National Institute of Environmental Health Sciences
Division of Translational Toxicology

Report on Carcinogens Handbook

National Academy of Sciences, Engineering and Medicine

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NIEHS, NIH

Outline

- Background
  - NIEHS and National Toxicology Program (NTP)
  - Report on Carcinogens (RoC)
- RoC Handbook
- Updated RoC Handbook: Process and What's new
- RoC Handbook Implementation
- NASEM Guidance
- Impact and Summary

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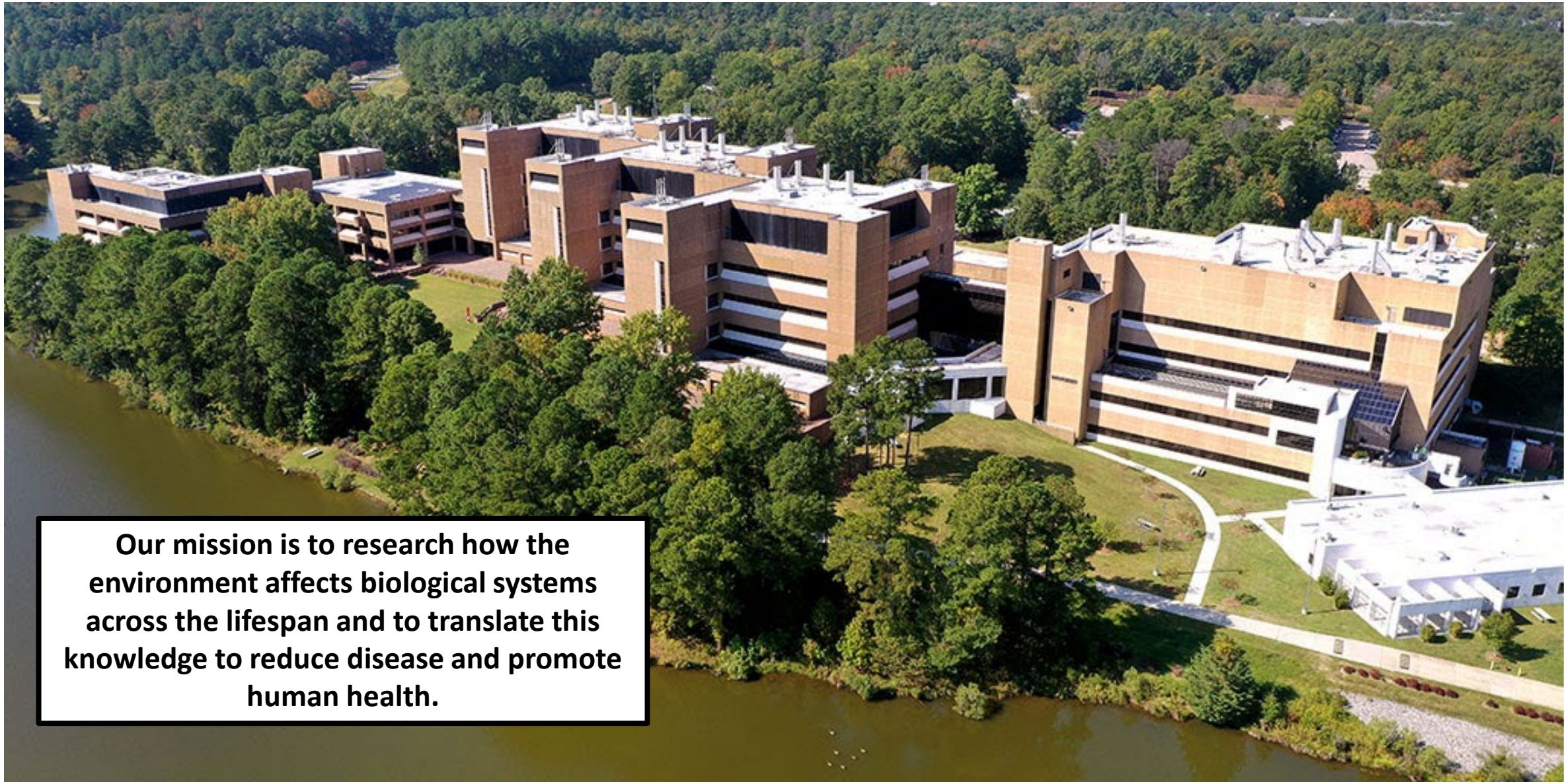
NIEHS



Our mission is to research how the environment affects biological systems across the lifespan and to translate this knowledge to reduce disease and promote human health.

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U.S. National Toxicology Program (NTP)

NTP Mission

- The RoC is an NTP publication.
- Partner to build knowledge and advance toxicological sciences to protect and promote human health.
- In carrying out its mission, the federal NTP partners develop and apply new approaches, technologies, and research methods, necessary to achieve the vision of innovative and trusted toxicological science that protects human health.

HHS Interagency Program

NIOSH

NCTR

NIEHS

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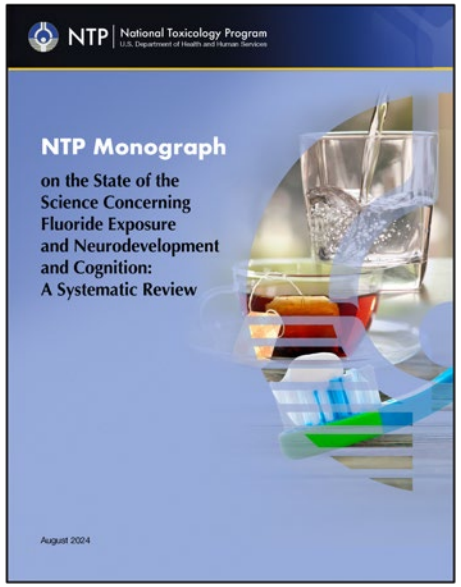
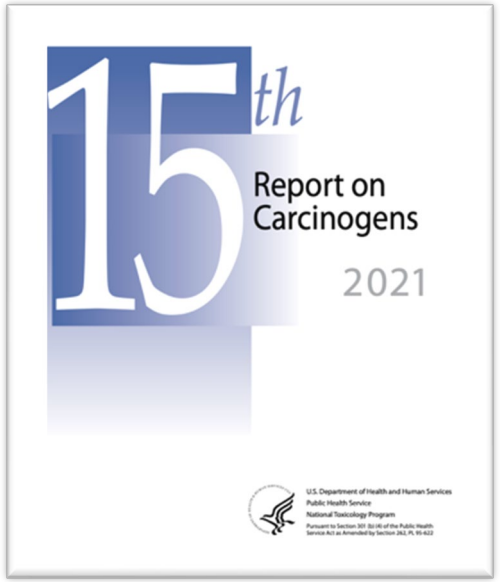
Hazard Identification at NIEHS

IHAB - Integrative Health Assessments Branch

- Home of the RoC team
- Evaluates evidence that environmental substances cause health effects by systematically assessing human, animal, and in vitro research data
  - Informs the public, government, scientific, and medical communities
- Literature-based assessments, systematic evidence maps, impact analyses, publications, workshops
  - Non-Cancer – Health Assessment and Translation
  - Cancer - Report on Carcinogens





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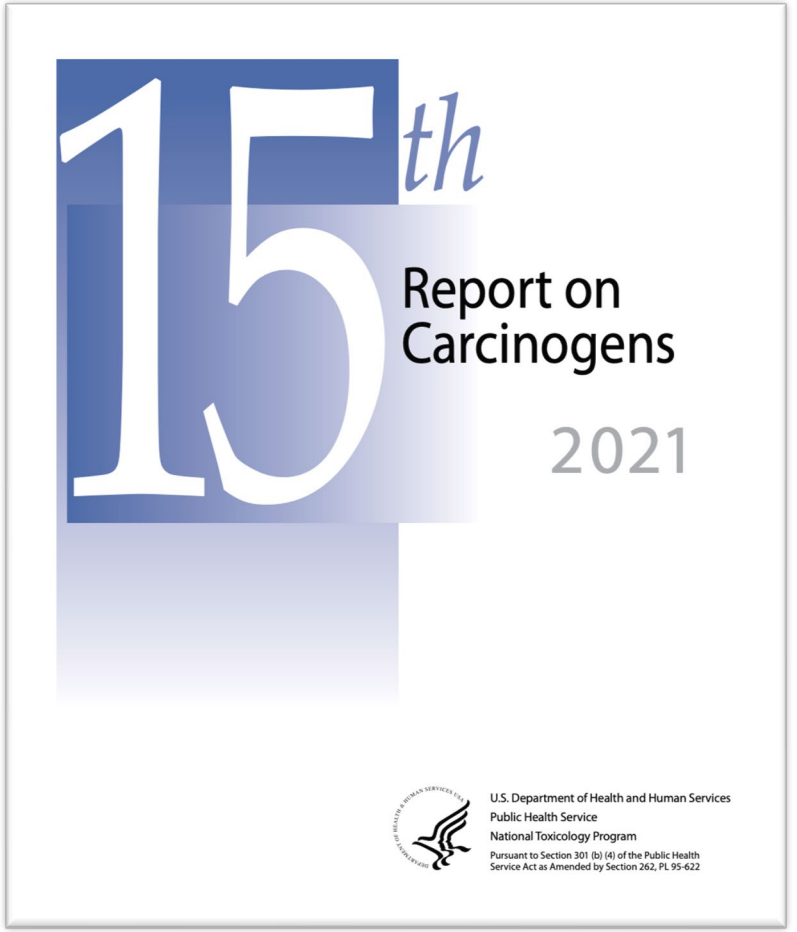
Cancer Identification Report

- Congressionally-mandated scientific document (Public Health Service Act of 1978) prepared by NTP on behalf of the Secretary, Health and Human Services
- Identifies substances that pose a cancer hazard to people residing in the United States using a formal process and established listing criteria
- Two listing categories:
  - ***Known*** *to be a human carcinogen*
  - ***Reasonably anticipated*** *to be a human carcinogen*
- Substances are listed in the RoC using a formal process and established listing criteria
- **The Report on Carcinogens Handbook** explains how NTP systematically reviews scientific research to evaluate substances for inclusion in the Report on Carcinogens



https://ntp.niehs.nih.gov/go/rocv/go/RoC15data

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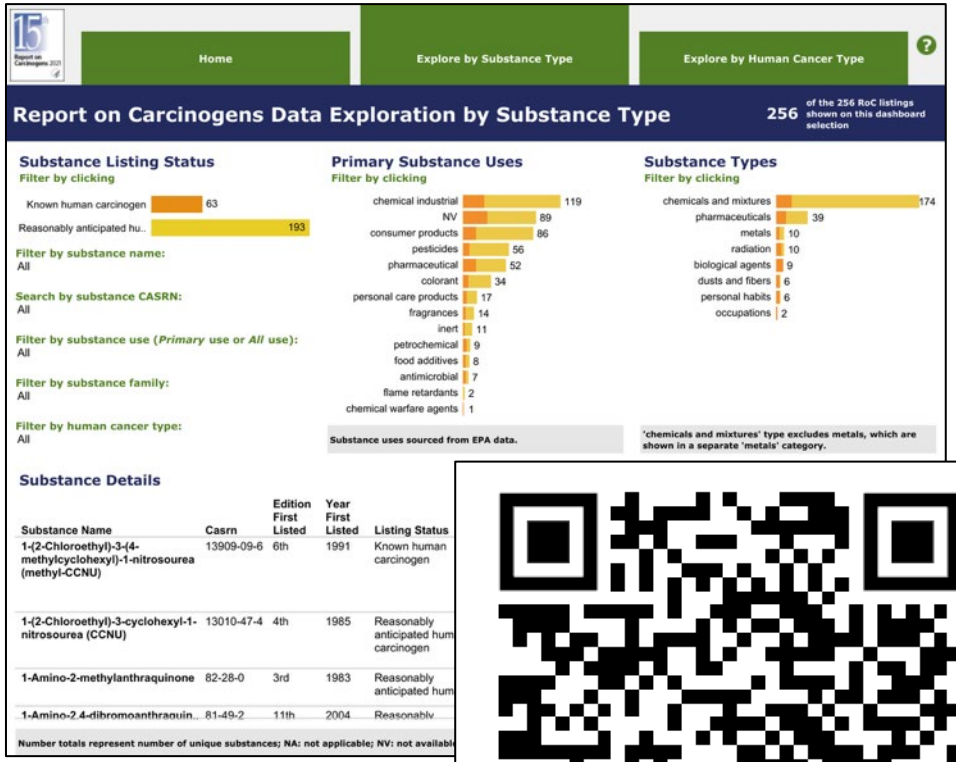
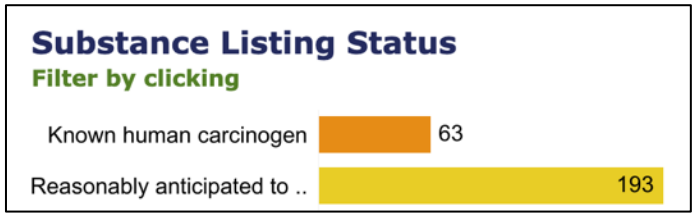
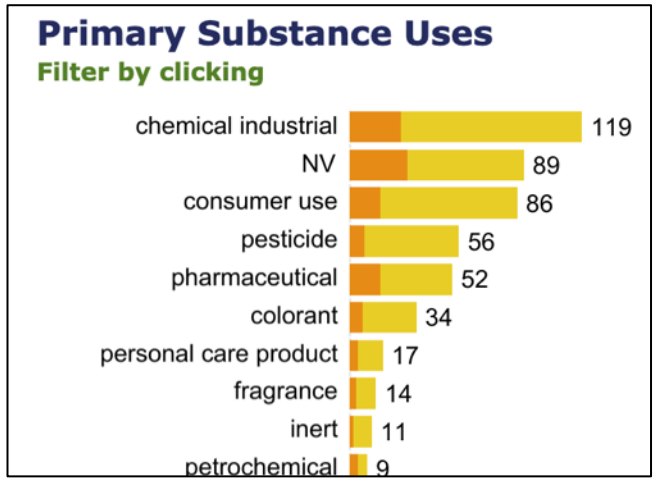
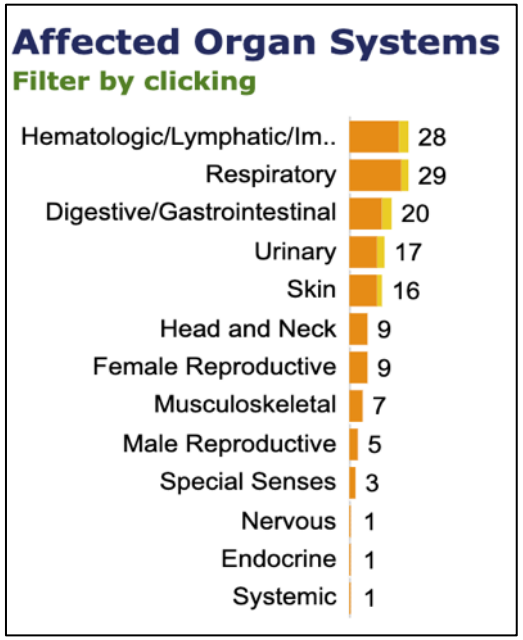
Interactive Dashboard

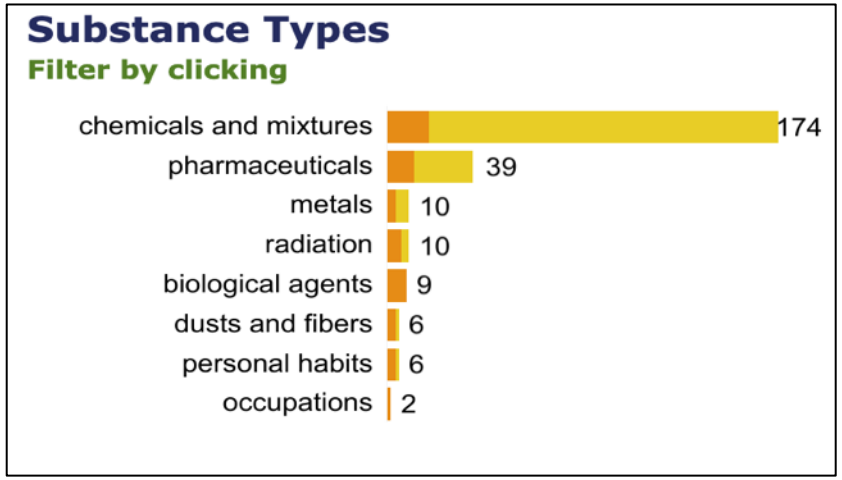
Listed substances are diverse and linked to many different types of human cancer











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RoC Process

Scientific input, public comments, peer review of science

Select substances for review

- Invite nominations
- Scope literature and develop concept
- Select substances
- NTP Director approval

Conduct cancer hazard evaluations

- Develop and publish protocols (methods) for cancer assessments
- Develop draft monographs
- Scientific & public input as needed
- Internal and interagency review of draft assessments/conclusions

Peer review and finalize monographs

- Release draft monographs to public
- Convene peer review of draft monographs
- Revise monographs based on peer review comments
- Finalize monographs

Publish and release RoC

- Share proposed listings with NTP Executive Committee
- Transmit to HHS Secretary for approval
- Publish & release RoC: Congress, NTP website, PubMed

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RoC Hazard Identification

Congress defines categories	National Toxicology Program establishes criteria		RoC Handbook provides guidelines for
	Level of evidence	Evidence requirements	
Known to be a human carcinogen	**Sufficient** evidence from human studies	*Human studies*: causal relationship	• Transparent and rigorous **Methods** • **Assessments** that span multiple evidence streams • Explains how the evidence support application of **Criteria** and **Conclusions**
Reasonably anticipated to be a human carcinogen	Any of the following: • **Limited** evidence from human studies	• Cannot reasonably rule out chance, bias, and confounding	
	• **Sufficient** evidence from animal studies	• Evidence from multiple species, routes of exposure, cancer sites	
	• **Convincing** mechanistic data	• Mechanisms would likely occur in humans	

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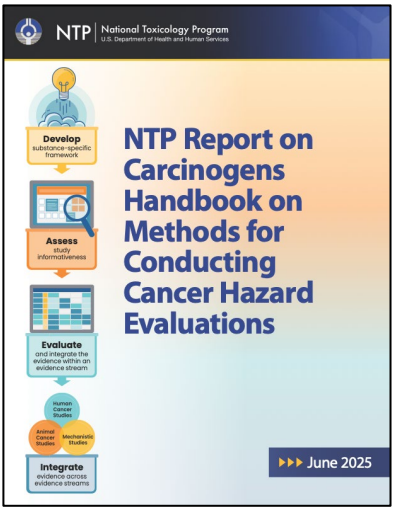
RoC Handbook History

Previous edition (2015)

- Incorporated systematic review (SR) methods to RoC evaluations
- Provided greater transparency in assessment process
  - How RoC criteria are applied to reach a hazard conclusion
- Was the foundation for updated Handbook



Updated edition (2025)

- Incorporated progression of systematic review methods within the scientific community
  - Keeping current with “best practices”
  - Includes refinements based on “real world” assessment experience
- Refined steps in the interpretation of scientific data
  - New tools, techniques and approaches to enhance guidance for assessments
- **Addressed underdevelopment in certain areas of the Handbook (e.g., mechanistic studies)**
- **GOAL: Obtain feedback and recommendations for the next version (est. 2030-2035)**

Updated RoC Handbook

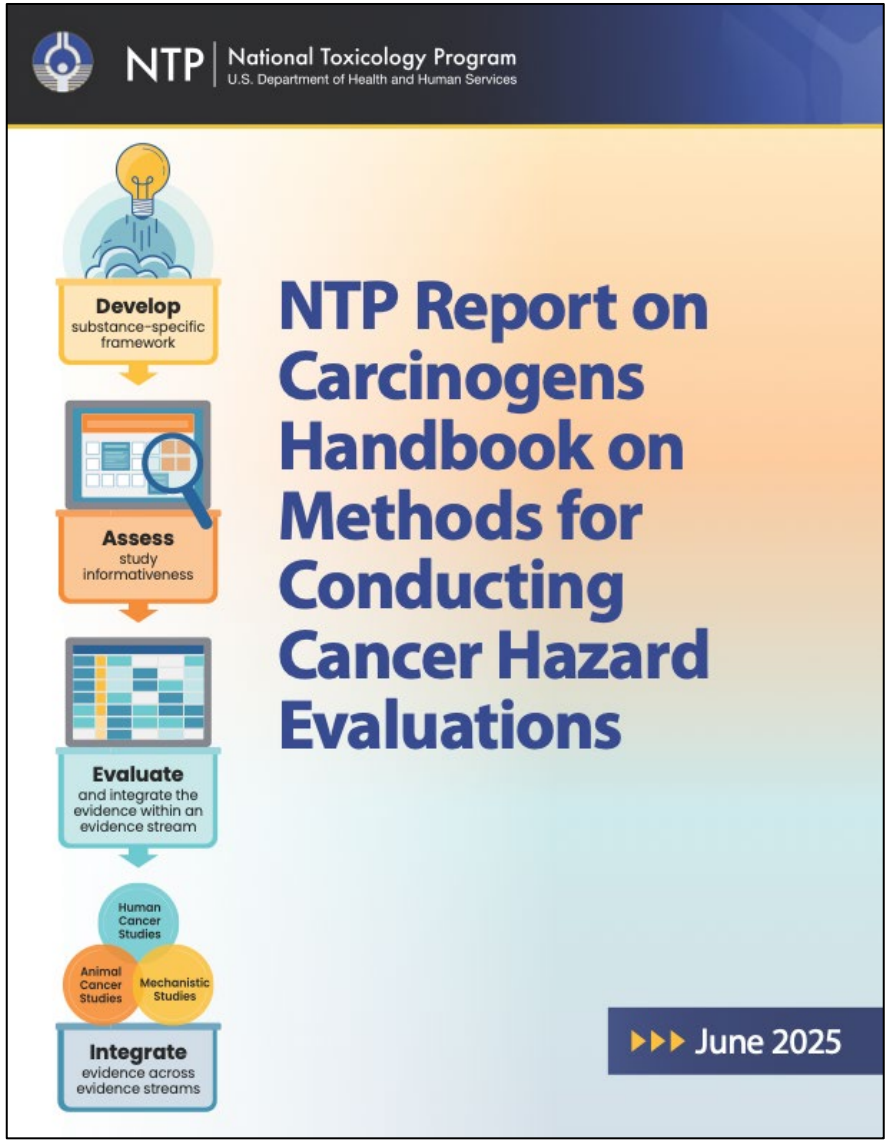
Sections in RoC Handbook

Seven Chapters

- Developing and planning the evaluation **framework**
- Human **exposure** data evaluation
- **Human cancer** studies evaluation
- **Experimental animal cancer** studies evaluation
- **Disposition and toxicokinetic** data evaluation
- **Mechanistic data** evaluation
- **Evidence integration** and cancer hazard **conclusion**

Appendices

- Glossary and information resources
- Tools
- KCC* biomarkers and indicators tables
- Literature search strings



*KCC = Key characteristics of carcinogens

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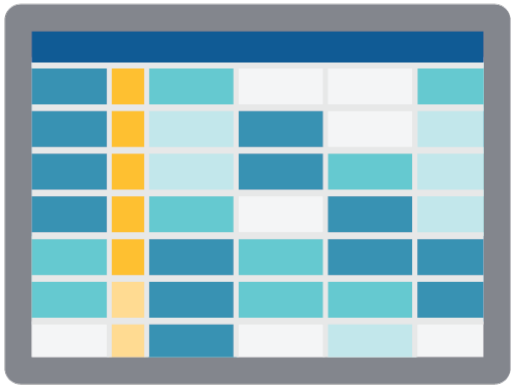
Overview of RoC Process

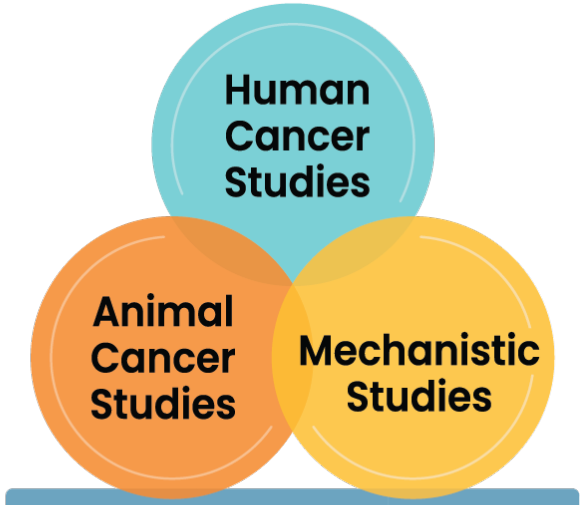
Health hazard conclusions are reached using systematic review methods, evidence integration, and established listing criteria

Develop substance-specific framework

Assess study informativeness



Evaluate and integrate the evidence within an evidence stream



Integrate evidence across evidence types to reach a cancer hazard conclusion

Step 1: Framework Development

Develop substance-specific framework

Sciences
Toxicology

Select substance for review → Develop Framework → Develop protocol

New!

- Incorporated systematic evidence maps
- Expanded and revised literature search strings for certain Key Characteristics of Carcinogens

Identify, select, and map studies based on PECO

Review literature, identify issues

Develop evaluation framework redefine PECO

New!

Developed strategy on how to evaluate mechanistic studies, framework for read-across

Greater emphasis on fit-for-purpose frameworks

Literature Screening Tools

HAWC HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

SWIFT REVIEW

SWIFT-ACTIVESCREENER

Systematic Evidence Mapping Tool

tableau

*PECO = Population, Exposure, Comparison group, Outcome

Assess study informativeness

ences
icology

Step 2: Study Evaluations

Process
Substance-specific guidance to evaluate individual studies Core and guiding questions Scientific judgment collectively reached considering all questions Bias evaluation is done independent of study results

New! Tool on newly developed questions and guidance for assessing human, animal, and *in vitro* mechanistic studies

Domains	
Epidemiology Studies	**Animal & *in vitro* Studies**
Study sensitivity*	Study sensitivity*
Selection bias	Study design
Exposure misclassification/ mismeasurement	Exposure conditions
Outcome misclassification	Outcome assessment
Confounding	Confounding
Analysis	Analysis

New tool! Expanded guidance on how to assess exposure misclassification in human studies, including new exposure assessment table

New! Clarified guidance for assessing study sensitivity in animal studies

Judgement
Concern + magnitude of bias (No/minimal, some, moderate/major, critical)
Direction of bias (above minimal)

*Ability to detect a true effect

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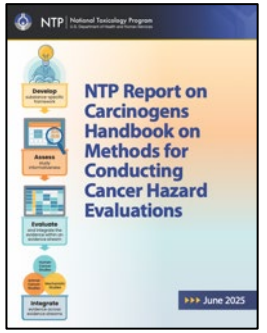
Step 3: Evaluate Individual Studies

Evaluate and integrate the evidence within an evidence stream

New! Revised guidance: Provided greater emphasis on bias impact and stratified analysis by key issues for human studies



Evaluating confidence in individual studies →

Strength of study findings (magnitude, exposure-response)

Direction, magnitude, and impact of biases and confounding on findings

Sensitivity of study to detect an effect

Internal consistency

→

Strong/moderate evidence

Some evidence

Null evidence

Inconclusive

*Based on scientific judgement of evaluation team, not a checklist or algorithmic approach

Evaluate and integrate the evidence within an evidence stream

Sciences
Toxicology

Step 3: Evidence Integration

Systematic assessment of biases, scientific issues (e.g., effect modifiers)

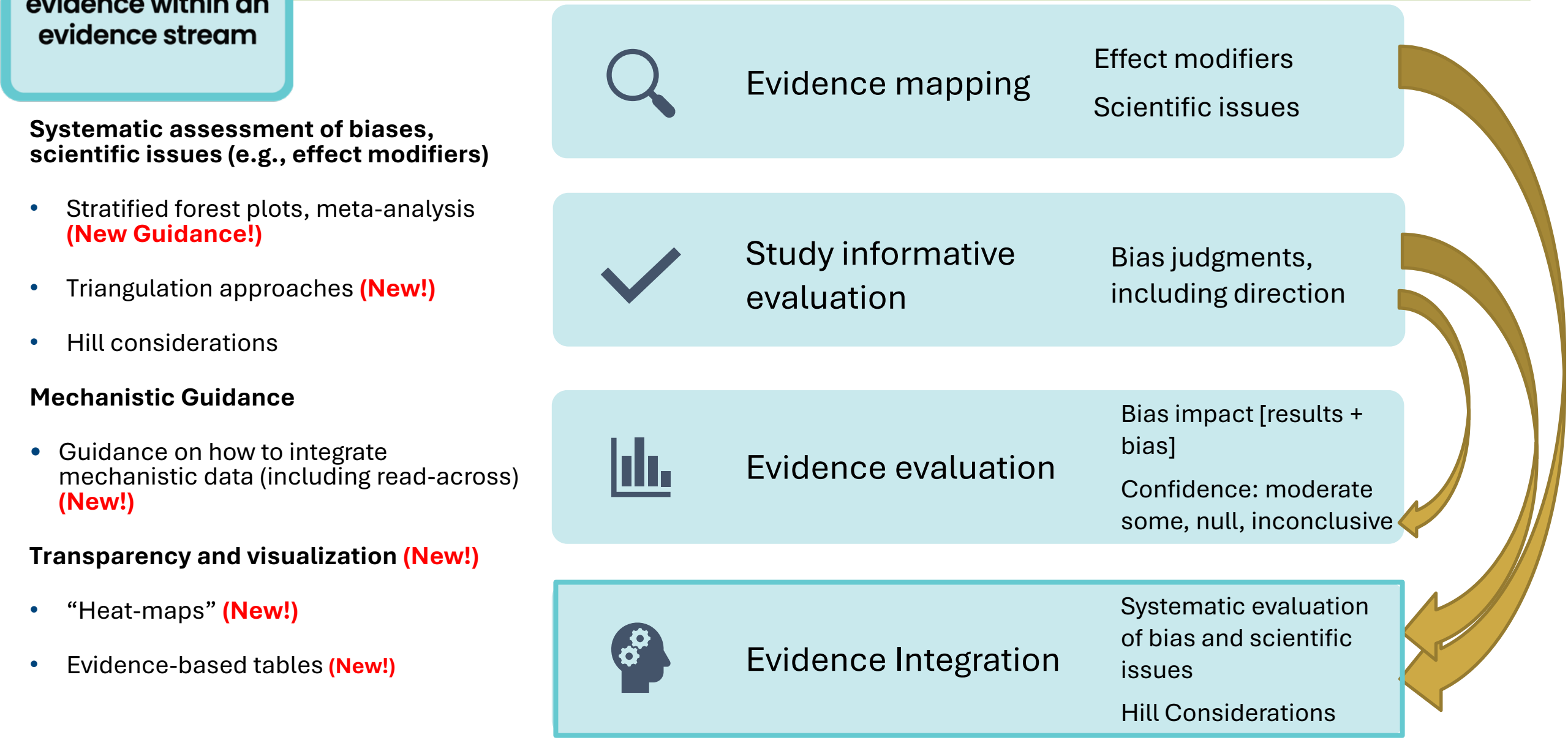
- Stratified forest plots, meta-analysis **(New Guidance!)**
- Triangulation approaches **(New!)**
- Hill considerations

Mechanistic Guidance

- Guidance on how to integrate mechanistic data (including read-across) **(New!)**

Transparency and visualization (New!)

- "Heat-maps" **(New!)**
- Evidence-based tables **(New!)**



Integrate evidence across evidence types to reach a cancer hazard conclusion

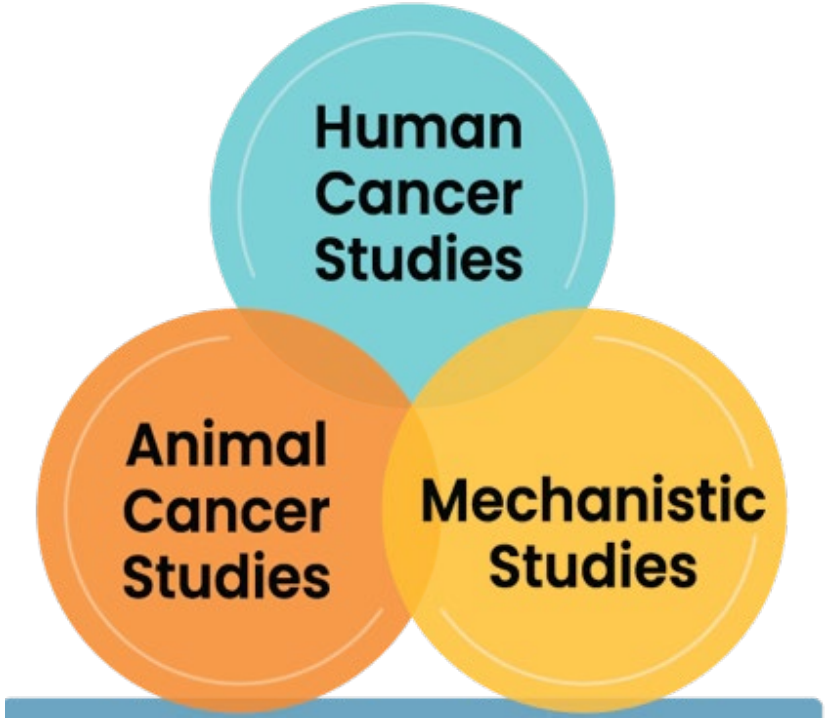
Step 4: Integration and Hazard Conclusion

Integrate evidence from studies in humans, animals, mechanistic data and apply RoC listing criteria to reach a preliminary listing recommendation

New!

Evidence-based tables for increased transparency in reaching overall hazard conclusion

Created structured guidance and strategy for integrating level of evidence conclusions of carcinogenicity for each evidence stream



Overall Evidence Integration

Reaching a listing recommendation: Integrating level of evidence conclusions

RoC criterion	Human cancer epidemiology	Animal cancer	Mechanisms: Overall	Mechanisms: Exposed humans	Listing
Sufficient evidence from studies in humans	Sufficient	Any	Any	Any	Known
	Limited	Any	Supporting	Robust	Known
Limited evidence from studies in humans	Limited	Any	Any	Not robust	RAHC
	Inadequate	Not sufficient	Convincing	Robust	RAHC
Sufficient evidence from studies in experimental animals	Inadequate	Sufficient	Any	Any	RAHC
Biological plausibility or member of a listed class	Inadequate	Not sufficient	Convincing	Any	RAHC

Known = known to be a human carcinogen, RAHC = reasonably anticipated to be a human carcinogen

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Mechanistic Evidence: Substantial Changes

Congress defines categories	National Toxicology Program establishes criteria		RoC Handbook provides guidelines for
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Reasonably anticipated to be a human carcinogen	Any of the following: • **Limited** evidence from human studies	• Cannot reasonal out chance, bias, confounding	
	• **Sufficient** evidence from animal studies	• Evidence from multipl species, routes of exposure, cancer sites	
	• **Convincing** mechanistic data	• Mechanisms would likely occur in humans	

Biological plausibility: biological effects (e.g., key characteristics of carcinogens), mechanisms of action

Provides guidance and a systematic review process for assessing the evidence from mechanistic studies

RoC solutions to challenges surrounding mechanistic data:

Large and diverse database

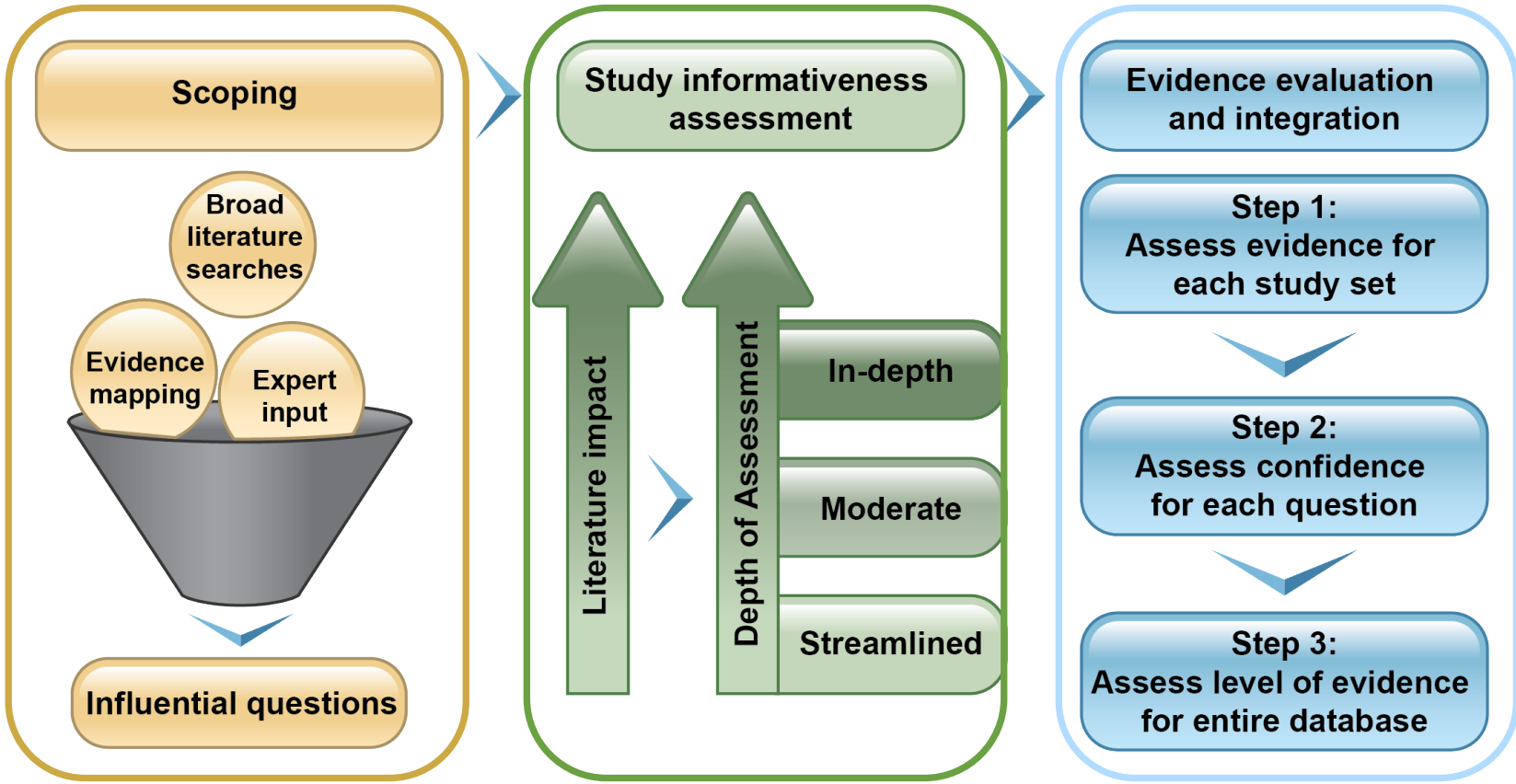
- Fit-for-purpose approach to allow flexibility

Paucity of bias tools

- New tools for study informativeness for ANY KIND of mechanistic data – key transformative upgrade

High Subjectivity

- The NEW structured process aims for greater consistency
- In depth guidance for each step in the evidence integration approach process aims to enhance transparency and reproducibility



Addresses challenges for assessing mechanistic data in the systematic review, hazard and risk assessment communities

(ALL New!)

Implementation of the RoC Handbook

Implementation Challenges

- Speeding up the entire process (18 months to 4 years)
- Developing operational read-across approaches for cancer hazard identification
- Optimizing resource-intensive methods, especially:
  - Systematic evidence mapping
  - Bias impact assessment methods
    - Exposure misclassification modeling not yet implemented and may require external expertise
  - Mechanistic evidence framework
    - Still very new and would benefit from expert input

Challenge: Achieving efficiency and greater speed while maximizing transparency and confidence in cancer hazard conclusions

The Next RoC Handbook

Invited NASEM Guidance for New Directions and Keeping the Handbook Current

- Incorporate AI while maintaining scientific judgment and transparency
  - Avoid non-algorithmic approaches or methods
  - AI needed for study selection, data extraction, modeling (such as exposure misclassification bias)
- Develop and implement systematic review methods for new approach methodologies (NAMs)
  - Integrate primary "omics" and other data analyzes into literature reviews
  - How to incorporate large –'omics data sets (ex. Tox 21 screening results)
    - *How advanced does NAM data need to be before it can confidentially be used for "stand alone" conclusions?*
  - Refine and strengthen read-across approaches
- Expand and update KCC biomarker and indicator resources (Appendix D)
  - Revisions and updates needed for the guidance on KCCs?
  - As written, Appendix D is not complete.

RoC Impact

RoC has had a major influence on cancer prevention efforts over a 40-year period

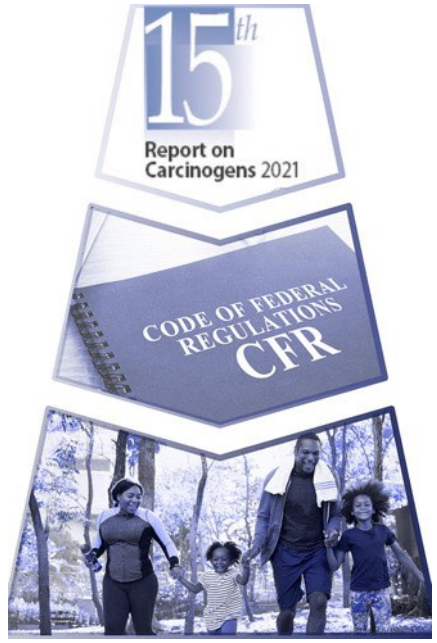
Used in a variety of contexts

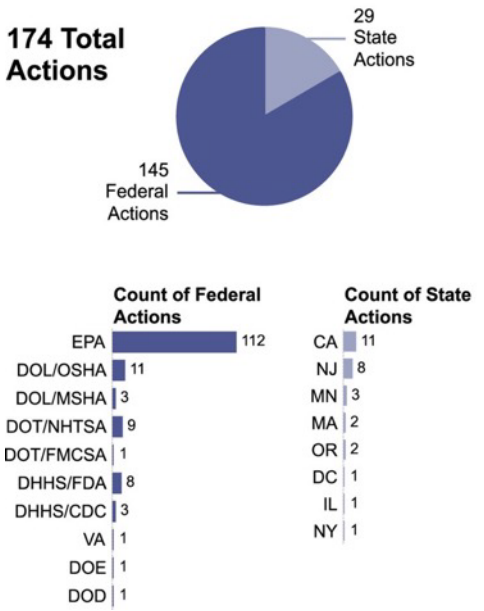
PubMed.gov

American Cancer Society

OSHA

U.S. Department of Labor MSHA Mine Safety & Health Administration





RoC-cited environmental and occupational regulations monetized **up to $8 billion USD/year** in benefits

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Acknowledgments

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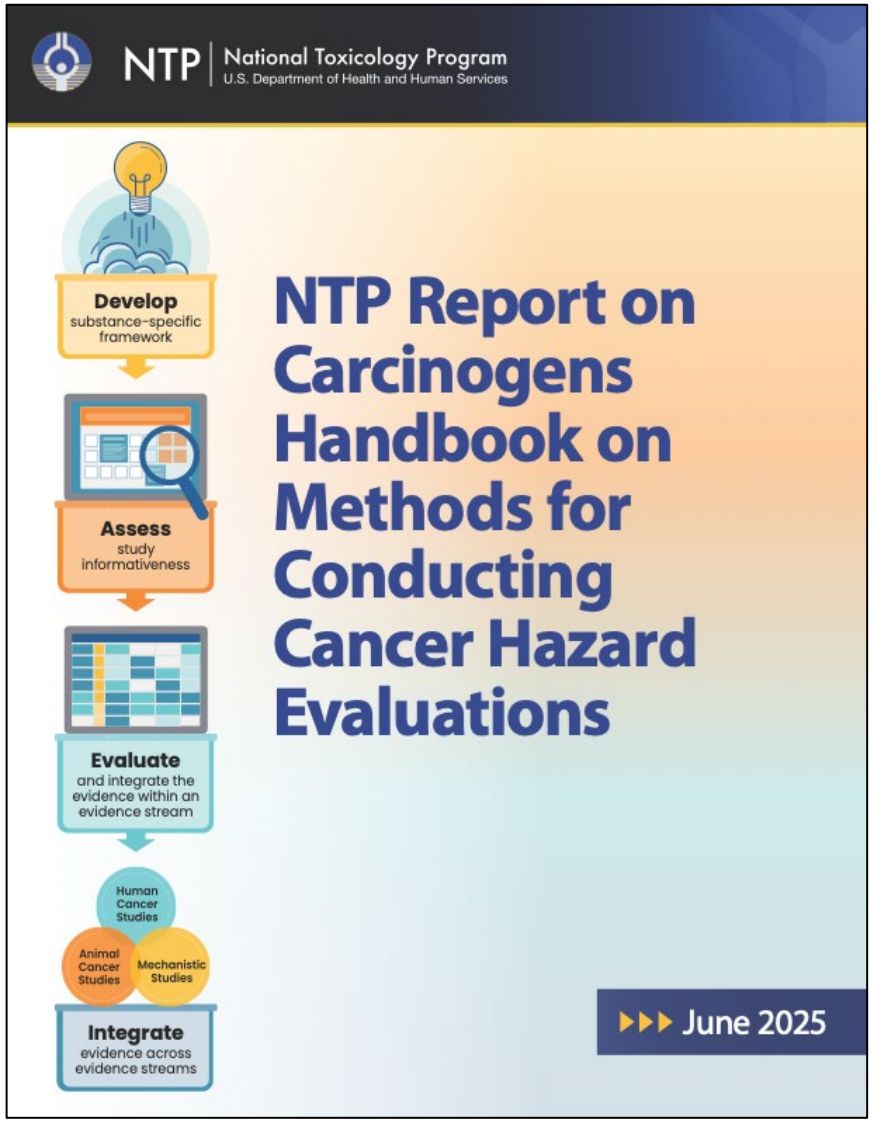

Link to RoC Handbook