrutiny

Is Oxybenzone safe for consumers when used at up to 4% in a sunscreen product?

Oxybenzone: Rules and Assumptions

- For the purposes of this exercise, it has been assumed that **no *in vivo* animal data exist on the ingredient**
- **Stand-alone illustration of how to assess systemic, developmental and reproductive effects** (not including genetic toxicity) **using NAMs**
  - Data shared today are from existing published sources
  - A comprehensive NGRA with new data generated by ICCS and led by colleagues at L'Oréal is being developed

Oxybenzone: Overall approach



* WITH RELEVANT EXISTING DATA

Oxybenzone: Use Scenario

- Oxybenzone (CAS 131-57-7) has been used in sunscreen products in many geographies for decades. In the EU it is approved for use at up to 2% and in the USA at up to 6%.

- The specific use scenario of this case study is for **dermal application** of a **leave-on sunscreen formulation containing oxybenzone at up to 4%, applied over 75% of the body surface area** at a dose of 2 mg/cm^{2*}.

*Golbamaki et al., 2025, Pharmaceuticals 18(11)1607) - Repeat exposure of one application on Day 1, followed by four applications per day on Days 2–4 with a 2 h interval modelled

Oxybenzone: Exposure Estimation

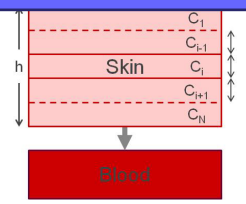
From applied dose to internal concentrations

External dose

- **Route of exposure**
- **Consumer use (Habits & Practices)**
- **Applied dose (external concentratio**

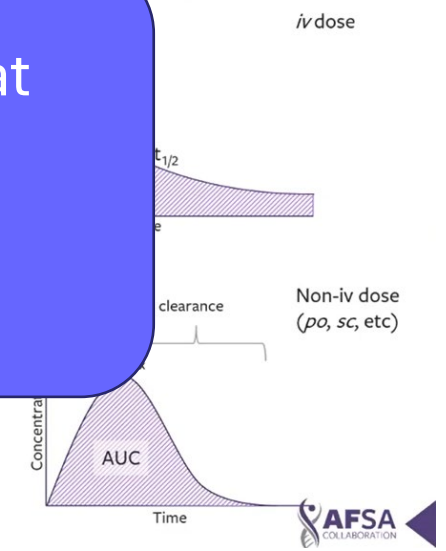
ADME parameters

Absorption
Distribution
Metabolism
Elimination



Kinetic profile of chemical

Physiologically-based kinetic (PBK) modelling – Internal concentration (plasma, urine, organ-level)



Images from: AFSA training module "Dosimetry (Internal Exposure)",2022

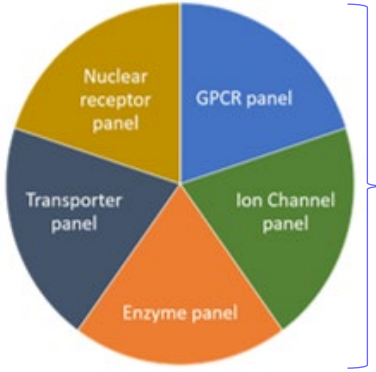
Predicted plasma exposure following repeat exposure = 0.56 µM

Golbamaki et al., 2025, Pharmaceuticals 18(11)1607

https://www.afsacollaboration.org/sciencex_event/dosimetry-internal-exposure-ivive/

Oxybenzone: Bioactivity NAMs

In vitro pharmacological profiling



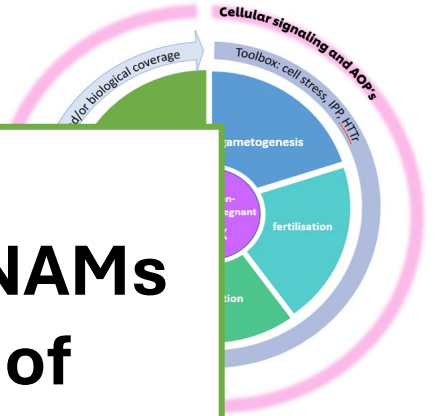
eurofins | Cerep

EATS assays

Bur

Developmental Assays

Induced pluripotent stem cell assays



HTTr

IPP

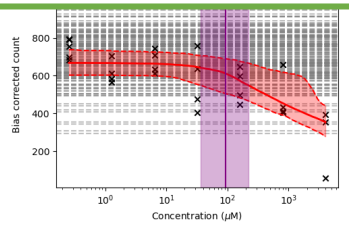
2022. Front Toxicol. 4:838466

This combination of bioactivity NAMs provides conservative points of departure for systemic, developmental and reproductive toxicity

Cable et al., 2025 Toxicol Sci 204(1)79-95
Mueller et al., 2025 Front Toxicol 7:1602065

High-Throughput

- TempO-seek technology panel
- 24hr exposure
- 7 concentrations
- Cell models: HepG2, MCF7, HepaRG and others
- Dose-response analysis using BMDExpress2 and BIFROST model



Reynolds et al. 2020. Comp Tox 16: 100138
Baltazar et al. 2020. Toxicol Sci 176(1): 236–252

- 8 concentrations
- Dose-response analysis using BIFROST model

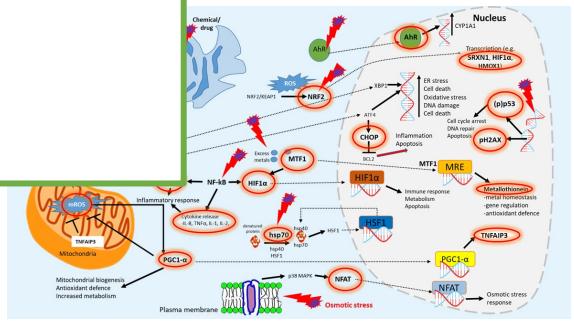


Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. Toxicol Sci 176(1): 11-33

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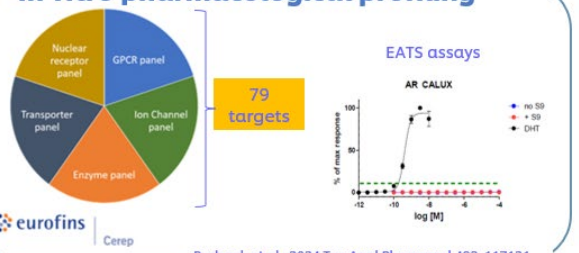
Bioactivity Exposure Ratios (BER)

BIOACTIVITY

In vitro pharmacological profiling



Burbank et al., 2024 Tox Appl Pharmacol 492: 117131

Developmental Assays

Induced pluripotent stem cell assays

ReproTracker

devTOX qP quickPREDICT

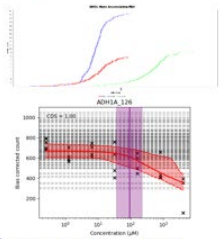
HTTr

IPP

Rajagopal et al. 2022. Front Toxicol. 4:838466

High-Throughput transcriptomics

- TempO-seek technology – full gene panel
- 24hr exposure
- 7 concentrations
- Cell models: HepG2, MCF7, HepaRG and others
- Dose-response analysis using BMDExpress2 and BIFROST model



Reynolds et al. 2020. Comp Tox 16: 100138
Baltazar et al. 2020. Toxicol Sci 176(1): 236–252

Cell stress panel (CSP)

- 36 biomarkers covering 10 cell stress pathways
- HepG2
- 24hr exposure
- 8 concentrations
- Dose-response analysis using BIFROST model

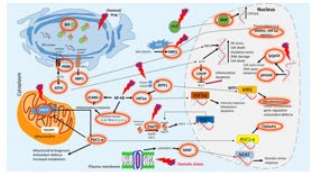
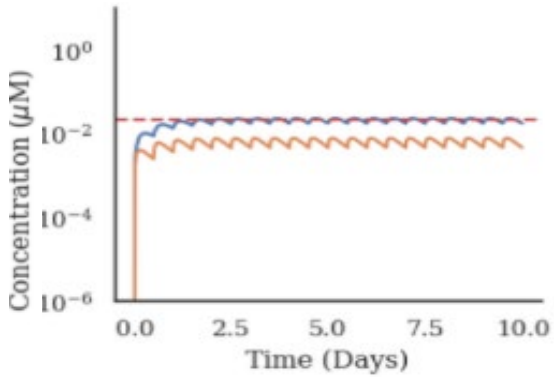


Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. Toxicol Sci 176(1): 11-33

Identify relevant point of departure (PoD), expressed in µM

EXPOSURE



Identify realistic worst-case plasma exposure (C_{max}) expressed in µM

$$\text{BIOACTIVITY EXPOSURE RATIO (BER)} = \frac{\text{BIOACTIVITY}}{\text{EXPOSURE}}$$

The bigger the BER, the greater the confidence that bioactivity will not occur in exposed population

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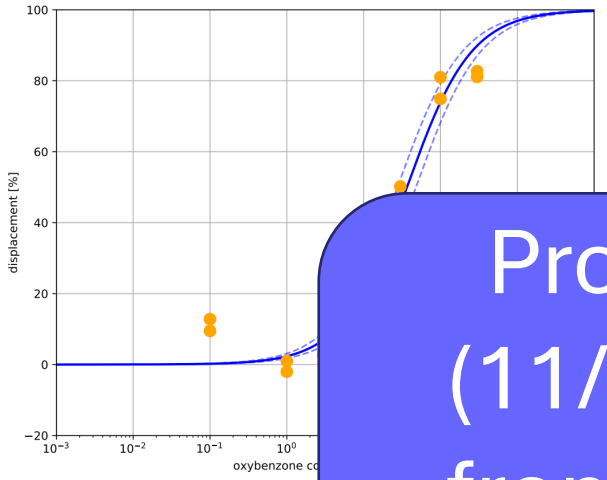
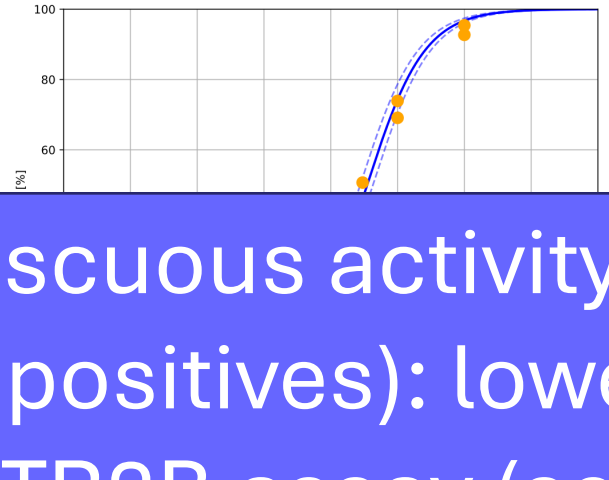
Oxybenzone: Key results – pharmacological profiling

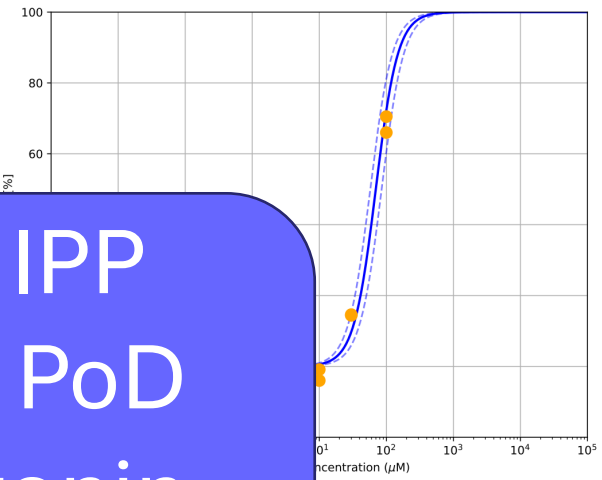
SLC6A3, 95% C.I.(IC50) = [28.0µM, 47.5µM]



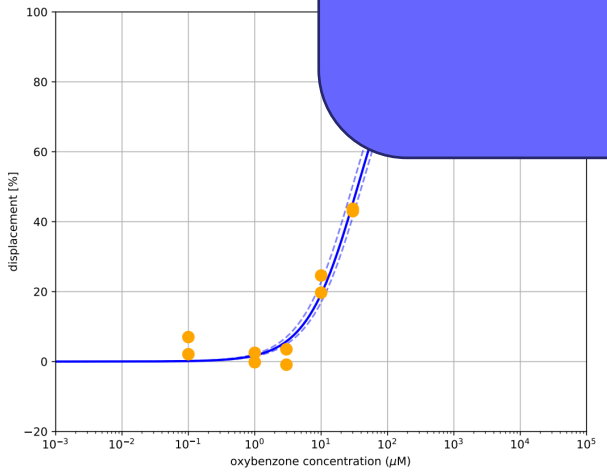
HTR2B, 95% C.I.(IC50) = [2.8µM, 4.3µM]

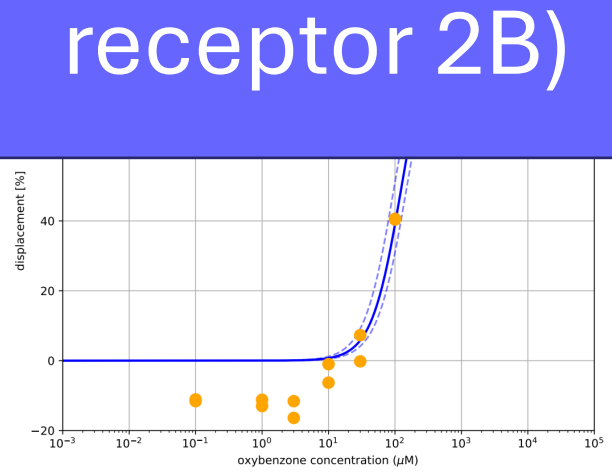


CAR, 95% C.I.(IC50) = [59.2µM, 84.1µM]

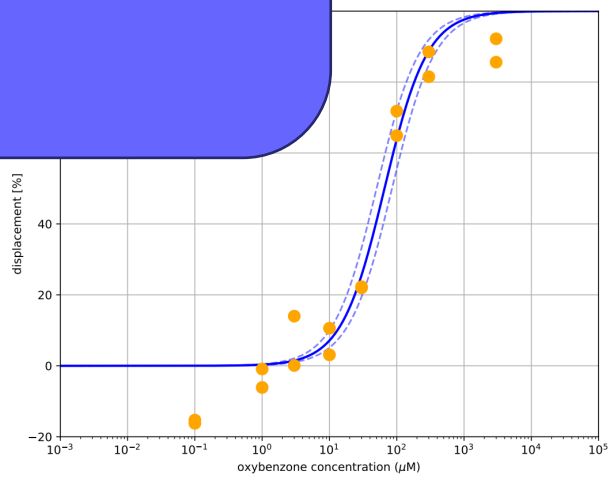


ADORA2A, 95% C.I.(IC





= [51.1µM, 85.1µM]



Promiscuous activity in IPP (11/79 positives): lowest PoD from HTR2B assay (serotonin receptor 2B)

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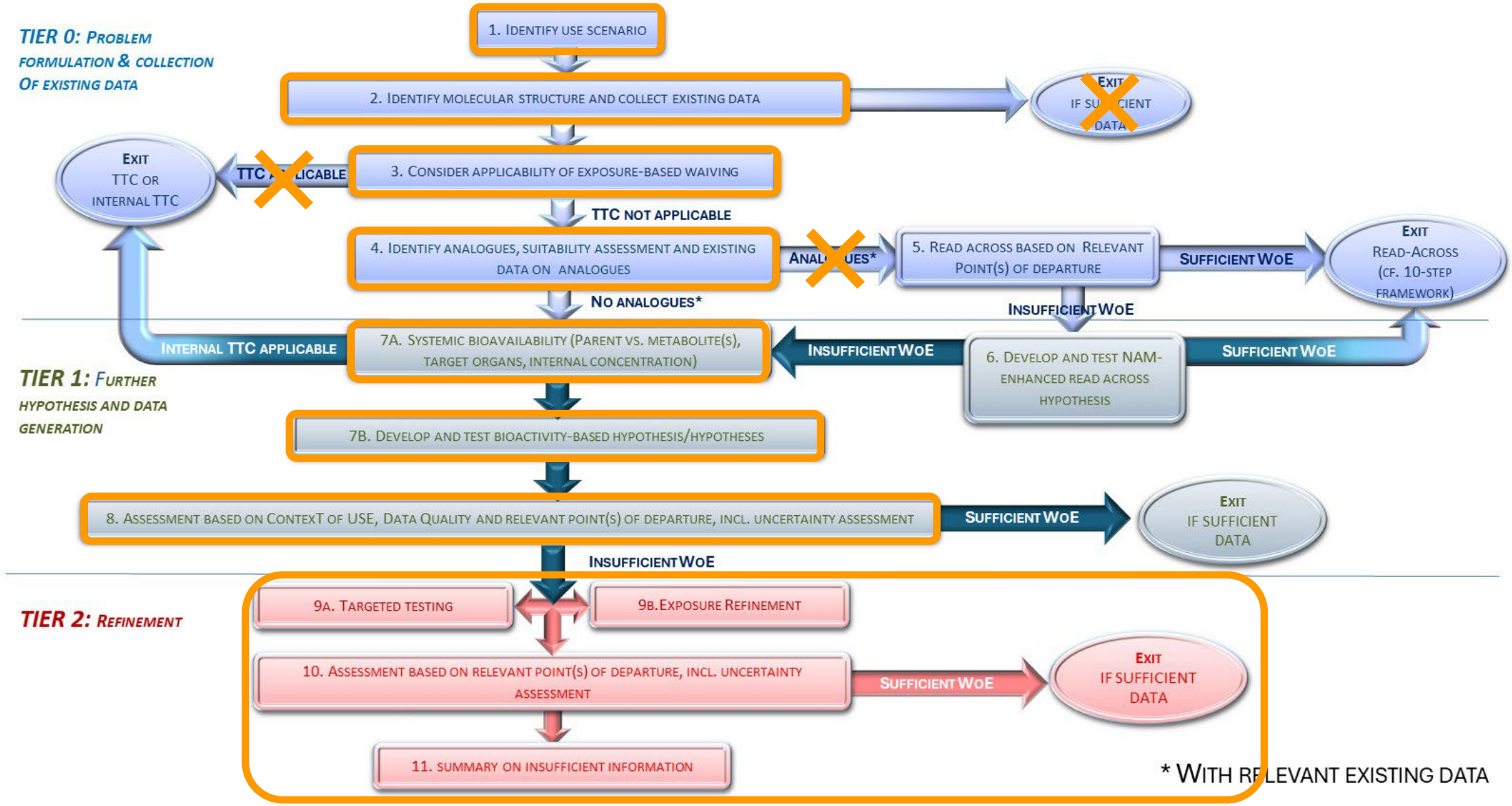
Middleton et al., 2022 Toxicol. Sci. 189/1: 124-147

Oxybenzone: Some illustrative PoDs and BERs

Cell Type	PoD type	PoD	BER
-	IPP Lowest AC_{50}	2.8	5.0
HepG2	Cell Stress	9.2	16.5
HepaRG	Gene level HTTr	4.9	8.7
HepG2	Gene level HTTr	6.3	11.3
MCF-7	Gene level HTTr	0.7	1.2
HepaRG	Pathway $BMDL_{10}$	91.8	163.7
HepG2	Pathway $BMDL_{10}$	35.7	63.7
MCF-7	Pathway $BMDL_{10}$	22.3	39.7

AREG:
transmembrane glycoprotein involved in signalling pathways related to cell growth and differentiation

Oxybenzone: Overall approach



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Conclusions and Reflections

- An exposure-led framework is needed to unlock the full potential of NAMs for safety decision making.
- NGRA allows protective (often very conservative) safety decisions to be made.
- Tiering is critical: bioactivity vs. adversity.
- Confidence can be built in the use of NAMs through application to real world safety decisions.

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Thank You