Using NAMs Under TSCA: A Guide to EPA's TSCA NAMs List and Assessing Carcinogenicity Under TSCA Using the ReCAAP Weight of Evidence Framework

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EPIC WEBINAR SERIES ON THE USE OF NAMs IN RISK ASSESSMENT

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Using NAMs Under TSCA: A Guide to EPA's TSCA NAMs List

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New Approach Methods (NAMs) in TSCA

- Toxic Substances Control Act (TSCA) Section 4(h):
  - TSCA Section 4(h)(2)(C) requires EPA to develop "a list, which the Administrator shall update on a regular basis, of particular alternative test methods or strategies the Administrator has identified that do not require new vertebrate animal testing and are scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate animal testing"
  - Encourage and facilitate …"scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions"
  - "…develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing"

New Approach Methods (NAMs) in TSCA

- Administrator Zeldin reaffirms EPA's commitment to advancing NAMs (January 2026)[1]
  - OCSPP continues to prioritize development and implementation of high-quality alternatives to reduce testing on vertebrate mammals
  - Incorporation of NAMs into risk assessment while ensuring best available science is being utilized

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Administrator Zeldin Gets EPA Back on Track to Eliminate Animal Testing After Biden Admin Halted Phase Out

January 22, 2026

Contact Information
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WASHINGTON – Today, U.S. Environmental Protection Agency (EPA) Administrator Lee Zeldin announced the agency was getting back on track with reducing mammalian animal testing and recommitting to the ambitious goal laid out during the first Trump Administration to eliminate the practice by 2035. The Biden Administration canceled the agency's animal testing phase-out deadlines, delaying scientific progress on developing alternatives that would save more animals from experimentation.

Since his time serving in Congress, Administrator Zeldin has been a leader in working to reduce animal testing. Under President Trump and Administrator Zeldin's leadership, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) will prioritize developing and implementing high-quality alternatives to reduce testing on vertebrate mammals, like rabbits, mice, rats, and dogs, to align with regulatory requirements, the high bar of gold standard science, and EPA's Make America Healthy Again agenda.

[1] https://www.epa.gov/newsreleases/administrator-zeldin-gets-epa-back-track-eliminate-animal-testing-after-biden-admin

List of Alternative Methods (NAMs)

- The NAMs presented in the list are not meant to be an exhaustive list of NAMs that could be used for TSCA decisions. Rather, the list provides representative NAMs that EPA may consider. Many of the NAMs have been reviewed and established by different organizations (e.g., OECD, ICCVAM, and ICATM) and meet the Section 4(h)(2)(C) criteria for scientific relevance (i.e., accuracy) and reliability (i.e., repeatability/reproducibility).

ICATM = International Cooperation on Alternative Test Methods; ICCVAM = Interagency Coordinating Committee on the Validation of Alternative Methods; OECD = Organisation for Economic Co-operation and Development

List of NAMs: June 2026

- TSCA NAMs List first published in June 2018, with updates in December 2019, February 2021, and June 2026
- June 2026 Update:
  - TSCA NAMs List was published as a webpage for the first time[1]
  - Formal process for nominating new methods to the NAMs List was published, outlining steps for submitting, evaluating, and approving nominations[2]
  - List is organized into 3 categories: OECD and EPA test guidelines; non-OECD methods, computational tools and models; and policy related documents that might be relevant to TSCA. This structure highlights the distinction between internationally harmonized OECD methods and all other approaches. Within each table, all newly added NAMs are denoted with "**NEW**" so stakeholders can easily see what has changed and where new content has been incorporated.

[1] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/list-alternative-test-methods-and-strategies-or-new
[2] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/list-alternative-test-methods-and-strategies-or-new#nominations

NAMs List: 3 Categories

OECD/EPA Test Guidelines

Health Effects

Source	Title	Information Gathered
OECD TG No. 428	Skin Absorption: In Vitro Method	Provides information on absorption of a test substance (can be from human or animal source)
OECD TG No. 430	In Vitro Skin Corrosion: Transcutaneous Electrical Resist (TER)	

EPA NAM-Related Guidance Documents/Policies Which May Be Relevant to TSCA

Title	Type of NAM	Information Gathered
NEW: Decision Framework for Hazard Identification of Skin Irritation and Corrosion	Prioritizes human cell-based tissue model NAMs	Decision framework for identification of skin irritation or corrosion hazards for new chemical
NEW: Decision Framework for Hazard Identification of Eye Irritation and Corrosion	Prioritizes human cell-based tissue model NAMs	

Data Integration Tools, Predictive Models, and Assessment Frameworks

Source	Description
Analog Identification Methodology (AIM)	Database tool to facilitate identification of analogs for read-across
NEW: Androgen Receptor (AR) pathway model	AR pathway model based on the full 11-assay ToxCast/Tox21 battery
Chemical Assessment Clustering Engine (ChemACE)	Database tool to facilitate structural clustering

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/list-alternative-test-methods-and-strategies-or-new

TSCA NAMs Nomination Process

- Stakeholders can submit NAMs related to chemical reviews and associated data to EPA through the agency's TSCA NAMs Nomination Process[1]
- EPA reviews these methods to make sure they are scientifically sound, looking at transparency of the approach, relevance to human biology, reliability and reproducibility of results, and whether the method is fit for its intended purpose.
- EPA anticipates considering nominated NAMs across multiple TSCA decision contexts, such as prioritization, screening, and informing risk determinations for new or existing chemicals, while applying a fit-for-purpose approach, recognizing that a method is suitable for one context and may not be appropriate for another.
- Most NAMs currently on the List are expected to contribute as part of a weight of scientific evidence framework for characterizing modes of action or hazards, though some may be combined to meet specific regulatory needs, such as OECD defined approaches that integrate results from multiple methods.

[1] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/list-alternative-test-methods-and-strategies-or-new#nominations

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Thank you for your attention.

Using NAMs Under TSCA: Assessing Carcinogenicity Under TSCA Using the ReCAAP Weight of Evidence Framework

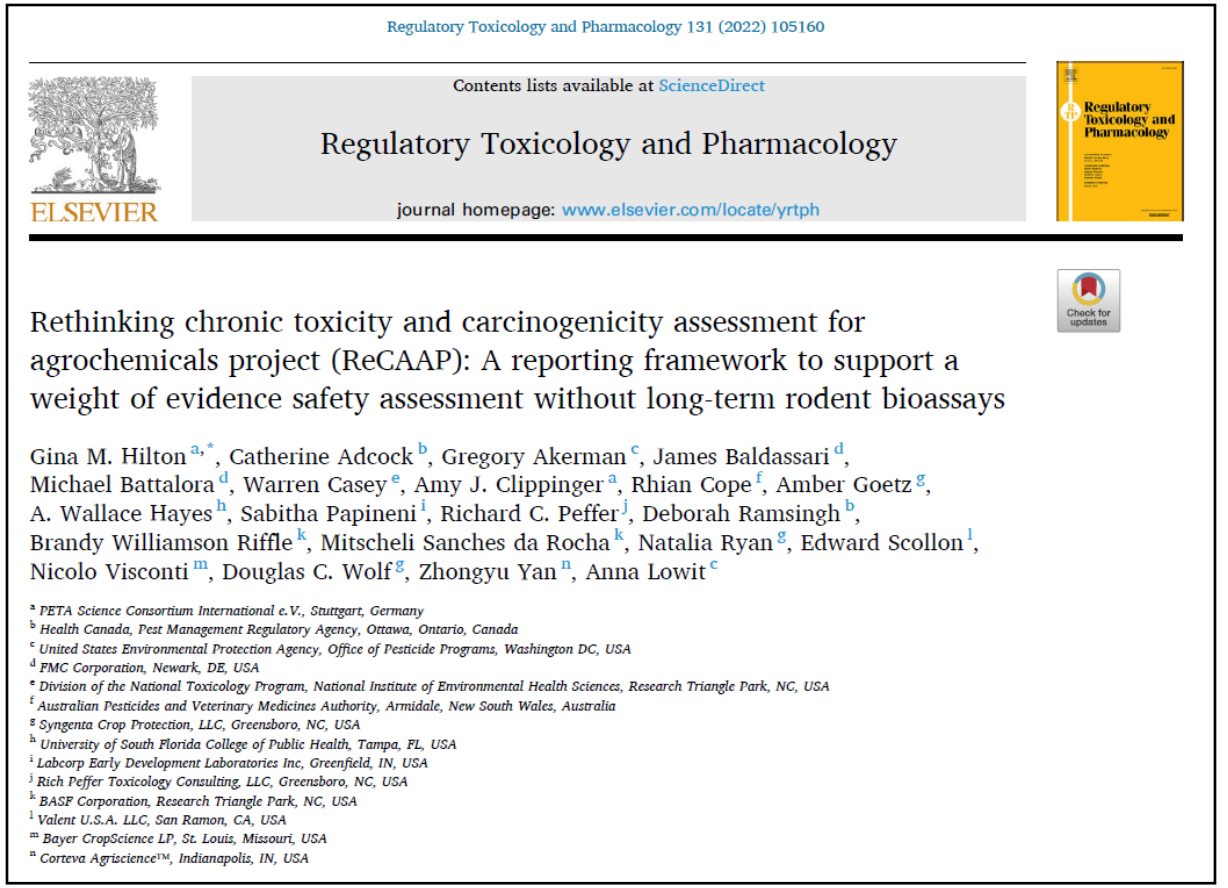
ANTHONY LUZ, Ph.D. (U.S. EPA)

Outline

- Introduction to ReCAAP WoE Framework and TSCA
- ReCAAP Case Studies:
  - Diisobutyl and dicyclobutyl phthalates (DIBP and DCHP)
  - 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB)
  - *Ortho*-dichlorobenzene (*o*-DCB)
  - *Trans*-1,2-dichloroethylene (TDCE)

ReCAAP Weight of Evidence (WoE) Framework

- Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) WoE Framework developed to support chronic toxicity and carcinogenicity study waiver rationale for agrochemicals (Hilton et al., 2022)
- Developed by scientists from government, academia, non-governmental organizations, industry stakeholders
- Principles in ReCAAP applicable to chemicals other than agrochemicals, including chemicals assessed under TSCA



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Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project (ReCAAP): A reporting framework to support a weight of evidence safety assessment without long-term rodent bioassays

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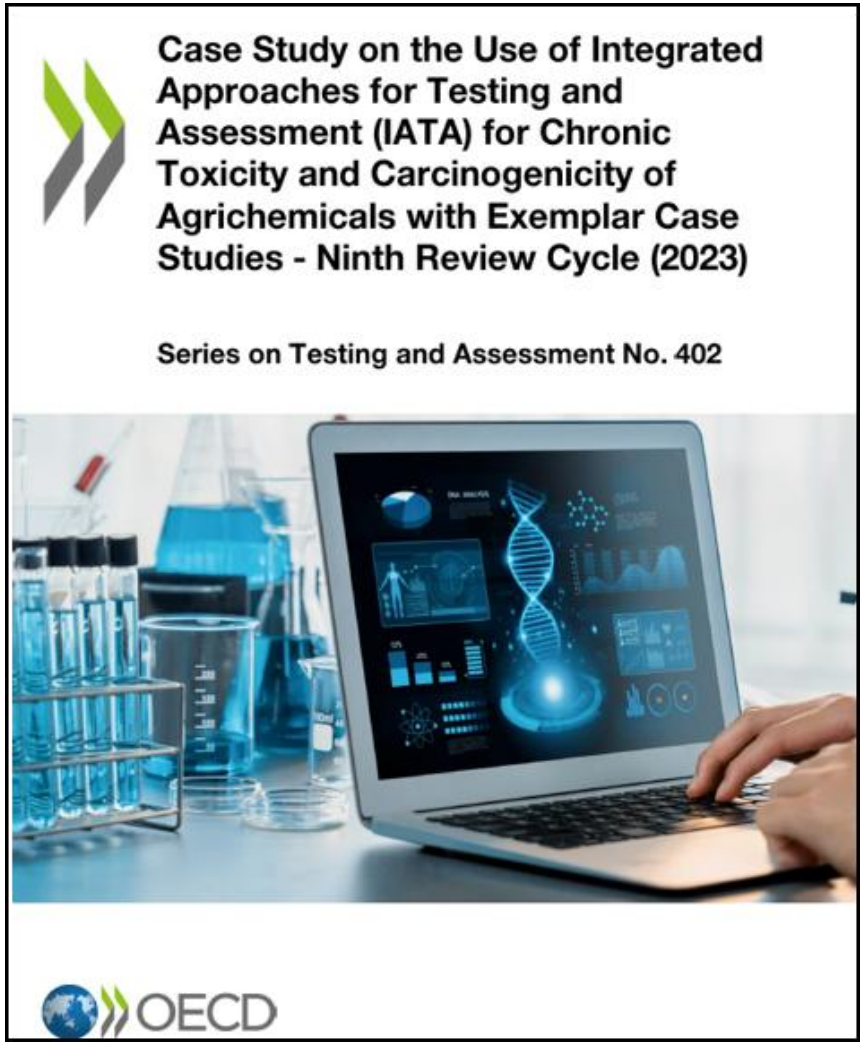
Hilton et al. (2022). Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project (ReCAAP). *Regulatory Toxicology and Pharmacology*, 131, 105160. http://dx.doi.org/10.1016/j.yrtph.2022.105160

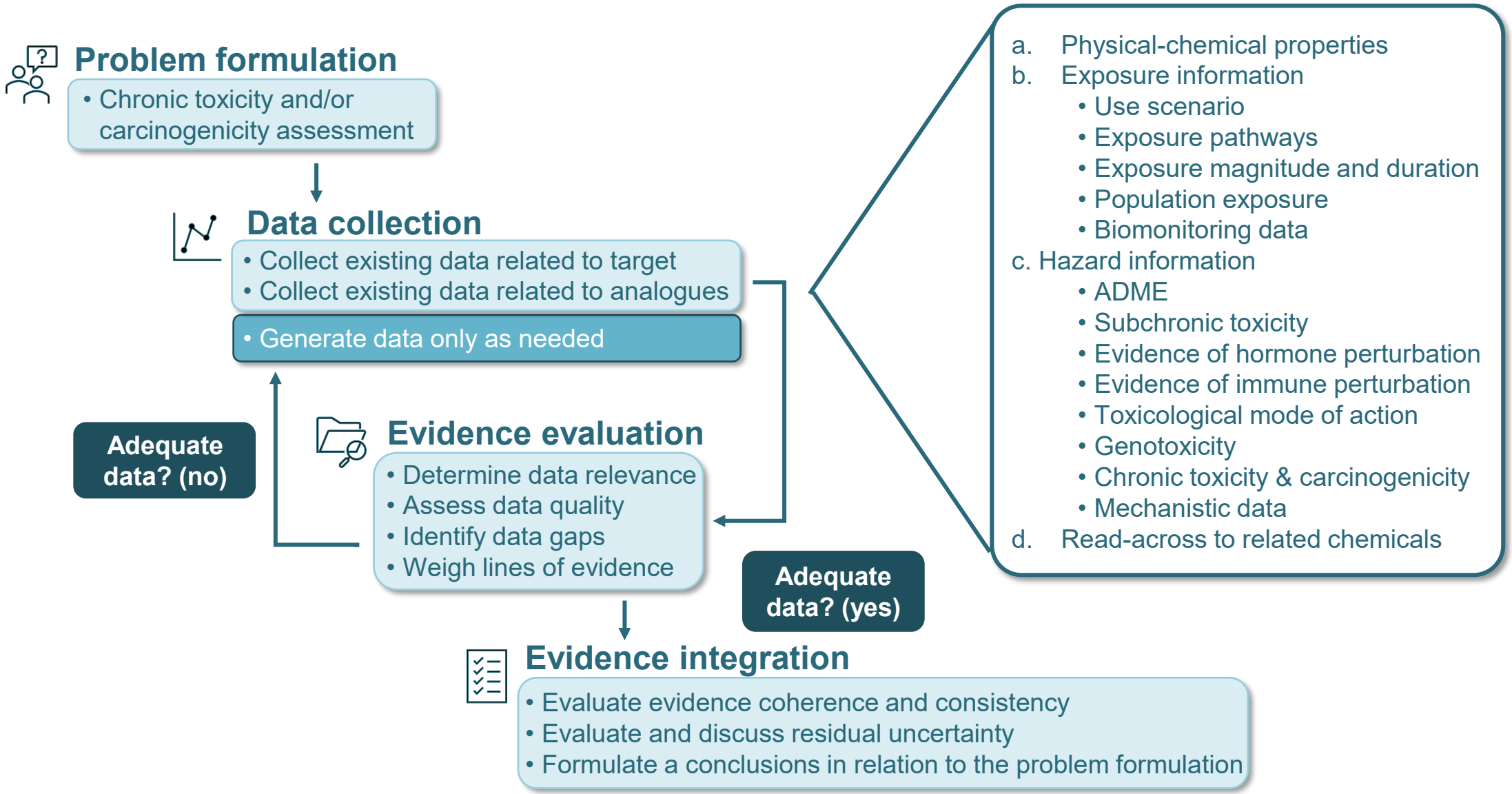
OECD Case Study

- OECD Integrated Approach to Testing and Assessment (IATA) case study developed for carcinogenicity assessment through ReCAAP WoE approach – without lifetime rodent bioassays (OECD, 2024)
- Goal of OECD framework:
  - Structure an integrated approach to determine when sufficient information is available for non-genotoxic chemicals to identify a health protective endpoint for risk assessment without conducting rodent chronic toxicity and carcinogenicity studies



OECD. (2024). Case study on the use of Integrated Approaches for Testing and Assessment (IATA) for chronic toxicity and carcinogenicity of agrichemicals with exemplar case studies - ninth review cycle (2023). In Series on Testing and Assessment No 402. Paris, France: OECD Publishing. http://dx.doi.org/10.1787/c3b9ac37-en

ReCAAP WoE Approach



Reducing the Need for Animal Testing

- Chronic toxicity and carcinogenicity testing in rodents can require 100s to 1,000s of animals per chemical
- ReCAAP WoE Framework can reduce the need for animal testing, if a health protective endpoint for risk assessment can be identified

Carcinogenicity Testing Requirements

- Dose-range finding studies
- Carcinogenicity studies in 2 species (e.g., rat, mouse)
- Control plus at least 3 dose groups
- 50 animals/sex/dose/species
- Inclusion of recovery groups and/or satellite groups to assess mechanistic endpoints further increases animal requirements

TSCA Existing Chemical Risk Evaluations

- In contrast to FIFRA requirements for pesticides and agrochemicals, TSCA does not have testing requirements
- Use all reasonably available information (*e.g.,* data submitted to U.S. EPA, data in public literature, etc.), and make decisions consistent with the best available science and the weight of scientific evidence
- U.S. EPA often relies on analogs, predictive models, or requests additional data

FIFRA = Federal Insecticide, Fungicide, and Rodenticide Act

ReCAAP WoE Framework Under TSCA

- Scientific principles in ReCAAP WoE Framework are applicable to TSCA risk evaluations
- ReCAAP WoE Framework used as organizational tool to assess carcinogenicity under TSCA
- Since there are no testing requirements under TSCA, the goal is not to waive carcinogenicity testing, but rather to evaluate the extent to which the lack of carcinogenicity studies imparts uncertainty on human health risk assessment

ReCAAP WoE Framework Considers:

- Physical and chemical properties
- Absorption, distribution, metabolism, excretion (ADME) properties
- Acute toxicity
- Evidence of hormone perturbation, developmental and reproductive toxicity
- Subchronic toxicity
- Immune system perturbation
- Genotoxicity
- Mode of action
- Chronic toxicity & carcinogenicity
- Epidemiology
- Read-across to related chemicals

Examples of Application of ReCAAP Under TSCA

Chemical Name	CASRN	U.S. EPA Status	External Peer-Review Meeting
Diisobutyl phthalate (DIBP)	84-69-5	Final	August 2025 SACC
Dicyclohexyl phthalate (DCHP)	84-61-7	Final	August 2025 SACC
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB)	1222-05-5	Draft	June 2026 SACC
o-Dichlorobenzene (*o*-DCB)	95-50-1	Draft	June 2026 SACC
Trans-1,2-Dichloroethylene (TDCE)	156-60-5	Draft	August 2026 SACC

SACC = Science Advisory Committee on Chemicals

ReCAAP Case Study: DIBP and DCHP

For further details on DIBP and DCHP case study see: U.S. EPA. (2025). Cancer Human Health Hazard Assessment for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), and Dicyclohexyl Phthalate (DCHP). (EPA-740-R-25-029). Washington, DC: Office of Pollution Prevention and Toxics. https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0433-0159

Evaluating Cancer Hazards of DIBP and DCHP using ReCAAP

- **Problem Formulation**: No chronic toxicity or cancer bioassays available for DIBP or DCHP
- **Data Collection, Evaluation, and Evidence Integration**:
  - Toxicologic information for DIBP and DCHP
  - Read-across to structurally and toxicologically similar phthalates (DEHP, BBP, DBP, DINP, DIDP) with oral cancer bioassay data that have also been recently assessed under TSCA

Information Considered:

- Physical and chemical properties
- Absorption, distribution, metabolism, excretion (ADME) properties
- Acute toxicity
- Evidence of hormone perturbation, developmental and reproductive toxicity
- Subchronic toxicity
- Immune system perturbation
- Genotoxicity
- Mode of action
- Chronic toxicity & carcinogenicity
- Epidemiological studies
- Read-across to related chemicals

BBP = butyl benzyl phthalate; DBP = dibutyl phthalate; DEHP = Di(2-ethylhexyl) phthalate; DIDP = diisodecyl phthalate; DINP = diisononyl phthalate

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FOR DIBP, DCHP, AND 5 READ-ACROSS PHTHALATES, U.S. EPA CONCLUDED…

- **Developmental/Reproductive Toxicity**: DIBP, DCHP, DEHP, DBP, BBP, DINP (but not DIDP) are antiandrogenic, disrupting testicular testosterone production & causing effects on the developing male reproductive system consistent with phthalate syndrome
- **Subchronic Toxicity**: Liver is a target organ in intermediate & subchronic oral studies
- **Mode of Action**: Evidence of PPARα activation in the liver
- **Immune System**: No evidence for immune system suppression
- **Epidemiology**: Evidence insufficient to identify an association between phthlate exposure and cancer outcomes
- **Genotoxicity**: These phthalates are not considered to be direct-acting genotoxicants or mutagens

PPARα = peroxisome proliferator-activated receptor alpha

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FOR DIBP, DCHP, AND 5 READ-ACROSS PHTHALATES, U.S. EPA CONCLUDED…

- Developmental toxicity is a more sensitive and robust outcome than chronic toxicity for deriving a point of departure (POD) for DEHP, DBP, BBP, DIDP
- Non-cancer chronic liver toxicity was a more sensitive outcome than developmental toxicity for DINP
- Although available carcinogenicity data support differing cancer classifications for 5 phthalates used for read-across, in no case was cancer risk quantified
  - **DEHP, DBP, BBP, DIDP**: *Not likely to be carcinogenic to humans*
  - **DINP***: Not likely to be carcinogenic to humans* at doses below levels that do not result in PPARα activation in the liver
    - Non-cancer PODs for DINP expected to adequately account for chronic toxicity & carcinogenicity

Weight of Scientific Evidence Conclusions Regarding Carcinogenicity of DIBP and DCHP

- Despite lack of chronic toxicity and carcinogenicity bioassays for DIBP and DCHP, a body of evidence suggests that this is not a significant remaining source of scientific uncertainty
- Non-cancer PODs for DIBP and DCHP based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome are health protective

ReCAAP Case Study: HHCB

For further details on draft HHCB case study see: U.S. EPA. (2026). Draft Human Health and Environmental Hazard Assessment for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB). (EPA-740-D-26-007). Washington, DC: Office of Pollution Prevention and Toxics. https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0430-0078

Acknowledgements: Dr. Lillie Barnett

Evaluating Cancer Hazards of HHCB using ReCAAP

- **Problem Formulation**: No chronic toxicity or cancer bioassays available for HHCB
- **Data Collection, Evaluation, and Evidence Integration**:
  - Toxicologic information for HHCB
  - Read-across considered but not employed (no analogs for HHCB with cancer bioassay data identified)

Information Considered:

- Physical and chemical properties
- Absorption, distribution, metabolism, excretion (ADME) properties
- Acute toxicity
- Evidence of hormone perturbation, developmental and reproductive toxicity
- Subchronic toxicity
- Immune system perturbation
- Genotoxicity
- Mode of action

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For HHCB, U.S. EPA Preliminarily Concluded…

- **ADME:** Low potential for bioaccumulation in human tissue
- **Acute Toxicity:** Not acutely toxic (lethality) via oral, dermal, inhalation routes, and is not an irritant or sensitizer
- **Genotoxicity**: Not considered to be genotoxicant or mutagenic
- **Immune System**: No evidence for immune system suppression
- **Endocrine Disruption**: Although HHCB shows weak receptor activity *in vitro*, strong WoE shows no endocrine disruption in *in vivo* rodent models (OECD 443, OECD 408, mouse uterotrophic assay)
- **Subchronic Toxicity**: No evidence of preneoplastic lesions (i.e., hyperplasia or foci formation) or other effects consistent with a non-genotoxic threshold MOA

Weight of Scientific Evidence Conclusions Regarding Carcinogenicity of HHCB

- Despite lack of chronic toxicity and carcinogenicity bioassays for HHCB, a body of evidence suggests that this is not a significant remaining source of scientific uncertainty
- Non-cancer POD for HHCB based on developmental toxicity (decreased offspring body weight in extended one generation study of reproduction) is health protective, including for potential cancer effects

ReCAAP Case Study: *o*-DCB

For further details on draft *o*-DCB case study see: U.S. EPA. (2026). Draft Human Health and Environmental Hazard Assessment for *o*-Dichlorobenzene. (EPA-740-D-26-016). Washington, DC: Office of Pollution Prevention and Toxics. https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0444-0077

Acknowledgements: Dr. Keith Jacobs and Dr. Abhilash Sasidharan

Evaluating Cancer Hazards of *o*-DCB using ReCAAP

- **Problem Formulation**:
  - Oral cancer bioassays of rats and mice available
  - No chronic toxicity or cancer bioassays available for the inhalation route, which is an important route of exposure
- **Data Collection, Evaluation, and Evidence Integration**:
  - Toxicologic information for *o*-DCB
  - Read-across to 3 structurally and toxicologically similar chemicals (*para(p)*-DCB, chlorobenzene, 1,2,4-trichlorobenzene) with available cancer bioassays
  - 5-day comparative transcriptomic study of *o*-DCB and *p-DCB* (inhalation route)

Information Considered:

- Physical and chemical properties
- Absorption, distribution, metabolism, excretion (ADME) properties
- Evidence of hormone perturbation, developmental and reproductive toxicity
- Subchronic toxicity
- Immune system perturbation
- Genotoxicity
- Mode of action
- Chronic toxicity & carcinogenicity
- Epidemiological studies
- Read-across to related chemicals

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For *o*-DCB and Analogs, U.S. EPA Preliminarily Concluded…

- **Immune System and Hormone Disruption:** Inadequate information, not assessed for *o*-DCB or analogs
- **Genotoxicity**: *o*-DCB and analogs are generally negative for mutagenicity in guideline studies; *o*-DCB was negative in cell transformation assay; some evidence of clastogenicity *in vivo*
- **Epidemiology**: Evidence insufficient to identify an association between *o*-DCB or analog exposure and subsequent cancer outcomes

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For *o*-DCB and Analogs, U.S. EPA Preliminarily Concluded…

- **Carcinogenicity in Rodent Cancer Bioassays:**
  - ***o*-DCB**: No treatment-related tumors in mice or rats (oral route)
  - ***p*-DCB**: Increased kidney tumors in male rats (oral route) and increased liver tumors in mice of both sexes (inhalation and oral routes), but occur via rodent-specific mechanisms (α2u-globulin and constitutive androstane receptor [CAR]) that are not human relevant; Slight increase in lung tumors in high-dose female mice (within historical control range), but not considered treatment-related (inhalation route)
  - **Chlorobenzene**: Increased incidence of neoplastic nodules in male rats (did not progress to liver tumors); No neoplastic changes in female rats or mice of either sex (oral route); No chronic toxicity study available for the inhalation route
  - **1,2,4-Trichlorobenzene**: Liver tumors observed in mice (but not rats) of both sexes (oral route). However, *o*-DCB did not induce liver tumors in its chronic oral bioassay. No preneoplastic or neoplastic findings in 26-week inhalation studies of rats, rabbits, or monkeys
- **Transcriptomic Evidence**: NIEHS 5-day inhalation transcriptomic study indicates *o*-DBP and *p*-DCB induce liver CAR activation and a pattern of gene expression consistent with acute non-cancer toxicity

Weight of Scientific Evidence Conclusions Regarding Carcinogenicity of *o*-DCB

- Applying the ReCAAP framework, EPA did not identify any human relevant cancer hazard and therefore did not derive a quantitative cancer value.
- Additional chronic rodent bioassays are unlikely to provide evidence leading to a different conclusion.
- Proposed non-cancer PODs for *o*-DCB are expected to be protective of any potential cancer effects. No tumors were observed in NTP two-year oral bioassays of *o*-DCB at doses similar to or higher than non-cancer PODs, suggesting tumor induction is unlikely at doses relevant to non-cancer risk

ReCAAP Case Study: TDCE

For further details on draft TDCE case study see: U.S. EPA. (2026c). Draft Human Health and Environmental Hazard Assessment for *trans*-1,2-Dichloroethylene. (EPA-740-D-26-31). Washington, DC: Office of Pollution Prevention and Toxics. https://www.regulations.gov/document/EPA-HQ-OPPT-2026-2246-0043

Acknowledgements: Dr. Keith Jacobs and Dr. Ali Shohatee

Evaluating Cancer Hazards of TDCE using ReCAAP

- **Problem Formulation**: No chronic toxicity or cancer bioassays available for any exposure route
- **Data Collection, Evaluation, and Evidence Integration**:
  - Toxicologic information for TDCE
  - Read-across to *cis*-1,2,-dichloroethylene and mixed isomers

Information Considered:

- Physical and chemical properties
- Absorption, distribution, metabolism, excretion (ADME) properties
- Evidence of hormone perturbation, developmental and reproductive toxicity
- Subchronic toxicity
- Immune system perturbation
- Genotoxicity
- Mode of action
- Epidemiological studies
- Read-across to related chemicals

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For TDCE and Analogs, U.S. EPA Preliminarily Concluded…

- **ADME:** TDCE exhibit suicide inhibition of cytochrome P450 enzymes, which can lead to decreased reactive metabolite formation over time; cis isomer also exhibits suicide inhibition, albeit to a lesser extent
- **Genotoxicity**: TDCE and analogs negative for genotoxicity in most *in vitro* and *in vivo* assays
- **Endocrine Disruption**: No evidence of endocrine disruption for TDCE or analogs
- **Subchronic Toxicity:** No preneoplastic lesions (i.e., hyperplasia, foci formation) or evidence of cellular regeneration for TDCE or the *cis* isomer; relatively high doses/concentrations required for most non-cancer effects, with overall low toxicity across most organ systems below typical limit doses (i.e., 1000 mg/kg-day)
- **Immune System**: TDCE caused immune system suppression, however, inflammation was not observed in subchronic studies

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For TDCE and Analogs, U.S. EPA Preliminarily Concluded…

- **Carcinogenicity (Rodents):** No bioassays available for TDCE or any analog
- **Epidemiology:** No statistically significant associations with cancer outcomes identified for TDCE or mixed isomers in three case-control studies
- **In Silico Models**: OncoLogic predicted “Marginal” level of concern for TDCE (likely to have equivocal carcinogenic activity or weakly carcinogenic at doses exceeding the maximum tolerated dose)

Weight of Scientific Evidence Conclusions Regarding Carcinogenicity of TDCE

- EPA preliminarily concluded that quantitative cancer risk assessment of TDCE is not warranted and carcinogenic effects from TDCE would not be expected
- The overall weight of scientific evidence supports this finding and indicates additional cancer bioassays would be unlikely to provide evidence leading to a different conclusion

Key Take Home Conclusions

- In the absence of traditional rodent cancer bioassays, the ReCAAP WoE Framework can be used to assess the carcinogenic potential of a chemical and the uncertainty associated with the absence of this data.
- Use of ReCAAP WoE Framework can reduce the need for animal testing.
- There are no specific data requirements for applying the ReCAAP WoE Framework. Instead, all available information should be considered as part of the WoE approach.

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Thank you for your attention.