

Approaches used to evaluate mechanistic data for the Report on Carcinogens (RoC) by the National Toxicology Program (NTP)

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Workshop on Strategies and Tools for Conducting Systemic Review of Mechanistic Data for Chemical Assessments
December 11 2018



- **What is Report on Carcinogens (RoC)?**
- **Approaches and tools to evaluate mechanistic information**
- **Examples of mechanistic information role in recent RoC evaluation**
 - **Monograph and draft monograph are prepared, but listings are not yet submitted to the Secretary, Department of Health and Human Services for approval**



- **What is Report on Carcinogens (RoC)?**



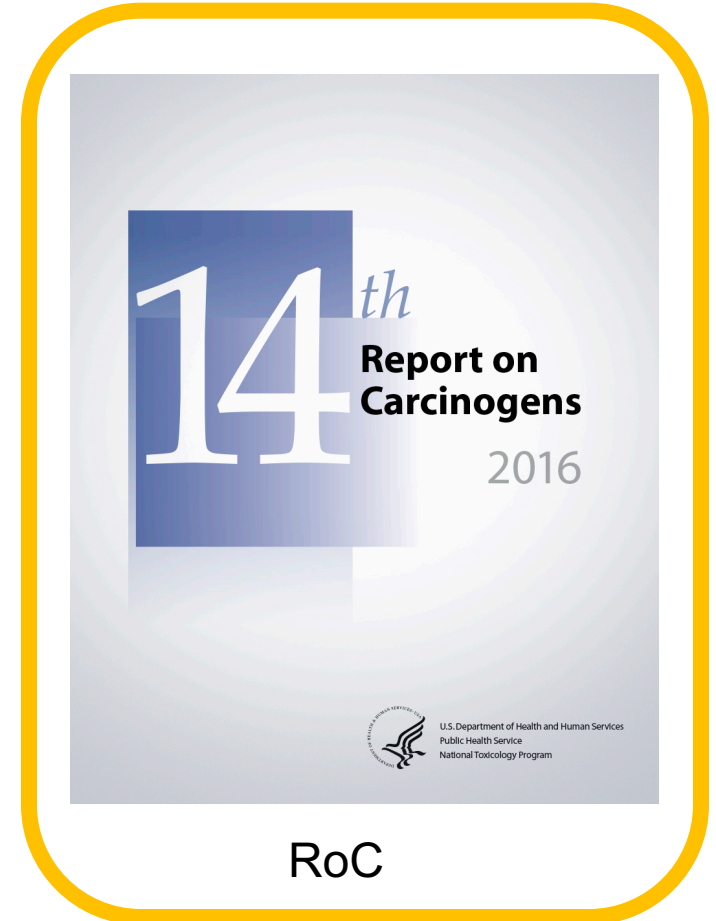
Rock
(rock, the moon)



Rock
(quartz, earth)



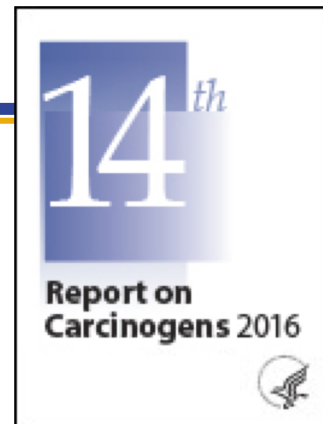
Roc
(myth, Middle East)



RoC



Report on Carcinogens (RoC)



- Mandated by



Congress, prepared by



for the Secretary,

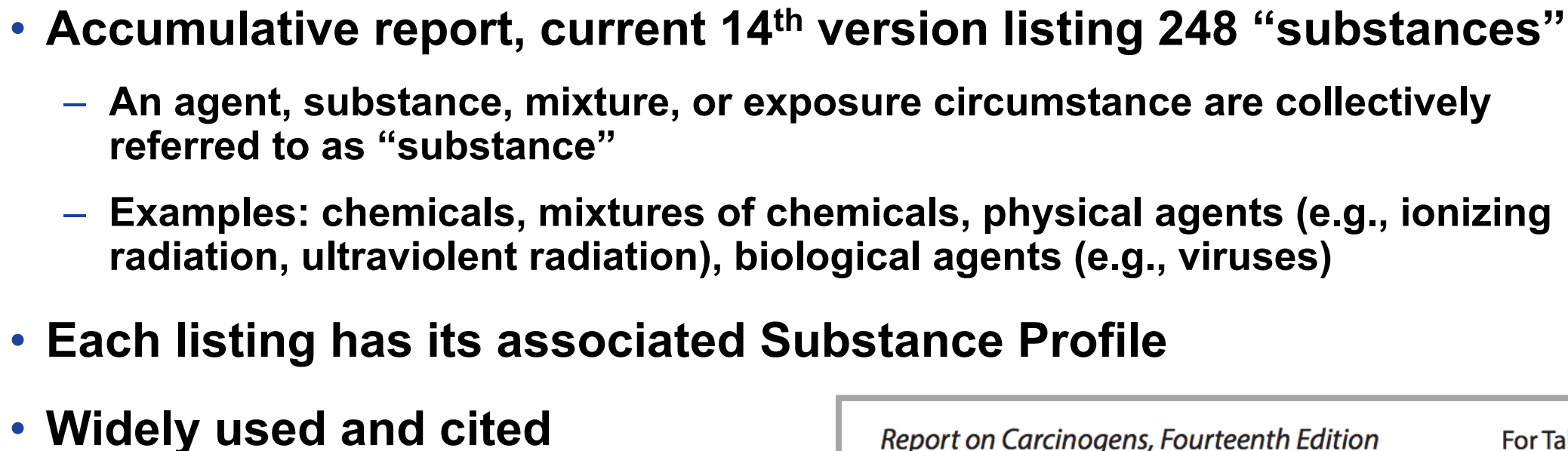


Department of Health and Human Services (HHS)

- Cancer hazard identification for people residing in United States

- A list of identified substances that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens*





Report on Carcinogens, Fourteenth Edition

For Table of Contents, see home p

Human Immunodeficiency Virus Type 1

CAS No.: none assigned

Known to be a human carcinogen

Also known as HIV-1

Carcinogenicity

Human immunodeficiency virus type 1 (HIV-1) is known to be a human carcinogen based on sufficient evidence from studies in humans. This conclusion is based on epidemiological studies show-

al. 2013, Helleberg *et al.* 2013). The excess cancer due to HIV-1 infection is not counted for by the types of

Infection-Related Cancers

Cancer Studies in Humans

Evidence for associations between alcohol consumption and cancer includes: alcohol consumption and cancer of the mouth, pharynx, larynx, esophagus, stomach, colon, rectum, liver, pancreas, breast, and bladder; alcohol consumption and non-Hodgkin lymphoma; alcohol consumption and prostate cancer; alcohol consumption and invasive anal cancer; and alcohol consumption and cervical cancer. This evidence is based on consistent findings from



Developing and preparing RoC monograph

Select substances for evaluation



Prepare draft RoC Monographs for selected substances



Peer review and finalize RoC Monographs



Approval of new listings and release the RoC

Key elements:
Scientific input
Public input
Peer review



Developing and preparing RoC monograph

RoC Monograph

Information on

- Chemical identification and properties
- Human exposure
- Disposition and toxicokinetics
- Human cancer studies
- Studies of cancer in experimental animals
- **Mechanistic** and other relevant data
- Evidence integration and preliminary listing recommendation

Substance profile



Known To Be Human Carcinogen

Reasonably Anticipated To Be Human Carcinogen

For full description, see

<https://ntp.niehs.nih.gov/pubhealth/roc/process/index.html>



Known To Be Human Carcinogen

- Sufficient evidence of carcinogenicity from studies in humans

Could be cancer epidemiological studies in human
Could be **mechanistic** information in exposed humans

Reasonably Anticipated To Be Human Carcinogen

- Limited evidence from studies in humans

OR

- Sufficient evidence from studies in experimental animals

OR

- Belongs to well-defined structurally related class of substances listed in the RoC **or** demonstrates **convincing mechanistic evidence**

Conclusions based on scientific judgment considering **all relevant information** such as chemical structure, metabolism, pharmacokinetics, genetic effects, and mechanisms of action



- What is Report on Carcinogens (RoC)
- **Approaches and tools to integrate mechanistic information**
 - (1) Gather information via a systematic review approach
 - (2) Evaluate and synthesize information via expert judgement
- Examples of mechanistic information role in recent RoC evaluation

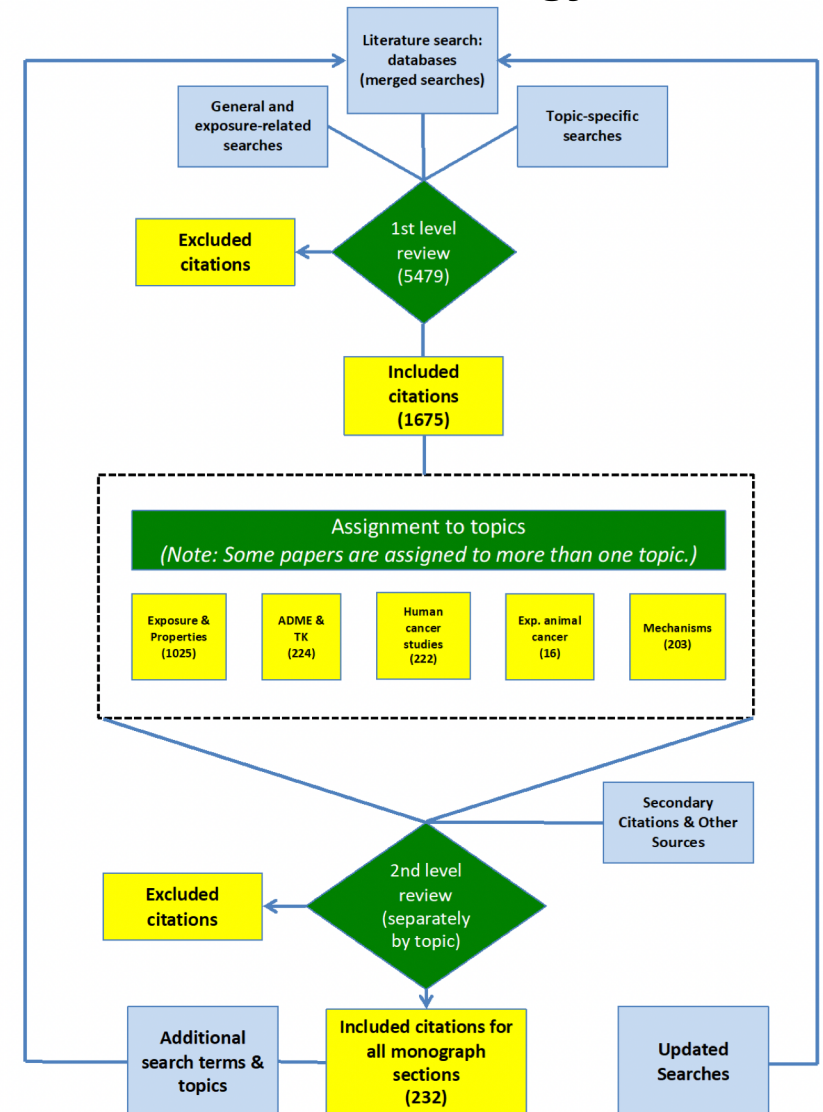


1. Gather mechanistic information

Systematic review approach

- **Main steps:**
 - (1) Search literature
 - (2) Screen references
- **Documentation:**
 - General approach is published in the handbook
 - Handbook for Preparing Report on Carcinogens Monographs (<https://ntp.niehs.nih.gov/go/rochandbook>)
 - Substance-specific approach is in the protocol of each project
 - Results are in the appendix of monograph

Literature search strategy and review





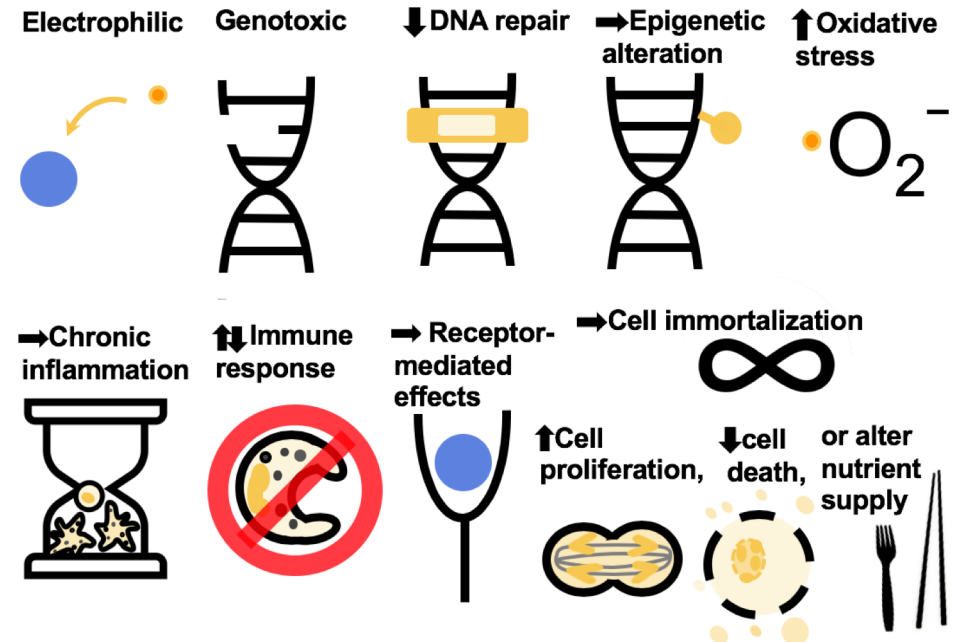
(1) Search literature of mechanic information

- **Authoritative reviews, governmental and organizational reports, and web sources**
 - Search by substance
- **PubMed and other biomedical literature database(s)**

**Substance search string
(project specific)**

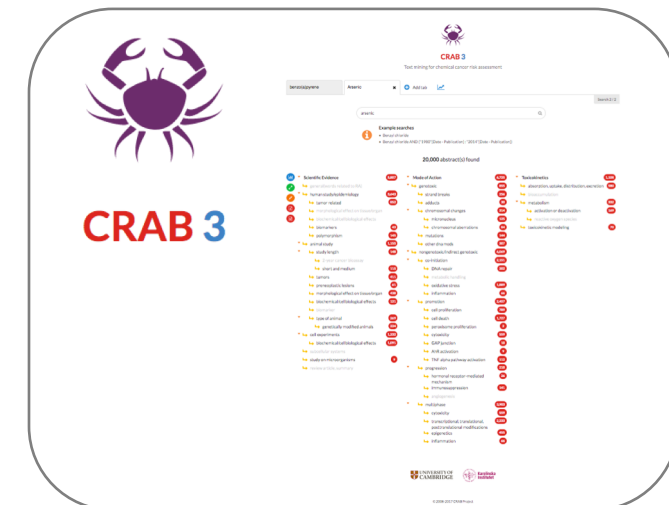
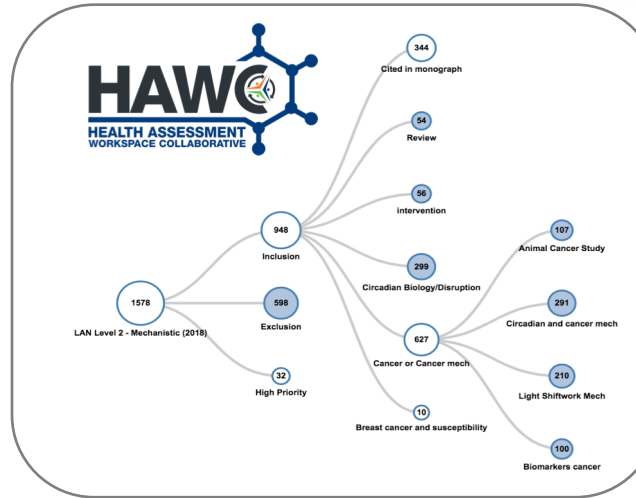
+

Mechanism search string (standard, unless specified)





- 

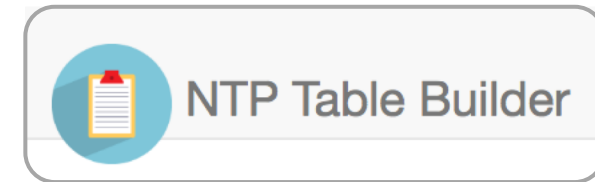




2. Evaluate and synthesize information

Expert judgement

- **Group references generally by key characteristics of carcinogens**
- **Read articles**
- **Extract data**
- **Assess study quality**
- **Assess study utility to inform carcinogenesis**
- **Determine level of confidence in the information**
 - **Examples: direct measurement vs. indicator; consistency across species, studies; potential causes of observed discrepancy**





- **The totality of the information**

- Endpoints → effects → key characteristics → overall
- Temporal relationship
- Dose-response relationship
- Human relevance

- **NTP is planning to update data extraction and study quality questions of genotoxicity studies**

Wang et al. Genetics and Environmental Mutagenesis
Society (GEMS) NC 2018 Fall Meeting



2. Evaluate and synthesize information

Tailored to projects based on key issues and available data

- **Tox21 and transcriptomic data were analyzed by NTP in antimony trioxide project**

High throughput screening results

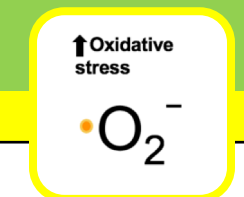
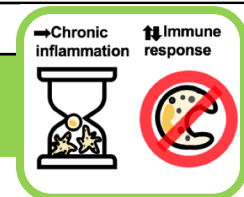
A total of six antimony compounds, not including antimony(III) trioxide, were found in the Tox21 and ToxCast results

In summary, the activities of antimony compounds in Tox21 assays were mostly antagonistic to nuclear receptors, possibly because of displacement of Zn(II) in the zinc finger structures of these receptors by antimony(III) ions. These assays also indicated an oxidative stress response.

Top ten canonical pathways affected by 6-hour exposure to 20 μ M antimony(III) potassium tartrate trihydrate

Order Ingenuity Canonical Pathways

- 1 Agranulocyte Adhesion and Diapedesis
- 2 Granulocyte Adhesion and Diapedesis
- 3 Eicosanoid Signaling
- 4 Role of Cytokines in Mediating Communication between Immune Cells
- 5 Role of Hypercytokinemia/hyperchemokine in the Pathogenesis of Influenza
- 6 Bladder Cancer Signaling
- 7 Crosstalk between Dendritic Cells and Natural Killer Cells
- 8 Role of IL-17A in Psoriasis
- 9 Role of Wnt/GSK-3 β signaling in the Pathogenesis of Influenza
- 10 Oxidizing GTP and dGTP Detoxification



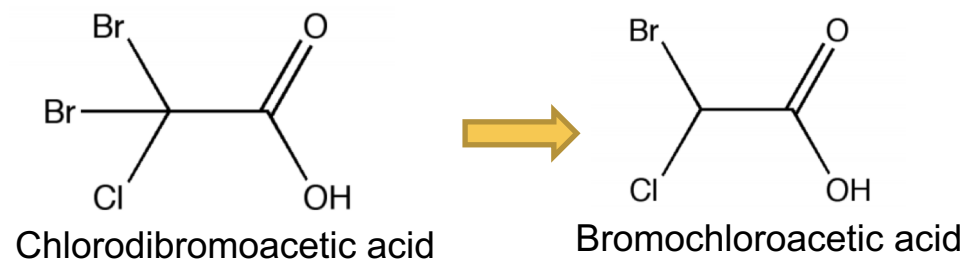
Final monograph
Status: NTP recommended listing
<https://ntp.niehs.nih.gov/go/809361>



2. Evaluate and synthesize information

Tailored to projects based on key issues and available data

- Read across was attempted in haloacetic acids project
- Two haloacetic acids without animal cancer data were recommended for listing based on
 - Metabolized to animal carcinogens
 - Supporting mechanistic evidence demonstrating biological plausibility for humans: oxidative stress and DNA damage



Final monograph
Status: NTP recommended listing
<https://ntp.niehs.nih.gov/go/790113>



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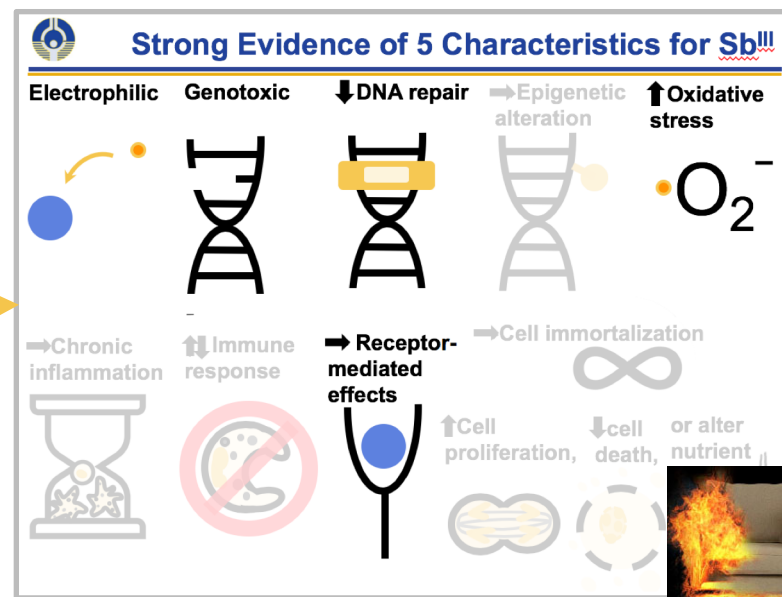
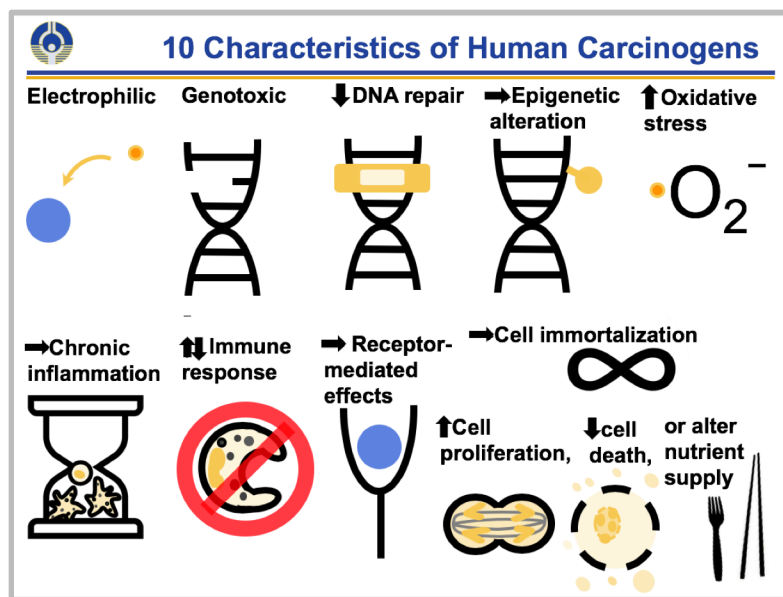


Role of mechanistic information in RoC (example 1)

Supporting evidence

Antimony trioxide has

- **Inadequate human evidence** to evaluate the relationship between human cancer and exposure specifically to antimony trioxide or antimony in general
- **Sufficient animal evidence** for antimony trioxide carcinogenicity
- **Supporting mechanistic information**



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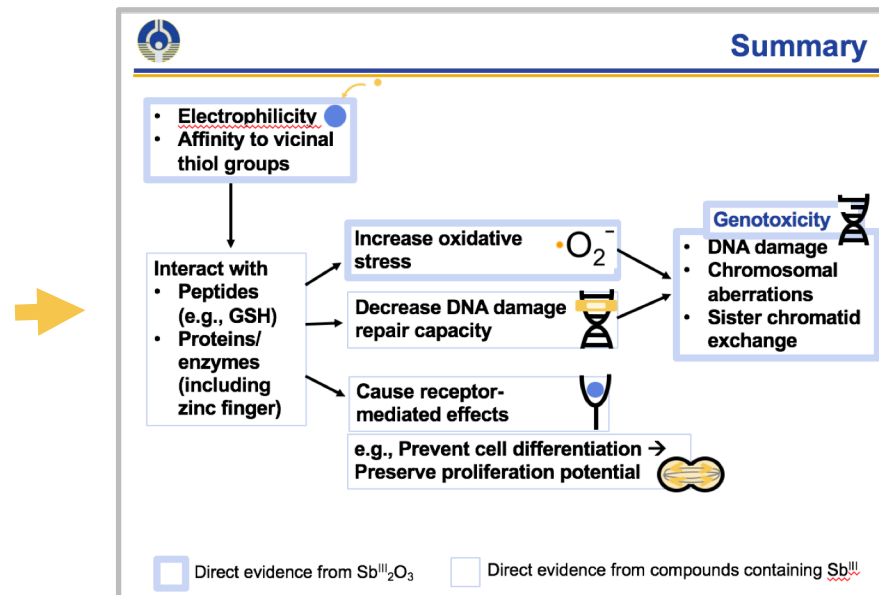


Role of mechanistic information in RoC (example 1)

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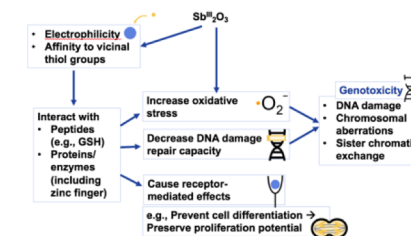


Answering Questions

- Does the available mechanistic data provide supporting evidence for the cancer effects observed in experimental animals?

Yes, mechanistic information is supportive.

- What are the major biological effects contributing to the carcinogenicity of antimony trioxide?



Some effects were seen in

- **cells at cancer sites**
- **human cells**

- Is there compelling data indicating that the agent acts through mechanisms which **do not** operate in humans? **No.**



Role of mechanistic information in RoC (example 2)

Further define the substance/exposure condition that is linked to cancer



Human mechanistic (night shift work)				
Animal mechanistic (simulated shift work or chronic jet lag)				
Human, animal, <i>in vitro</i> mechanistic (circadian disruption)				

- **Persistent** night shift work **that causes circadian disruption**



Draft monograph
Status: Preliminary NTP recommended listing
<https://ntp.niehs.nih.gov/go/717273>



The role and importance of mechanistic understanding in hazard identification will increase

- Fewer traditional carcinogenicity studies
- Mechanistic and other relevant information will have a bigger role in identifying potential carcinogens
 - Potentially from shorter term *in vivo* studies, *ex vivo*, *in vitro* studies, and/or *in silico* predictions
 - More mining and data analysis from data repositories (i.e., using “raw data” from various studies)
- Approaches will need to remain scientifically sound, but take less time
- Tools can further facilitate the process, but expert judgment is still critical



Approaches used to evaluate mechanistic data for RoC

- **Systematic review approach is applied**
 - Search, screen literature
- **Mechanistic information is organized by key characteristics**
- **Expert judgment and tailored approaches based on key questions and available data of the project are used**
- **We are updating the RoC handbook to provide more guidance on mechanistic data evaluation and integration**
- **Many tools are helpful, and we continue to explore and refine tools via collaborations**



- **Ruth Lunn**
- **John Bucher**
- **Gloria Jahnke**
- **Suril Mehta**
- **Other NTP members**
- **ILS and ICF support**
- **All members of information group, internal review committee, technical advisors, peer review committee, Board of Scientific Counselors**