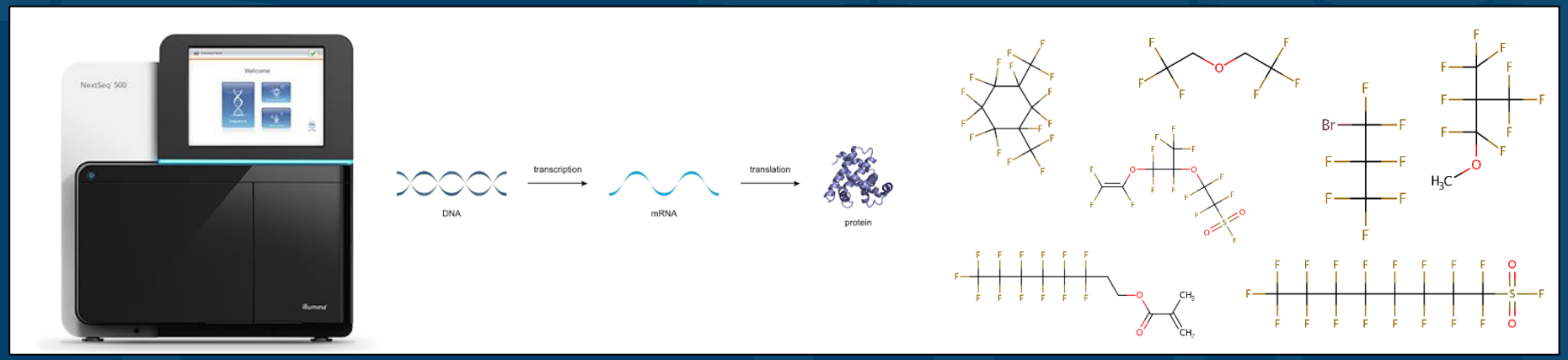
Briefing on the Draft EPA Transcriptomic Assessment Product (ETAP)



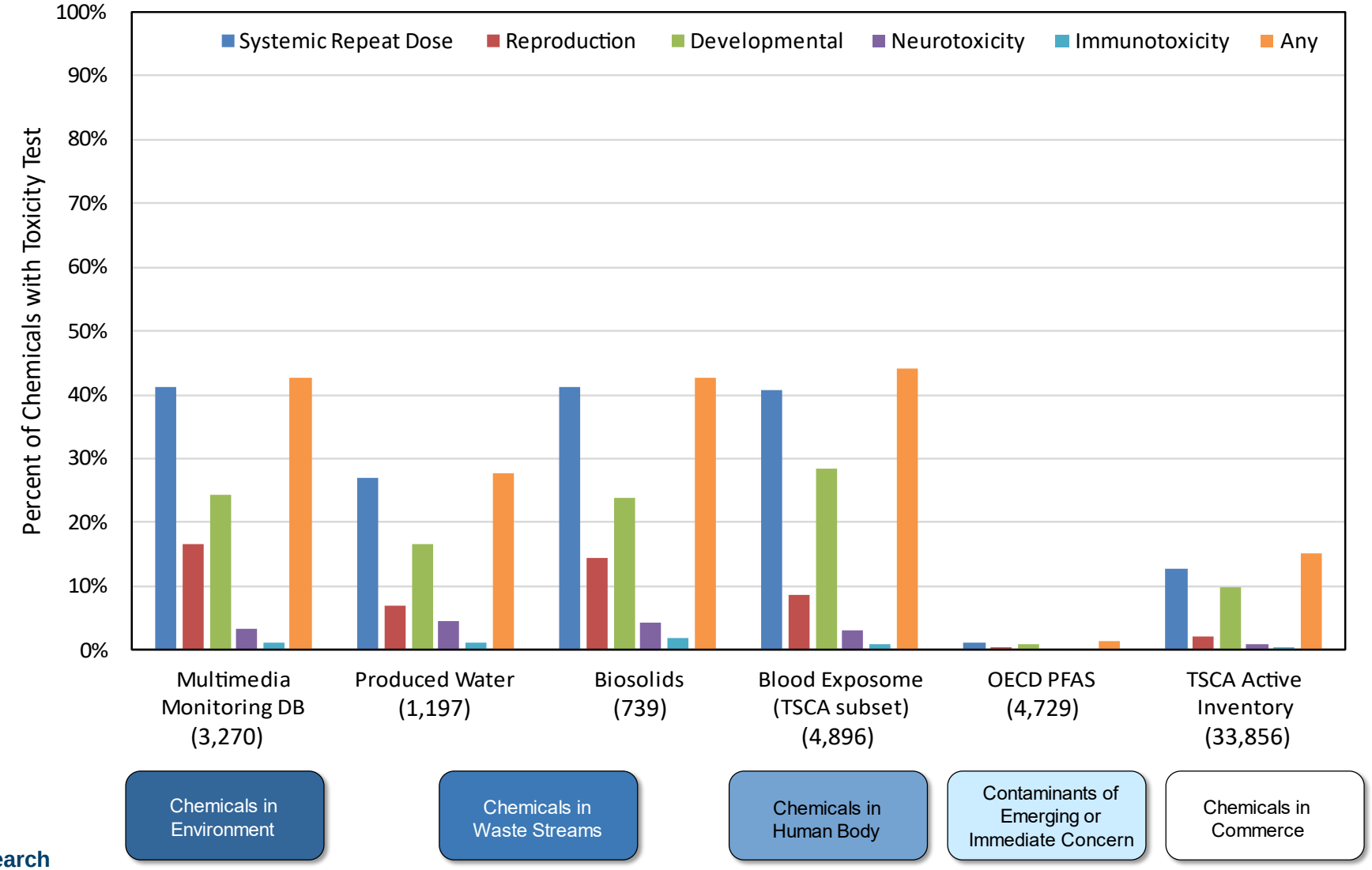
EPA Executive BOSC Committee Meeting

October 26, 2023

Alison Harrill, PhD. Associate Director for Toxicology (CCTE)

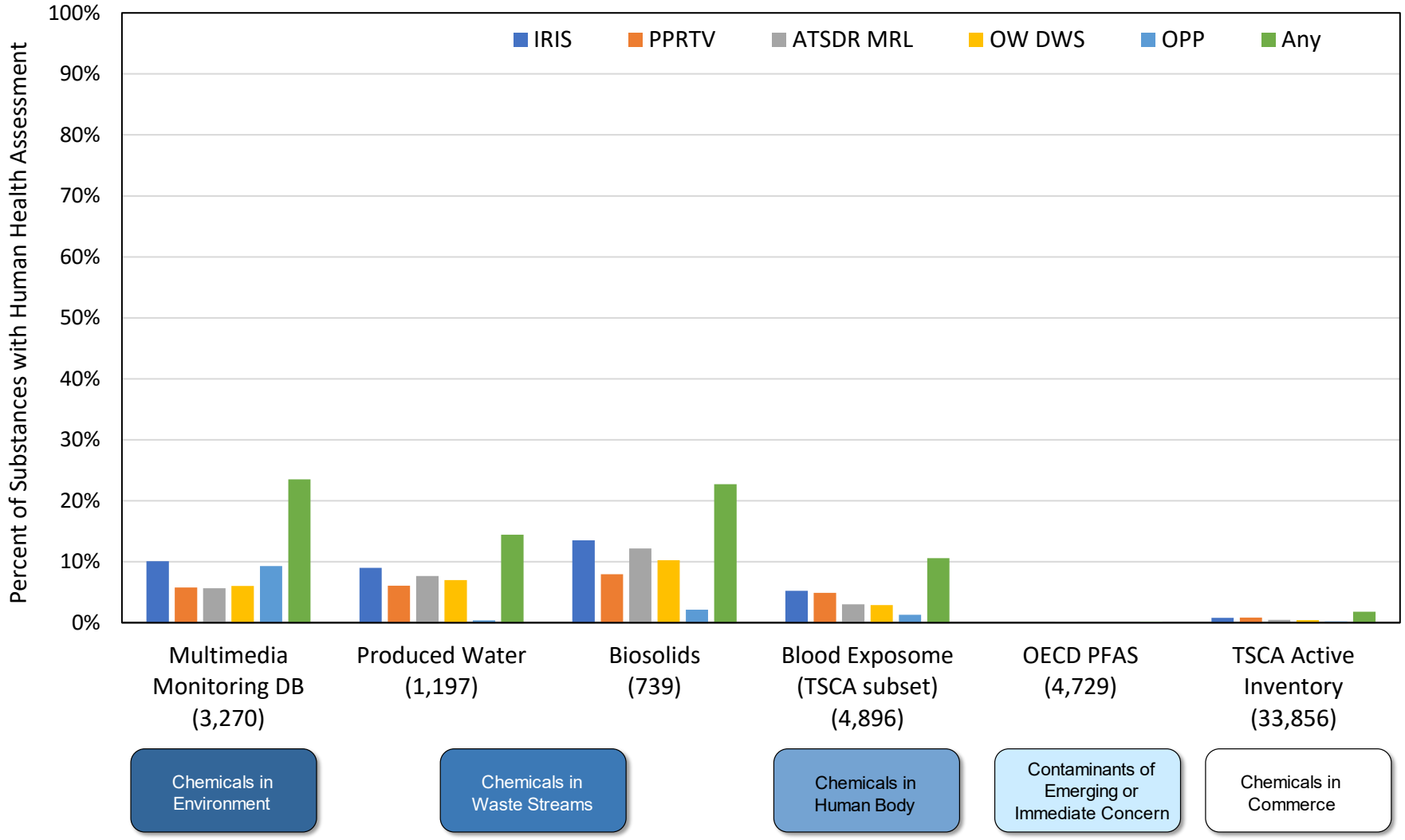
Center for Computational Toxicology and Exposure and Center for Public Health and Environmental Assessment

Less Than Half of Chemicals Within the Representative Sets Have Traditional Toxicity Testing Data



*Toxicity testing data obtained from ToxVal v9.4

Relatively Few Chemicals in Different Exposure or Regulatory Contexts Have Human Health Assessments



IRIS – US EPA Integrated Risk Information System

PPRTV – US EPA Provisional Peer Reviewed Toxicity Values

ATSDR MRL – Agency for Toxic Substances and Disease Registry Minimal Risk Levels

OW DWS – US EPA Office of Water Health Advisories

OPP – US EPA Office of Pesticide Programs

Time and Resources From No Data to a Human Health Assessment Using Traditional Approach Are Significant

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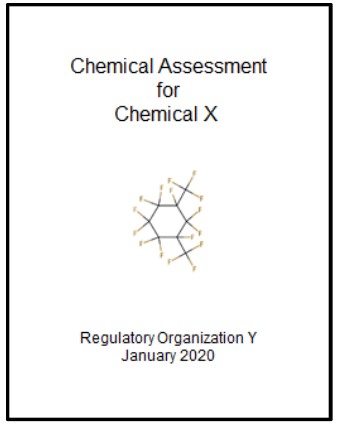


= 6 – 14+ years

- Time from chemical identification to finalizing report can range from 2 – 10 years

- Time to perform a typical chemical assessment is 4+ years (Krewski *et al., Arch Toxicol.,* 2020).
- More complex assessments can take substantially longer (NASEM, 2009).

EPA is Proposing New Human Health Assessment Product Based on Transcriptomics

EPA is obtaining scientific peer-review and public comment on a new draft ORD human health assessment product for data poor chemicals and a case study evaluating the human health and economic trade-offs of the draft assessment product.

<u>EPA Transcriptomic Assessment Product (ETAP) *ad hoc* Board of Scientific Counselors Meeting</u>

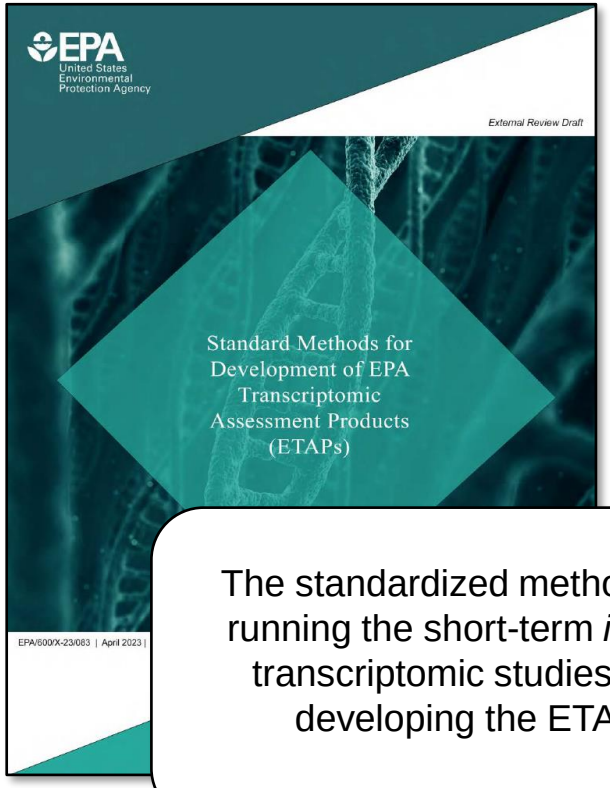
- July 11 – 12, 2023
- Committee details, meeting notice, and scientific reports available at: https://www.epa.gov/bosc/epa-transcriptomic-assessment-products-etap-panel

<u>ETAP Value of Information Case Study *ad hoc* Board of Scientific Counselors Meeting</u>

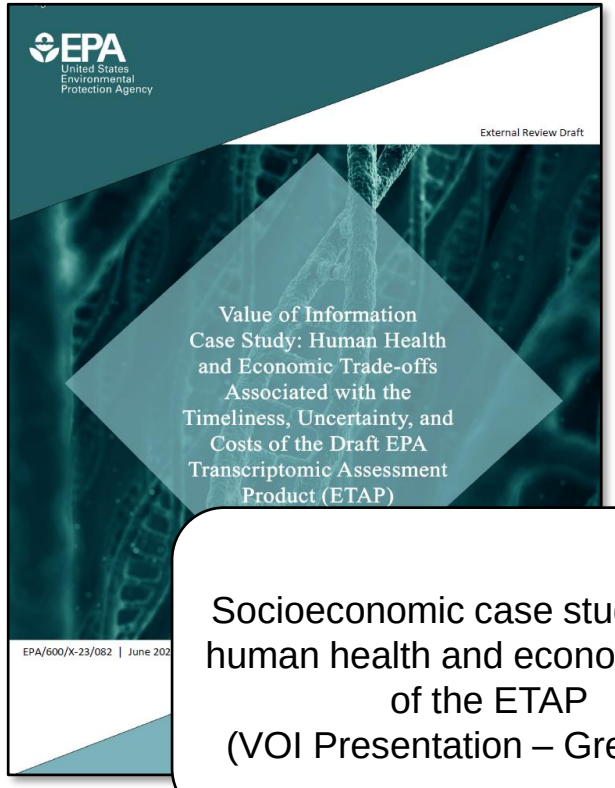
- July 25 – 26, 2023
- Committee details, meeting notice, and scientific reports available at: https://www.epa.gov/bosc/value-information-voi-panel

Three EPA Reports Developed for BOSC Review

Scientific support for developing and applying transcriptomic points-of-departure



The standardized methods for running the short-term *in vivo* transcriptomic studies and developing the ETAP

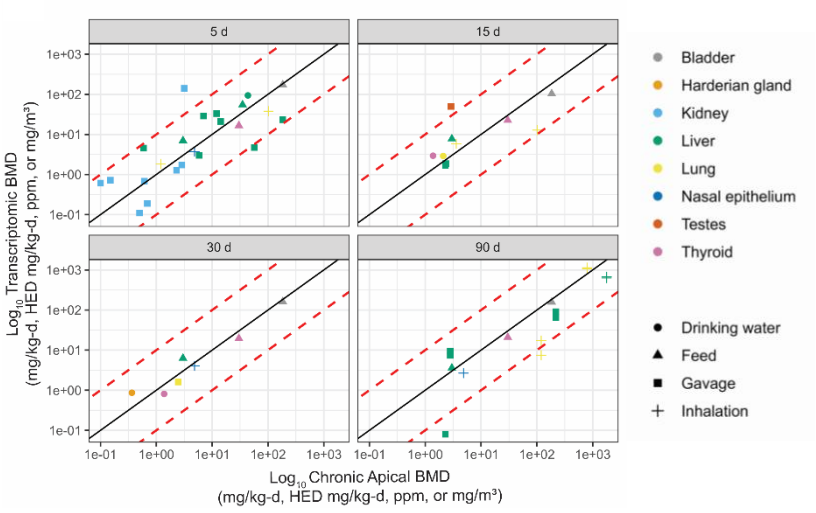


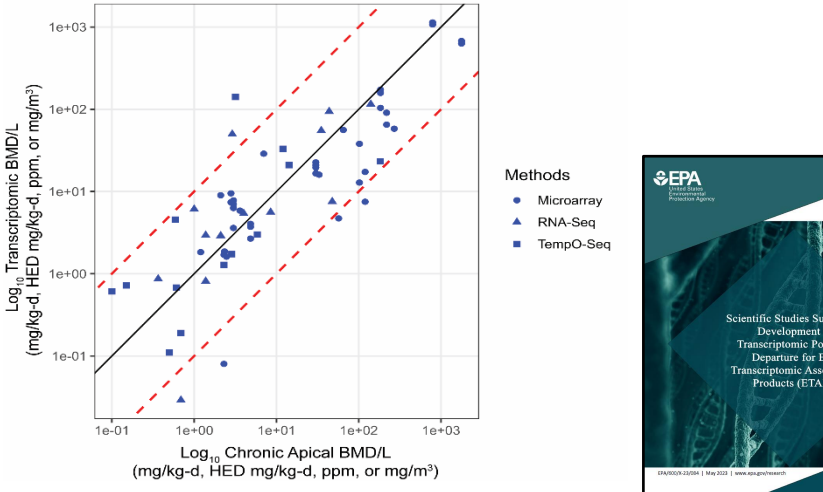
Socioeconomic case study on the human health and economic value of the ETAP
(VOI Presentation – Greg Paoli)

BOSC Panel #1

BOSC Panel #2

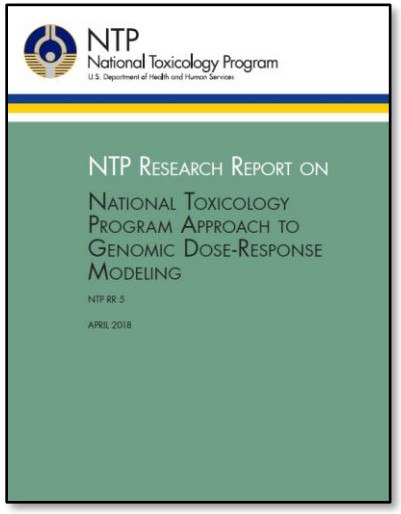
Comprehensive Literature Review Supports Dose Concordance Between Gene Activity Changes and Toxicity

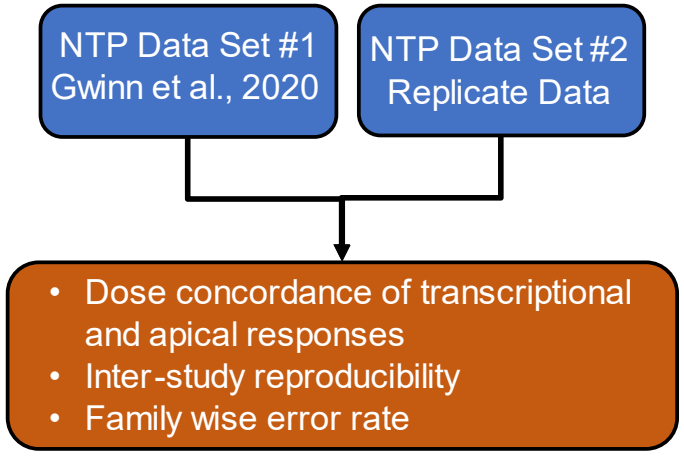




- Literature review identified 140 chemicals in 32 studies
- Across all studies examined, the Pearson's correlation coefficient for the transcriptomic versus the chronic, apical point-of-departure was 0.842 with an RMSD of 0.565 (log_{10} mg/kg-d) and a mean absolute fold-change difference of 4.5 ± 7.3 (SD)
- The RMSD is similar to the range of inter-study standard deviation estimates for the lowest observable adverse effect levels (LOAELs) for systemic toxicity in repeated dose studies (0.45-0.56) (Pham *et al. Comp Toxicol.*, 2020)
- Dose concordance was robust across exposure durations, exposure routes, species, sex, target tissues, physical chemical properties, toxicokinetic half-lives, and technology platforms

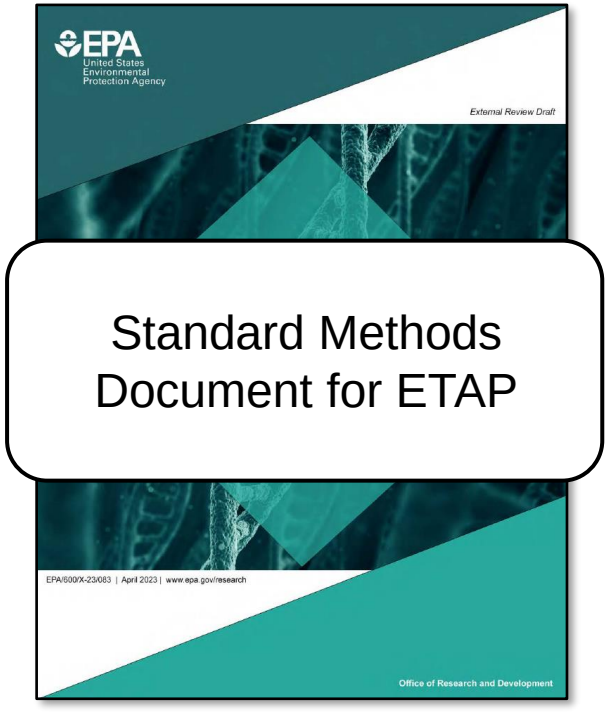
Leverage NTP Report and Data Sets to Standardize Dose Response Analysis Methods for ETAP





- Leveraged peer-reviewed NTP Report on Genomic Dose Response Modeling as basis for transcriptomic dose response analysis process
- Used two existing NTP data sets to refine dose response analysis parameters:
  - Multiple chemicals with both 5 day transcriptomic study and chronic rodent bioassay
  - Replicate studies on a subset of chemicals to assess reproducibility
- Evaluated 48 combinations of dose response analysis parameter choices consistent with NTP consensus recommendations
- Statistical analysis suggests that the error associated with the concordance between the transcriptomic and apical is approximately equivalent to the combined inter-study variability and the false identification of points-of-departure is <1% (0.006), using the optimized parameter set

Conceptual Approach of the EPA Transcriptomic Assessment Product (ETAP)



Standard Methods Document for ETAP

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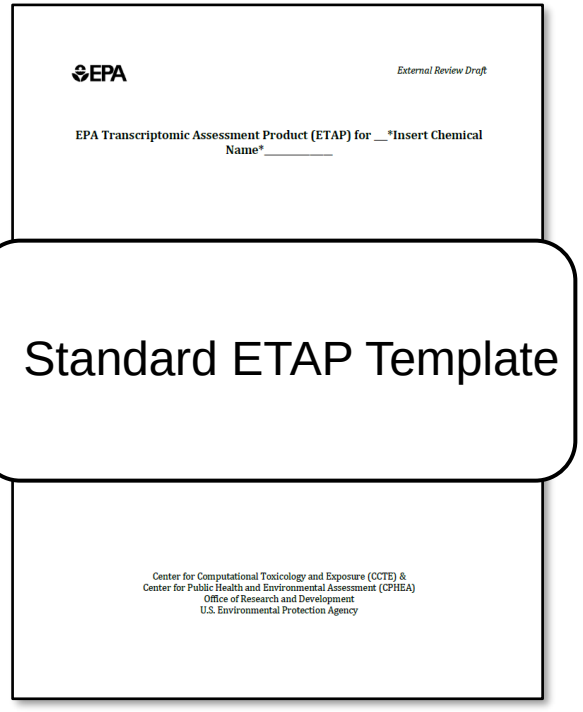

Standard ETAP Template

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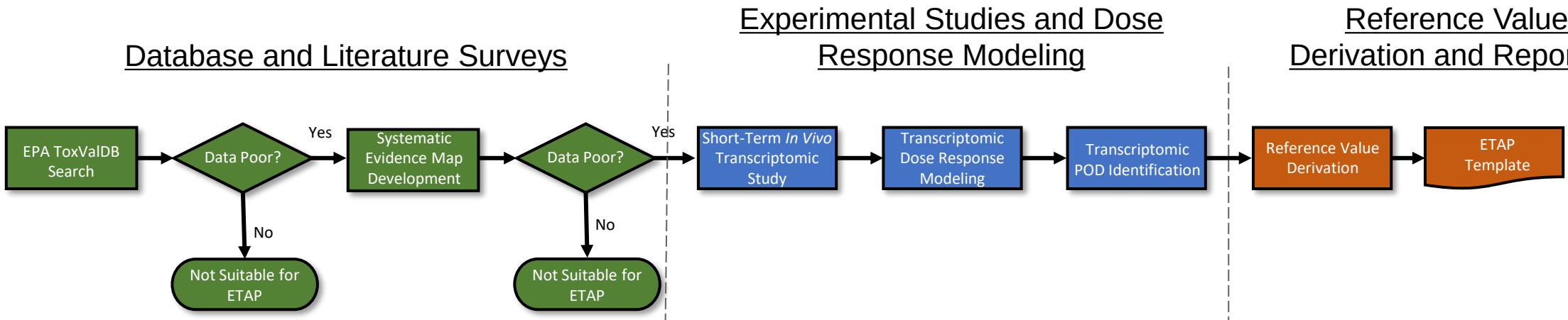
- Streamlined experimental execution
- Prescriptive review process
- Target time from initiation to release is < 9 months
- Scalable
- Potential broad application

- More specific than normal guidance
- Method subject to peer-review and public comment
- Focused only on data poor chemicals

- Highly standardized assessment template
- Minimal free-form text and no subjective interpretation
- Data quality audit by EPA QA staff
- Internal technical review by ORD scientists

ETAP Development Includes Three Main Components



- Initial screening using available EPA databases
- If no suitable studies are identified, a Systematic Evidence Map is initiated
- Only chemicals confirmed to have no publicly available mammalian *in vivo* repeat dose toxicity studies or suitable human evidence (as defined by SEM criteria) are eligible to progress

- Five day, repeat dose study in male and female Sprague Dawley rats
- Gene expression measurements in 12 tissues
- Benchmark dose analysis to define transcriptomic point-of-departure (BMDL) as the experimentally determined dose at which there were no coordinated transcriptional changes that would indicate a potential toxicity of concern

- Convert transcriptomic BMDL to human equivalent dose
- Apply standard set of uncertainty factor values consistent with Agency guidance
- Toxicity reference value (TRV) defined as an estimate of a daily oral dose that is likely to be without appreciable risk of adverse effects following chronic exposure

Comparison of TRV with Other EPA Reference Values for Chemicals Used to Optimize Dose Response Analysis Methods

Chemical	TRV (mg/kg-day)	RfD/ p-RfD (mg/kg-day)	TRV-to RfD Ratio	Source, Sex, Species, Study Type
Acrylamide	1.6E-04	2.0E-03	0.08	IRIS 2010; Male Rats; Chronic
Di(2-ethylhexyl) phthalate	1.1E-02	2.0E-02	0.55	IRIS 1987; Female Guinea Pigs; Subchronic-Chronic
Hexachlorobenzene	2.4E-05	8.0E-04	0.03	IRIS 1988; Male and Female Rats; Chronic
Furan	3.5E-04	1.0E-03	0.35	IRIS 1987; Male Mice; Subchronic
Perfluorooctanoic acid	3.1E-05	2.0E-05	1.55	OW 2016; Male Mice; Developmental
Tris(2-chloroisopropyl) phosphate	6.7E-03	1.0E-02	0.67	PPRTV Chronic 2012; Male Mice; Subchronic
Pentabromodiphenyl ether mixture (DE71)	4.1E-04	2.0E-03	0.21	IRIS 1987; Male Rats; Subchronic

Median Absolute Ratio = 2.9 $\pm$ 1.4 (MAD)

TRV, Transcriptomic Reference Value; IRIS, EPA Integrated Risk Information System; PPRTV, EPA Provisional Peer Reviewed Toxicity Values; OW, Office of Water; MAD, median absolute deviation

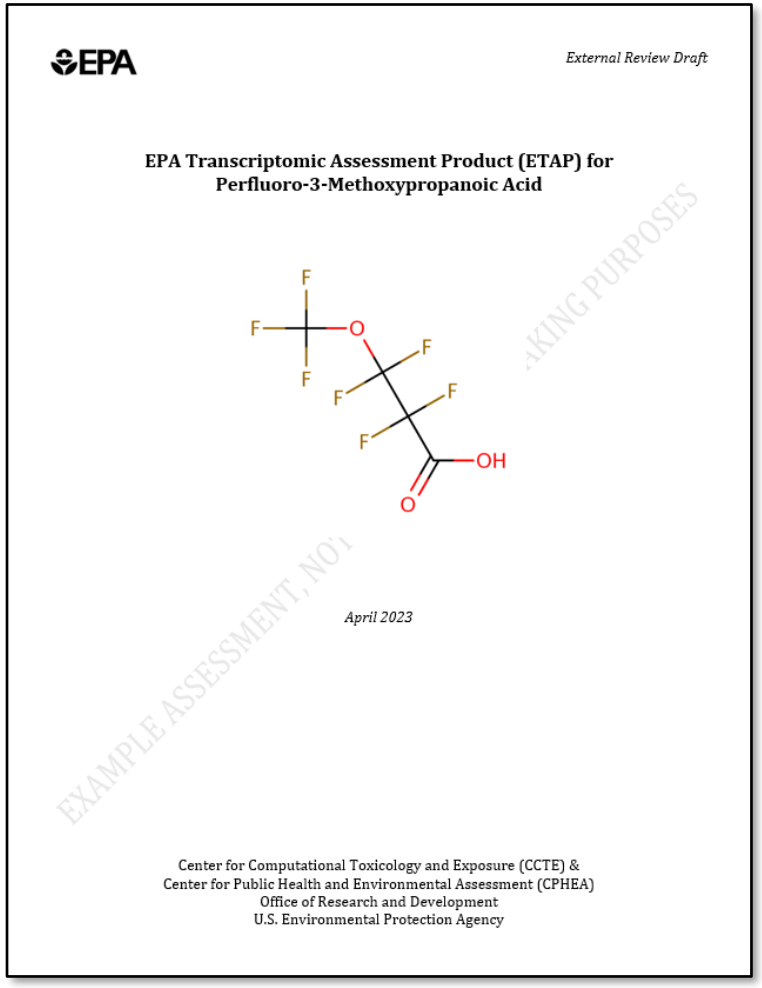
Comparison of TRV with Other EPA Reference Values for Chemicals Identified in the Literature Review

Chemical	TRV (mg/kg-day or mg/m^3)	Exposure Duration (d)	Sex, Species, Tissue	Reference	RfD or RfC (mg/kg-day or mg/m^3)	Source, Sex, Species, Study Type	TRV-to-RfD Ratio
Acrylamide	2.4E-03	31	Male Rats, Testis	(Recio et al. 2017)	2.0E-03	IRIS 2010, Male Rats, Chronic	1.20
Allyl alcohol	1.8E-03	8	Male Rats, Liver	(Johnson et al. 2020)	5.0E-03	IRIS 1987, Male Rats, Subchronic	0.37
Benzo[a]pyrene	9.4E-05	3	Male Mice, Liver	(Moffat et al. 2015)	3.0E-04	IRIS 2017, Rats, Developmental	0.31
Bromobenzene	3.4E-03	8	Male Rats, Liver	(Johnson et al. 2020)	8.0E-03	IRIS 2009, Male Mice, Subchronic	0.43
Choroprene[a]	1.4E-02	5	Female Mice, Lung	(Thomas et al. 2013a)	2.0E-02	IRIS 2010, Male and Female Rats, Female Mice, Chronic	0.68
Dichloroacetic acid	3.5E-02	6	Male Mice, Liver	(Cannizzo et al. 2022)	4.0E-03	IRIS 2003, Male and Female Dogs, Subchronic	8.67
...	...	...	...	...	...	...	...
A total of 20 chemicals (47 chemical x tissue x time point combinations) had IRIS/PPRV assessments.							

Overall Median Absolute Ratio = 2.3 ± 1.1 (MAD)
Median Absolute Ratio (Non-Matched Species) = 3.2 ± 1.3 (MAD)
Median Absolute Ratio (Matched Species) = 1.5 ± 1.1 (MAD)

IRIS, EPA Integrated Risk Information System; PPRTV, EPA Provisional Peer Reviewed Toxicity Values; MAD, median absolute deviation

Example ETAP for Perfluoro-3-Methoxypropanoic Acid



- Nine doses plus control (0.01 – 300 mg/kg-d)
- Tissues evaluated:
  - Male – adrenal gland, brain, heart, kidneys, liver, lung, spleen, testis, thyroid, and thymus.
  - Female – adrenal gland, brain, heart, kidneys, liver, lung, ovary, spleen, thyroid, thymus, and uterus.
- Most sensitive transcriptional response was in female uterus

Calculation of the $BMDL_{HED}$ for perfluoro-3-methoxypropanoic acid				
Endpoint	Sex	Organ	BMDL (mg/kg-d)	$BMDL_{HED}$ (mg/kg-d)
Transcriptional changes	Female	Uterus	0.121	0.0279

$$TRV = \frac{0.0279\ mg/kg{-}d}{300} = 0.00009\ mg/kg{-}d$$

*$BMDL_{HED}$ = BMDL Human Equivalent Dose

**For comparison, the TRV for perfluoro-3-methoxypropanoic acid is
~5X lower to the chronic RfD for PFPrA (0.0005 mg/kg-day).
~3X lower than the EPA chronic RfD for PFBS (0.0003 mg/kg-day).
~30X higher than the chronic RfD for GenX (0.000003 mg/kg-day).

Summary of Proposed ETAP

- Relatively few chemicals have traditional toxicity testing data or human health assessments
- Literature review and the transcriptomic dose response analysis studies showed high concordance in point-of-departure between transcriptomic studies and apical endpoints derived from traditional animal studies
- A new draft human health assessment was developed utilizing transcriptomic points-of-departure defined as the dose with no coordinated transcriptional changes that would indicate a potential toxicity of concern, but not linked to a specific hazard
- Transcriptomic reference values are derived using a standardized set of uncertainty factors due to the carefully prescribed design of the animal studies and data analysis procedures
- Comparison of transcriptomic reference values with traditional reference doses demonstrated similar levels of protection across a broad range of chemicals and effects
- The streamlined experimental execution, standardized reference value derivation, and defined review process will allow the scalable development and release of human health assessments in <9 months

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