Summary of Scientific Studies Supporting Development of Transcriptomic Points of Departure for ETAPs

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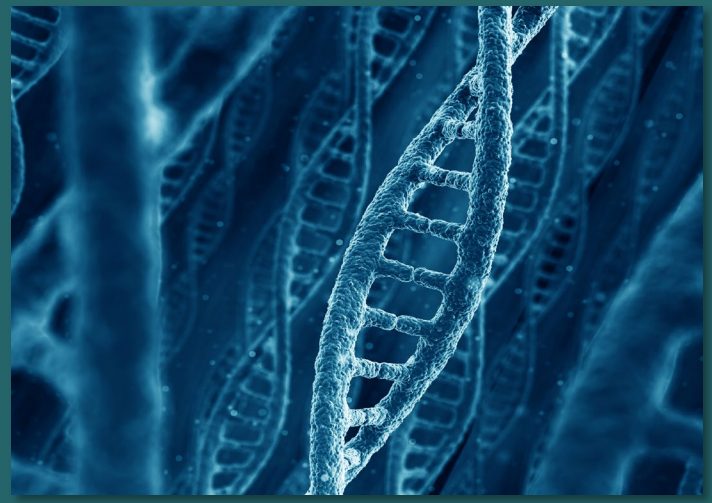

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Scientific Studies Recap

Regulatory agencies, including EPA, face substantial challenges in evaluating and managing human health risks of the thousands of chemicals and mixtures on their respective inventories

Technologies, such as transcriptomics, have the potential to more expediently evaluate potential human health effects and to fill data gaps in toxicity testing and human health assessment

Scientific Studies Recap

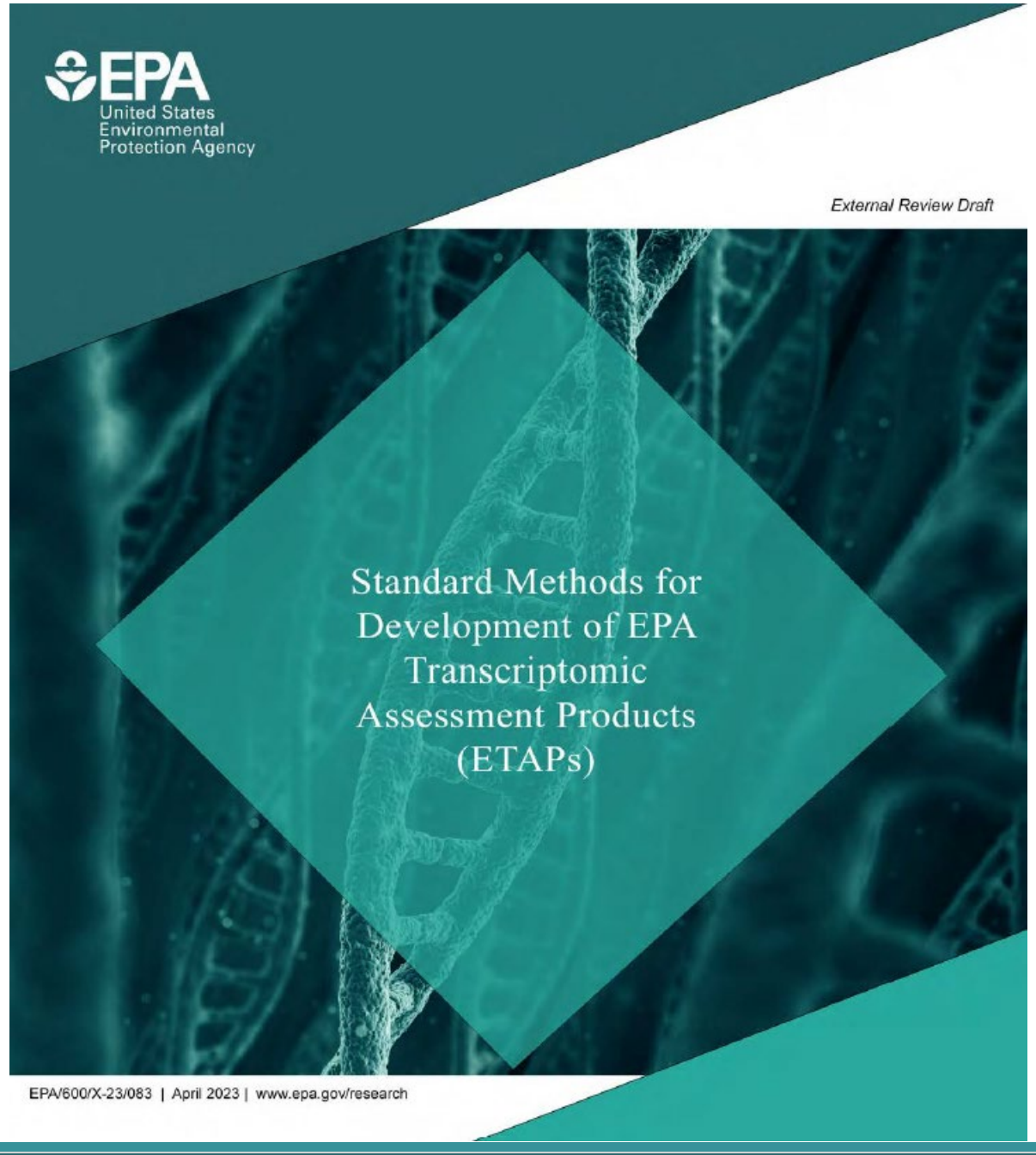
- EPA guidance, white papers, and reports recognized potential for transcriptomics and identified barriers to implementation that have been addressed
  - Included creating technical framework for genomic data analysis, criteria for data submission and presentation, and consistency in methods for analyzing data
  - These have been addressed by MAQC/SEQC studies on reproducibility, software development, NTP consensus report on transcriptomic dose response modeling, OECD reporting template
- A literature review was conducted comparing concordance between transcriptomic PODs from short-term *in vivo* rodent studies with apical PODs from traditional *in vivo* studies
  - The results suggest that the error associated with the concordance between the transcriptomic BMD values versus apical BMD values is approximately equivalent to the inter-study variability in the repeated dose toxicity study itself

Scientific Studies Recap

- A defined study design and data analysis process was evaluated to derive transcriptomic PODs based on recommendations in the peer-reviewed NIH National Toxicology Program Approach to Genomic Dose Response Modeling report (NTP 2018)
- The transcriptomic dose response modeling follows a stepwise process that utilizes BMD modeling approaches that are commonly employed in chemical risk assessment. A transcriptomic dose response modeling process was identified, refined, evaluated, and contextualized with BMD variance in apical endpoints

Scientific Studies Recap

- The overall conclusions from the literature survey, evaluation of the transcriptomic dose response analysis methods, and the statistical comparison of the concordance with inter-study variances support the use of transcriptomic PODs from 5-day, repeated dose in vivo rodent studies in quantitative human health assessments
- The historical barriers that thus far limited application of transcriptomics in regulatory decision-making have mostly been addressed and the methods have undergone extensive peer-review in the individual publications and NTP report
- EPA's ORD is proposing to apply these methods in a standardized human health assessment framework to address the substantial data gaps that exist among chemicals that lack traditional toxicity testing data



The EPA Transcriptomic Assessment Product

- Day 2 agenda will cover ETAP process, methods, and discuss a PFAS substance that was taken through the workflow under review
- Presentations will begin at 9:00 am Eastern time on July 12, 2023