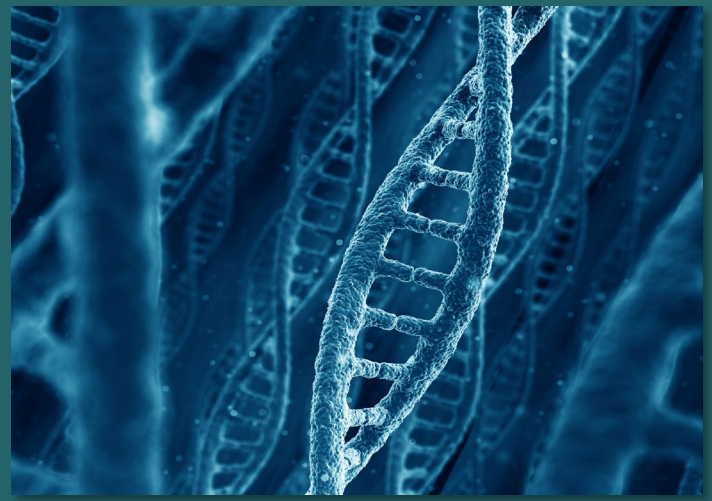
Background on Underlying Toxicity Testing and Human Health Assessment Needs

Alison Harrill, Ph.D. – Associate Director for Toxicology

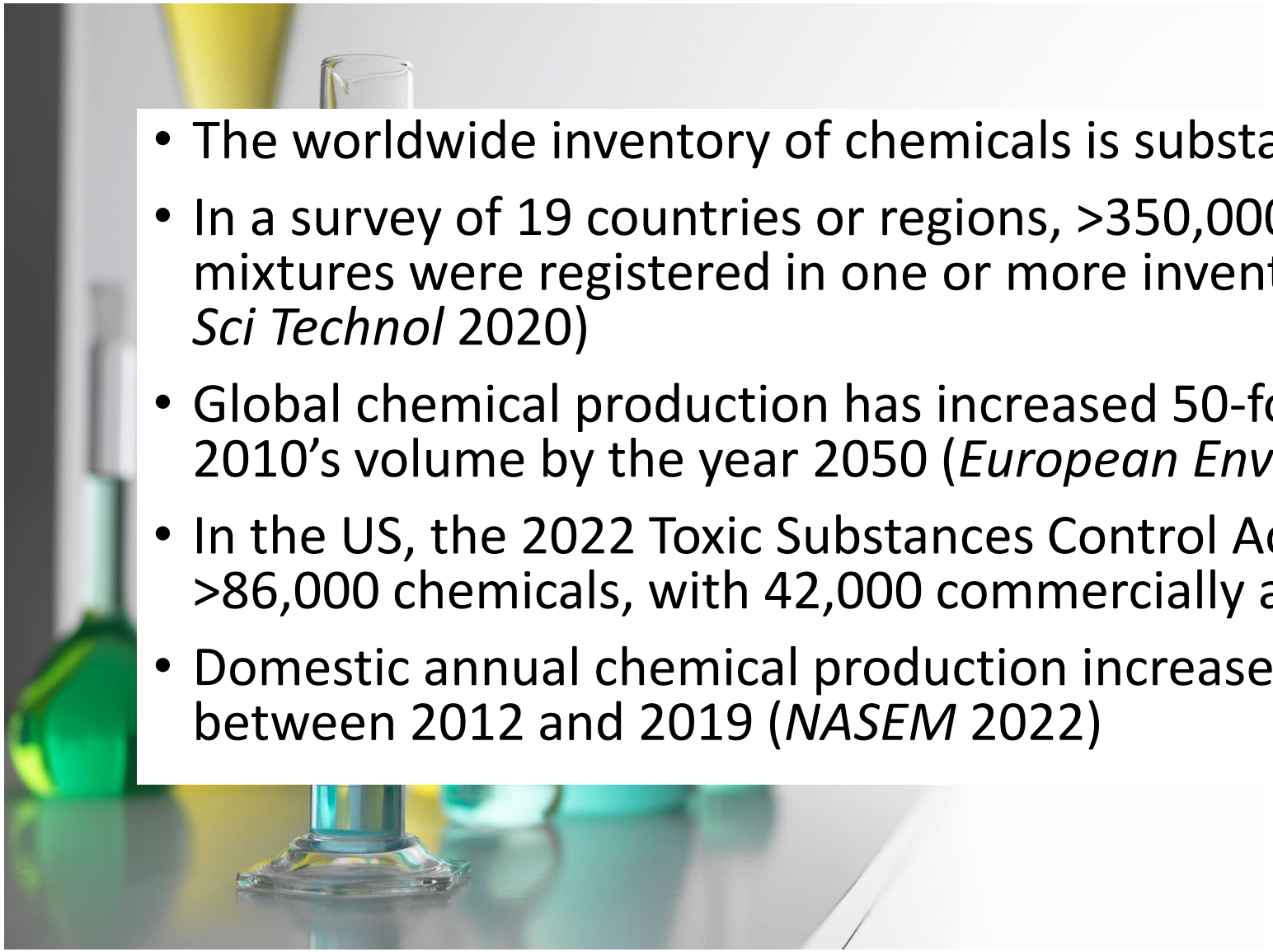


The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

Objectives

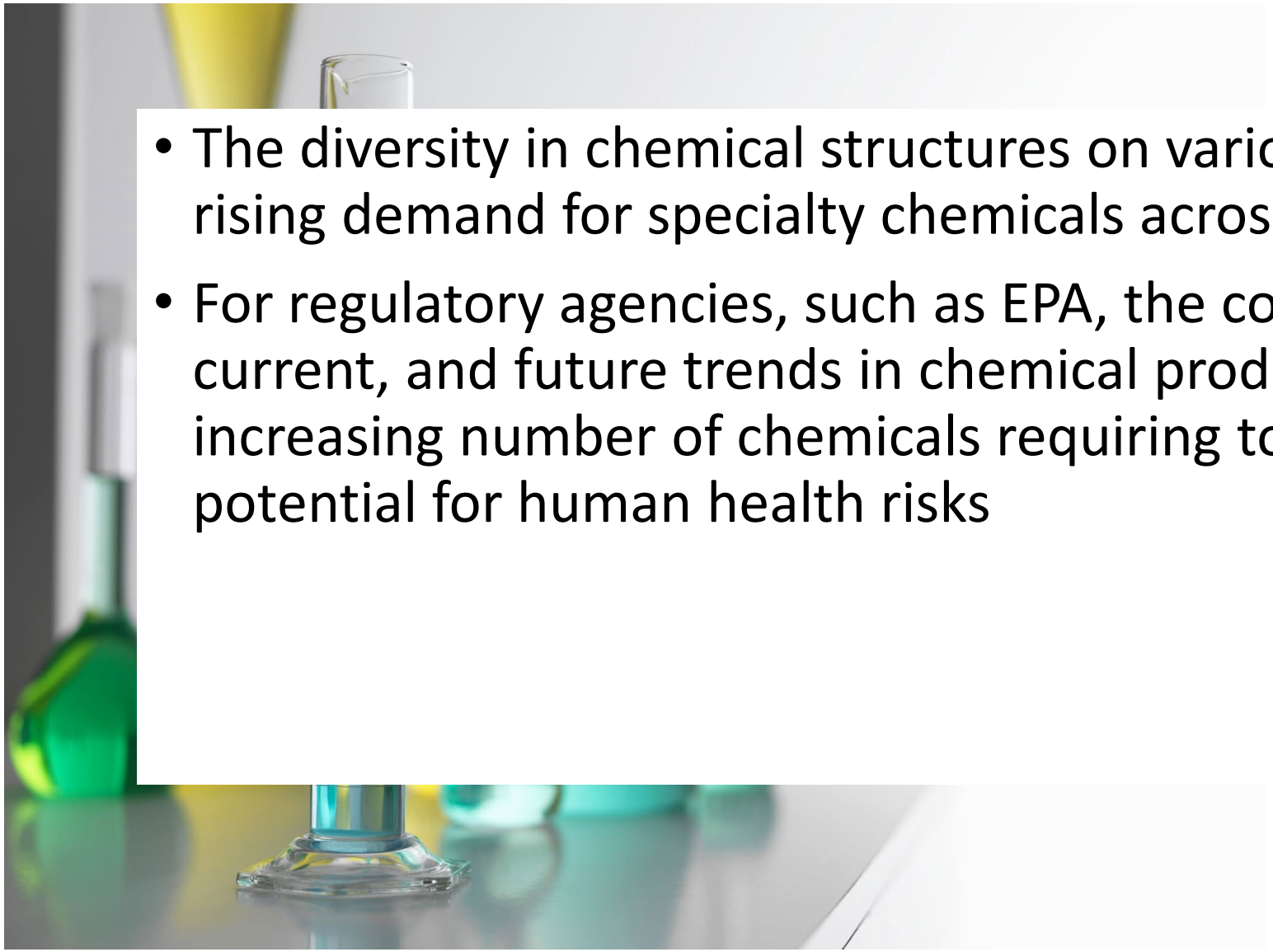
- Provide a high-level overview of the need for an additional ORD assessment product
- Summarize worldwide and domestic chemical and toxicity testing and human health assessment landscape
- Discuss EPA Office of Research and Development science assessments and opportunities for innovation
- Introduce opportunity for using value of information to inform human health assessment processess

Chemical Landscape



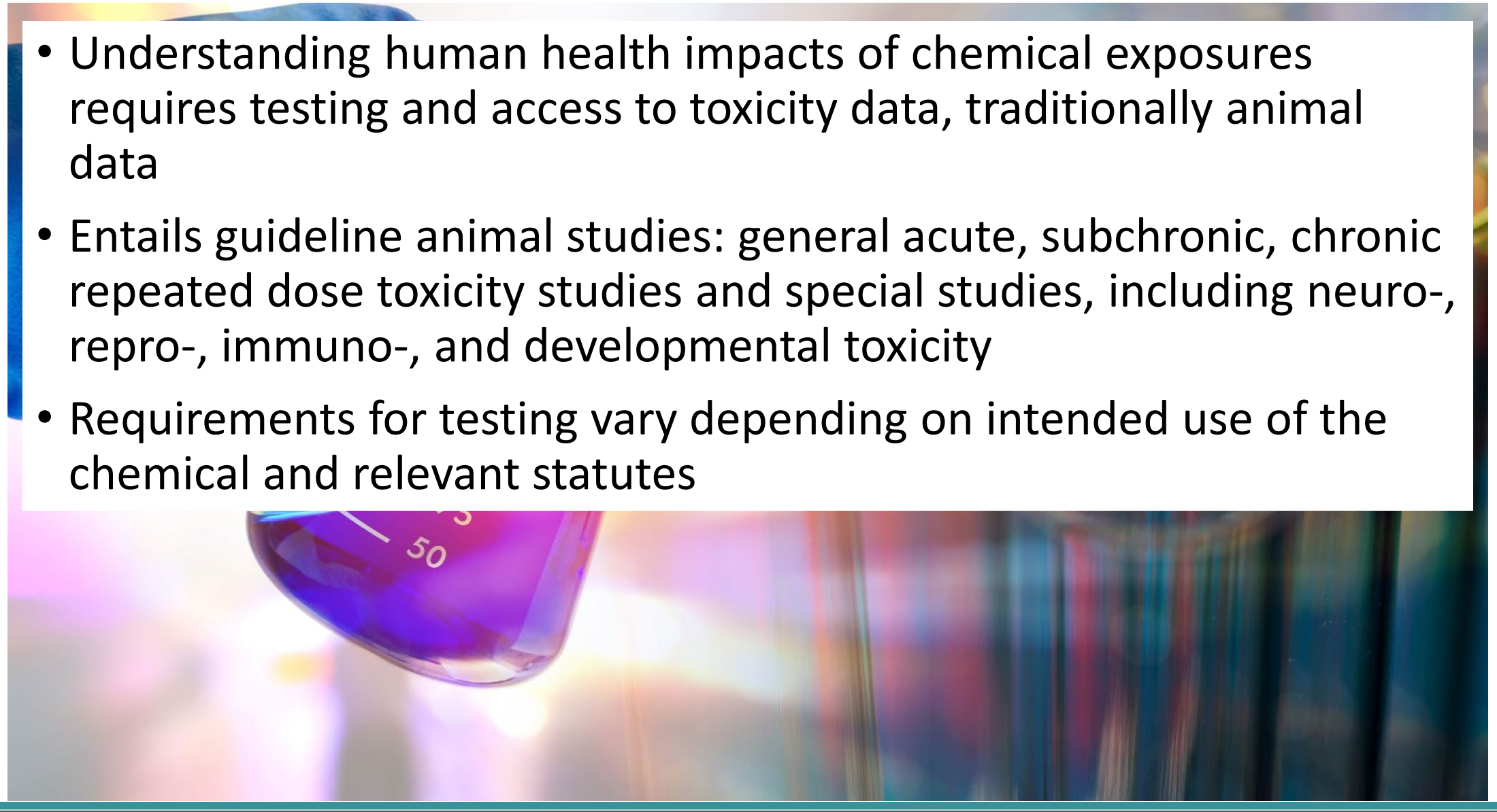
- The worldwide inventory of chemicals is substantial and continues to grow
- In a survey of 19 countries or regions, >350,000 chemicals and chemical mixtures were registered in one or more inventories (Wang et al. *Environ Sci Technol* 2020)
- Global chemical production has increased 50-fold since 1950, and will triple 2010's volume by the year 2050 (*European Environment Agency* 2018)
- In the US, the 2022 Toxic Substances Control Act (TSCA) inventory contains >86,000 chemicals, with 42,000 commercially active
- Domestic annual chemical production increased an average of 3% per year between 2012 and 2019 (*NASEM* 2022)

Chemical Landscape



- The diversity in chemical structures on various inventories is driven by rising demand for specialty chemicals across a range of industries
- For regulatory agencies, such as EPA, the consequence of historical, current, and future trends in chemical production is a substantial and increasing number of chemicals requiring toxicity testing to evaluate potential for human health risks

Toxicity Testing Landscape



- Understanding human health impacts of chemical exposures requires testing and access to toxicity data, traditionally animal data
- Entails guideline animal studies: general acute, subchronic, chronic repeated dose toxicity studies and special studies, including neuro-, repro-, immuno-, and developmental toxicity
- Requirements for testing vary depending on intended use of the chemical and relevant statutes

% of TSCA Inventory Chemicals with Available Toxicity Data

Does the chemical on the 2022 TSCA active inventory have a repeated dose toxicity study?

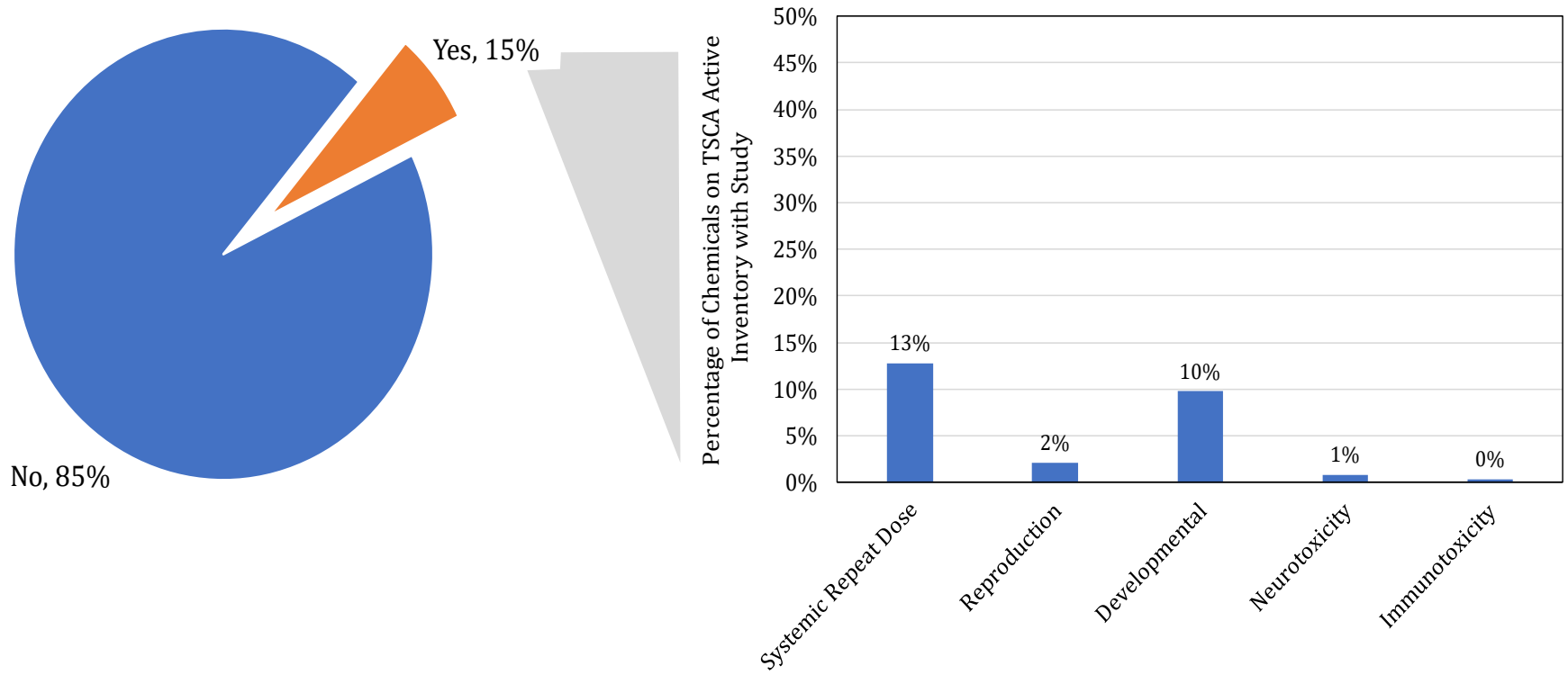


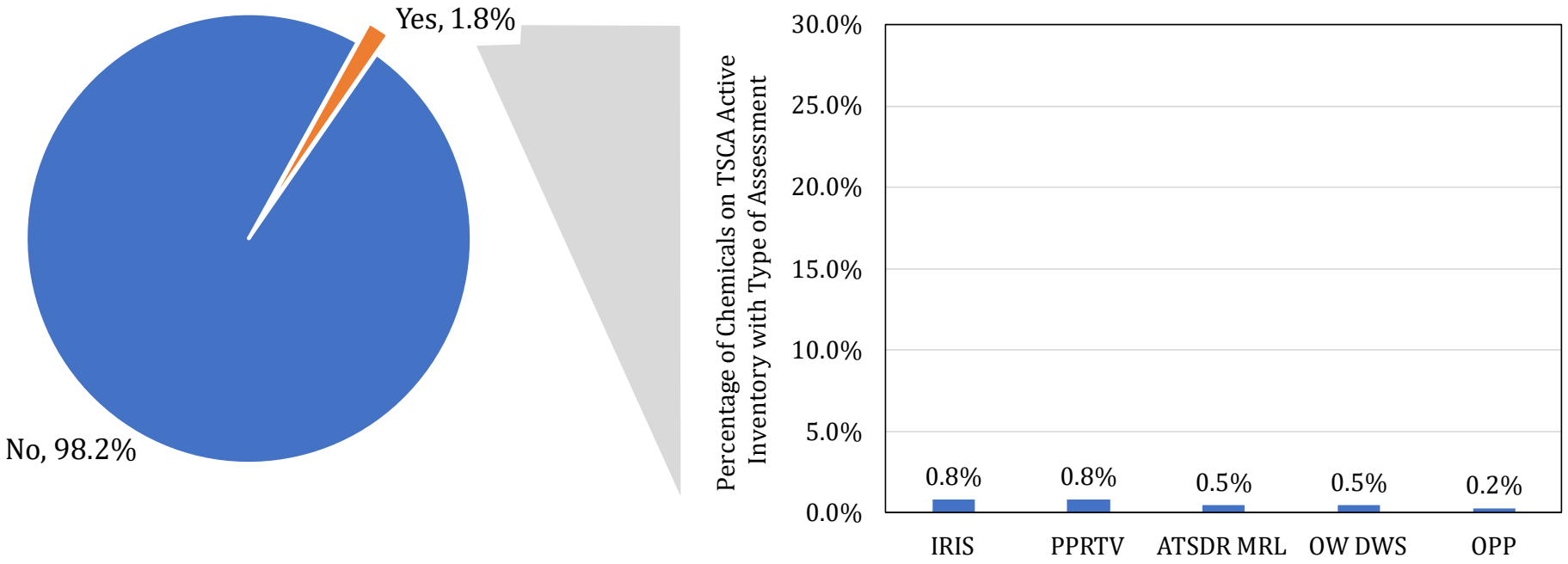
Figure 2-1. In the US, the 2022 Toxic Substances Control Act (TSCA) inventory contained more than 86,000 chemicals, of which **approximately 42,000** are considered commercially active.

Human Health Assessment Landscape

- Human health assessments integrate the results of human epi and animal toxicity tests and other relevant information to identify exposure levels at which no adverse health effect(s) is anticipated over a given duration (*e.g.* lifetime)
- Significant effort is required to develop a human health assessment
  - 15-36 months to review testing results of a conventional agricultural pesticide following data collection (*FIFRA SAP 2011*)
  - It can take ≥4 years to develop human health assessment for industrial and commercial chemicals (Krewski *et al.* 2020)
  - More complex assessments can take substantially longer (*NASEM* 2009)
- Insufficient data, coupled with the required time and resources has led to fewer chemicals with reference values for regulatory applications

% of TSCA Chemicals with Human Health Assessments

Does the chemical on the 2022 TSCA active inventory have a human health assessment?



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

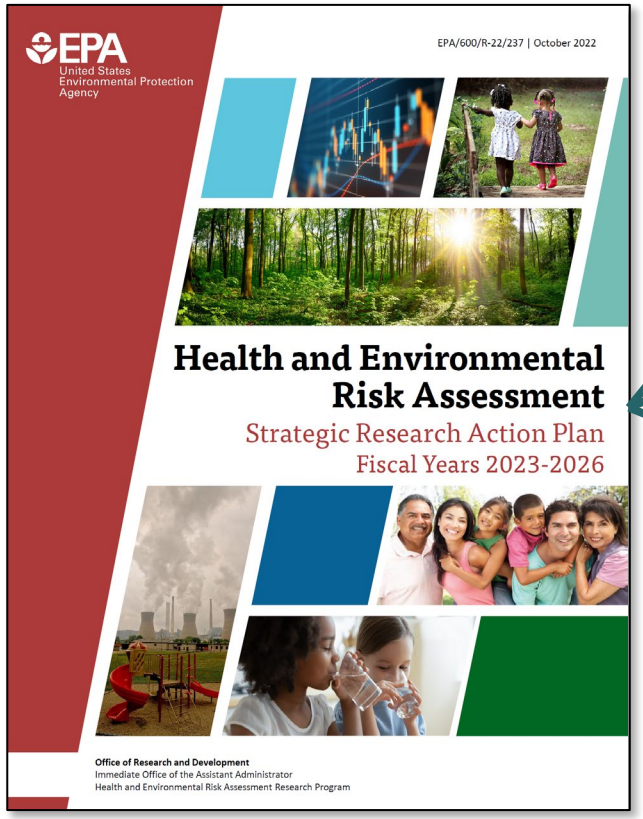
OW DWS – US EPA Office of Water Drinking Water Standards

OPP – US EPA Office of Pesticide Programs

Figure 2-2. In the US, the 2022 Toxic Substances Control Act (TSCA) inventory contained more than 86,000 chemicals, of which approximately 42,000 are considered commercially active.

Science Assessments

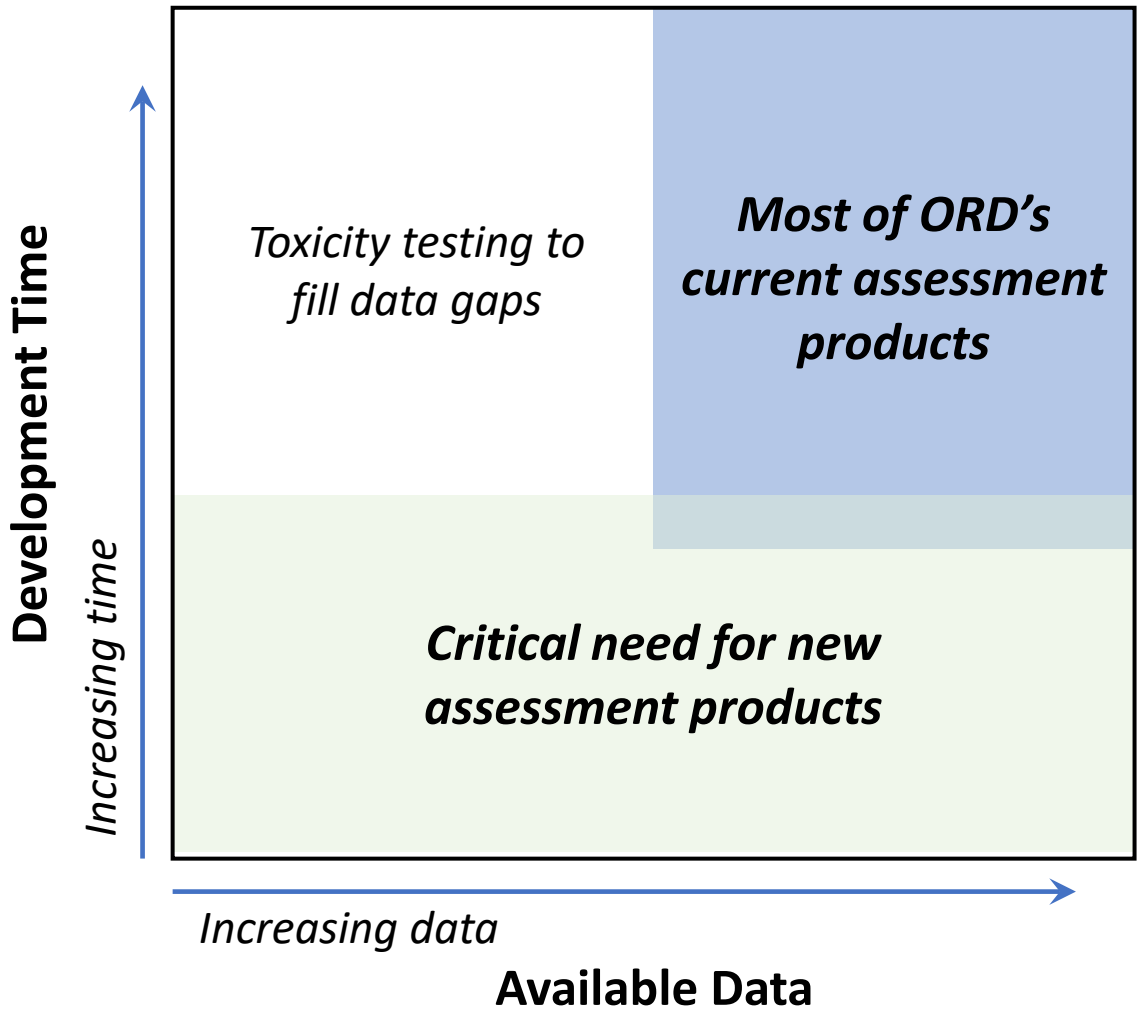
ORD is focused on producing **high quality**, **transparent**, **consistent**, and **scientifically defensible** assessment products to meet EPA's diverse statutory and policy needs.



- Integrated Science Assessments (ISAs) → National Ambient Air Quality Standards (NAAQS)
- Integrated Risk Information System (IRIS) → National and site-specific decisions
- Provisional Peer-Reviewed Toxicity Values (PPRTVs) → Superfund risk assessments
- Provisional Advisory Levels (PALs) → Emergency response actions

Need for More Assessments, Faster

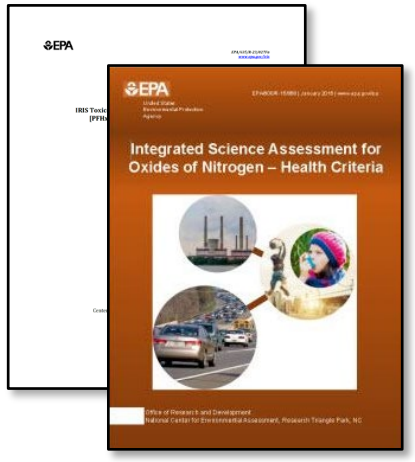
- Timely chemical assessments have been an ongoing challenge for the environmental health community
  - Limited data
  - Long development processes
- Improve timeliness of assessments by:
  - Matching needs and assessment products ("fit-for-purpose")
  - Utilizing new scientific approaches



A Portfolio of Assessment Products

ORD is developing new assessment products to provide **actionable science** to decision-makers **sooner**.

Data-Rich — **Relative Data Availability** — Data-Poor

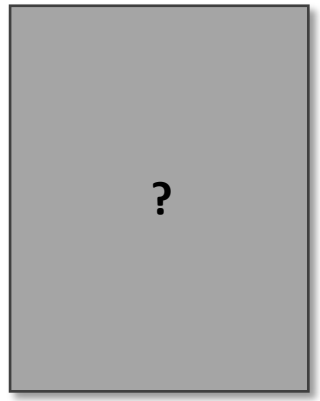


ISAs, IRIS

PPRTVs, PALs

Human Health Toxicity Assessments

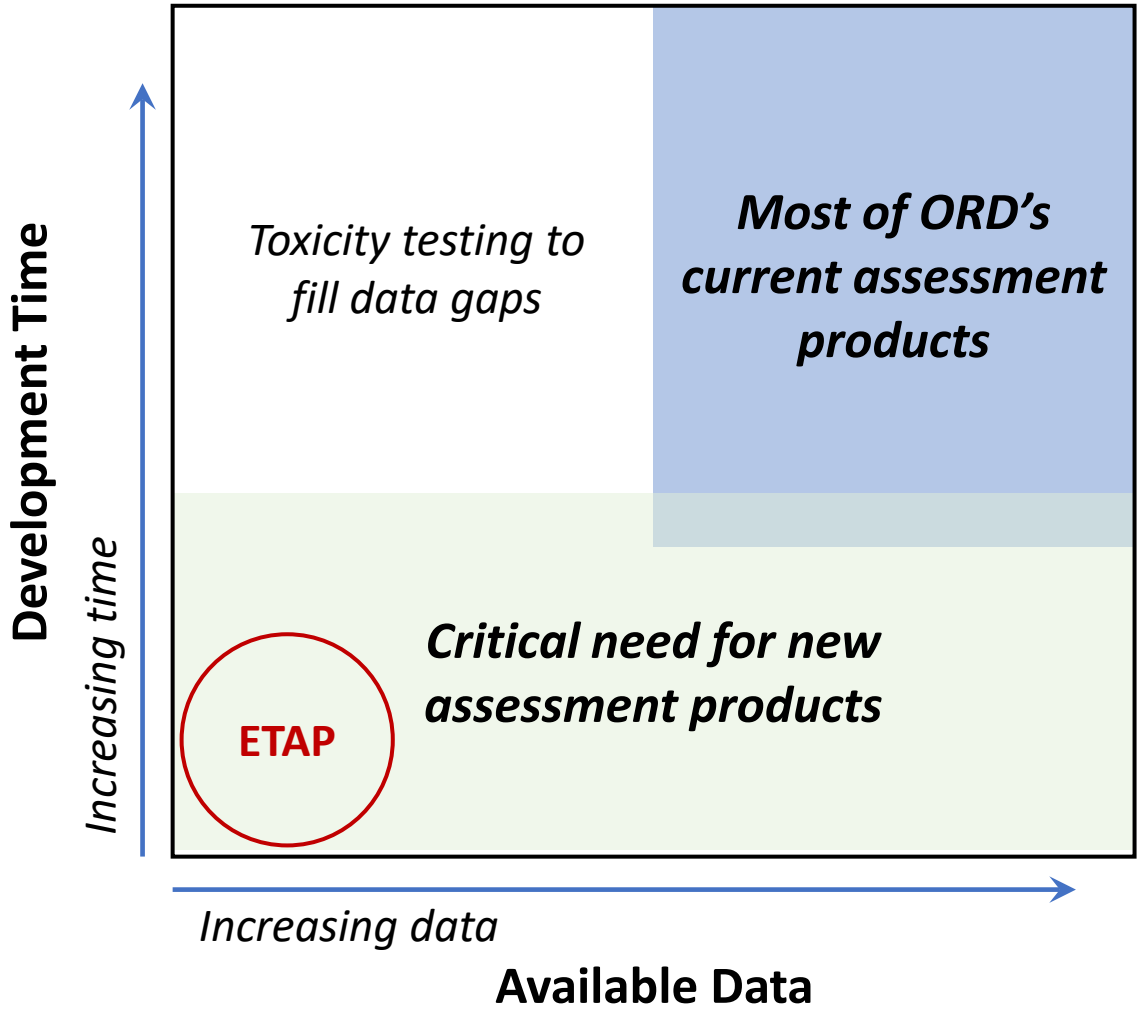
Fit-for-purpose



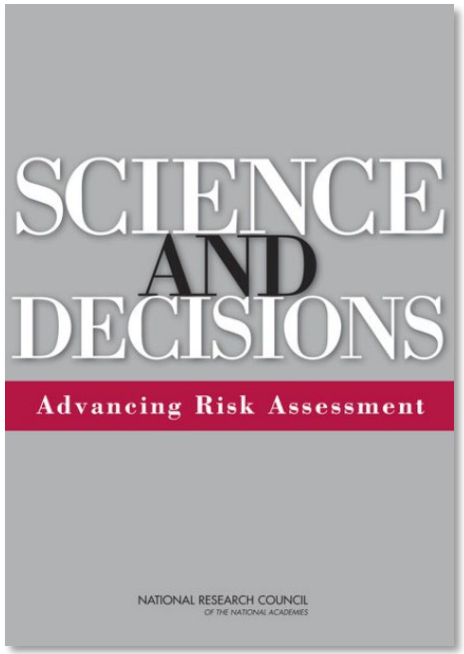
Longer — **Relative Development Time** — Shorter

EPA Transcriptomic Assessment Product

- Potential new assessment product (and the subject of this BOSC meeting)
  - For data-poor chemicals
  - Prescriptive process
- Could enable development and release of chemical assessments in as little as 9 months, from chemical procurement to assessment release



How Can ORD Assess the Value of a New Assessment Paradigm, Like ETAP?



NRC, 2009

- The National Research Council committee reflected that **time** is a "major and rarely acknowledged influence in the nature and quality" of a risk assessment
- Additional studies or improvements in the assessment may reduce uncertainty, but they require additional resources and the delay "can have significant impact on communities who are awaiting risk assessment results."
- A Value of Information (VOI) analysis was listed as a recommendation in the report to provide a more objective decision framework in assessing the trade-offs of time, uncertainty, and cost
- VOI is a method for quantifying the expected gain in economic terms for reducing uncertainty through the collection of additional data or information
- VOI has been applied or proposed in toxicology and chemical risk assessment but to date has not considered the impact of time

Evaluating the Value of Information Framework in a Case Study

DOI: 10.1111/risa.13931

ORIGINAL ARTICLE

A value of information framework for assessing the trade-offs associated with uncertainty, duration, and cost of chemical toxicity testing

Shintaro Hagiwara[1,2] | Greg M. Paoli[1] | Paul S. Price[3] | Maureen R. Gwinn[4] | Annette Guiseppi-Elie[3] | Patrick J. Farrell[2] | Bryan J. Hubbell[5] | Daniel Krewski[1,6] | Russell S. Thomas[3]

[1]Risk Sciences International, Ottawa, Canada
[2]School of Mathematics and Statistics, Carleton University, Ottawa, Canada
[3]Center for Computational Toxicology and Exposure, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA
[4]Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA
[5]Air, Climate, and Energy Research Program, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA
[6]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

Correspondence
Shintaro Hagiwara, Risk Sciences International, 700-251 Laurier Avenue West, Ottawa, ON K1P 5J6, Canada.
Email: shintaro.hagiwara@carleton.ca

Abstract

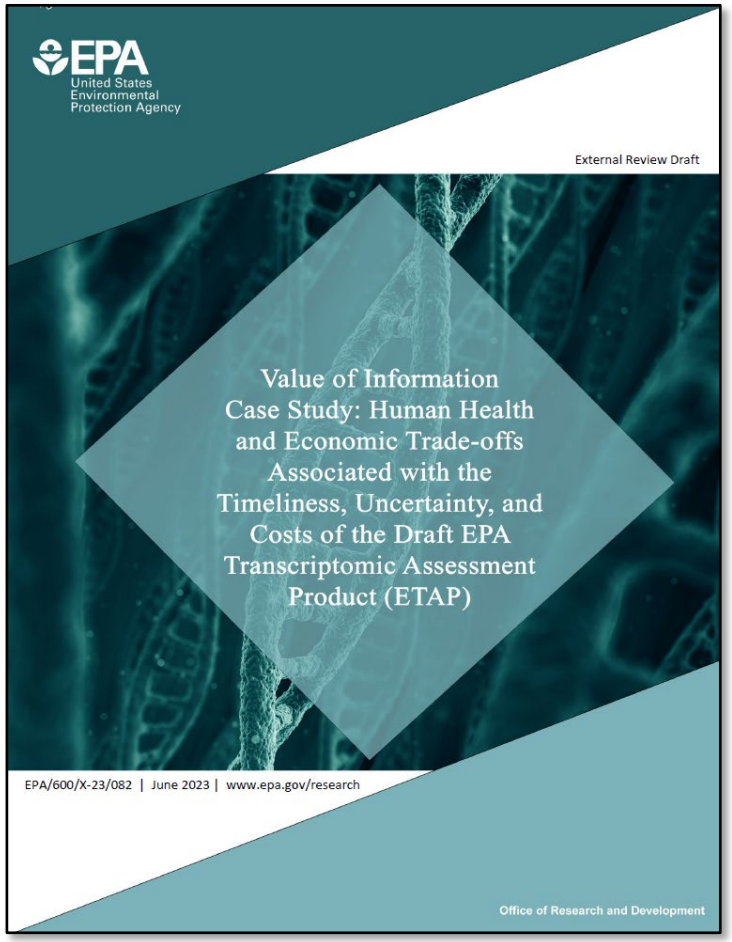
A number of investigators have explored the use of value of information (VOI) analysis to evaluate alternative information collection procedures in diverse decision-making contexts. This paper presents an analytic framework for determining the value of toxicity information used in risk-based decision making. The framework is specifically designed to explore the trade-offs between cost, timeliness, and uncertainty reduction associated with different toxicity-testing methodologies. The use of the proposed framework is demonstrated by two illustrative applications which, although based on simplified assumptions, show the insights that can be obtained through the use of VOI analysis. Specifically, these results suggest that timeliness of information collection has a significant impact on estimates of the VOI of chemical toxicity tests, even in the presence of smaller reductions in uncertainty. The framework introduces the concept of the expected value of delayed sample information, as an extension to the usual expected value of sample information, to accommodate the reductions in value resulting from delayed decision making. Our analysis also suggests that lower cost and higher throughput testing also may be beneficial in terms of public health benefits by increasing the number of substances that can be evaluated within a given budget. When the relative value is expressed in terms of return-on-investment per testing strategy, the differences can be substantial.

KEYWORDS
cost of delay, return on investment, risk decision making, social cost, toxicity testing, value of information

1 | INTRODUCTION

Evidence-based risk assessment has become a cornerstone of public and population health risk decision making, integrating evidence on toxicity and exposure from multiple evidence streams. When the available evidence is insufficient to allow a decision to be made with confidence, consideration can be given to gathering additional evidence to strengthen the evidence base. The present paper focuses on the use of value of information (VOI) analysis to evaluate the utility of gathering additional evidence on the toxicity of chemicals. Specifically, we present a VOI analytic framework that builds on previous methodological work in this field, explicitly incorporating the value of additional test data resulting from reductions in the uncertainty in estimates of a chemical's toxicity, the cost of delay in decision making that results

Hagiwara *et al., Risk Analysis*, 2022



https://www.epa.gov/bosc/voi-july-25-26-2023-meeting

ORD is proposing a new human heath assessment product undergoing review by an *ad hoc* BOSC panel

Provides an opportunity to apply the VOI framework via a case study that informs the value of a new approach when compared to the traditional approach under real-world exposure scenarios