NTP
National Toxicology Program

Use of the 10 Key Characteristics of Carcinogens and Evidence Integration in National Toxicology Program Cancer Hazard Assessments

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Disclosures

- The author declares no conflicts of interest
- Views expressed are my own

Outline

Background

- Key characteristics of carcinogens
- NTP cancer hazard evaluations

Methods for evaluating mechanistic data

Three case studies

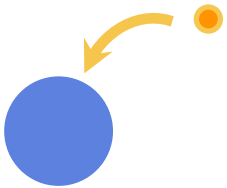
- Antimony trioxide
- Haloacetic acids (HAAs)
- Night shift work (NSW)

Conclusions and future directions

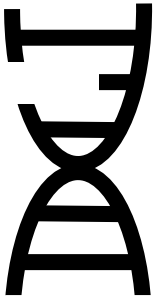
10 Key Characteristics of Carcinogens (KCCs)

Review of IARC group 1 carcinogens

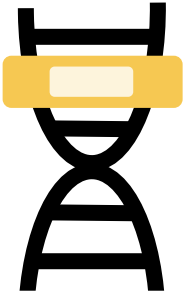
1. Electrophilic



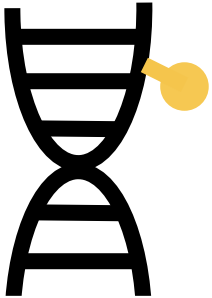
2. Genotoxic



3. DNA repair or genomic instability



4. Epigenetic alterations



5. Oxidative stress

$$\cdot O_2^-$$

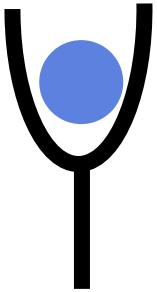
Smith et al. 2016. EHP 124(6):713-721

10 Key Characteristics of Carcinogens (KCCs)

6. Chronic Inflammation

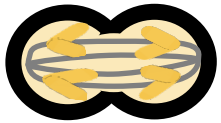
7. Immuno-modulation*

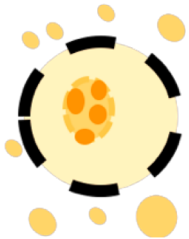
8. Receptor-mediated



9. Cell immortalization

10. Alters cell proliferation, cell death, or nutrient supply





*Immunosuppressive in Smith et al. 2016

NTP Cancer Hazard Evaluations

Rigorous methods & structured approach

- Handbook
  - Systematic review methods
  - Specific evaluation criteria
  - Transparent approach for evidence integration
- Scientific input, public comments, public peer review

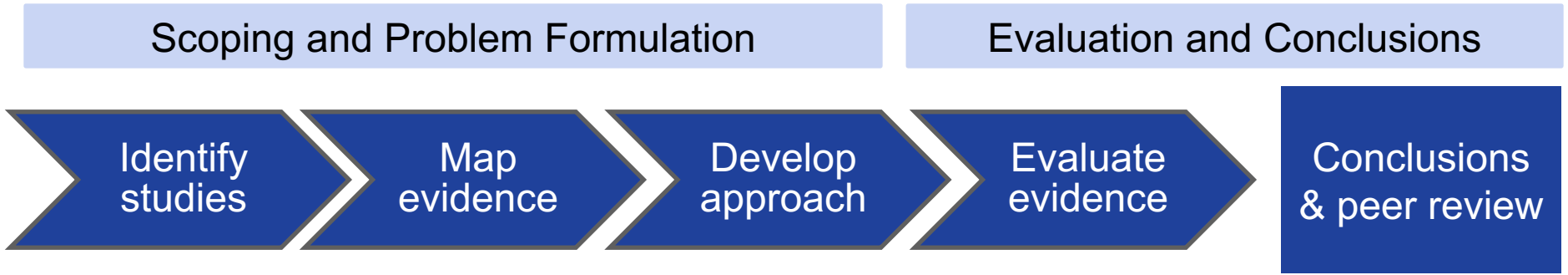
Types of evaluations

- Report on Carcinogens (RoC)
  - Congressionally mandated
  - 248 listings in 14th edition
- Other cancer hazard evaluations
  - Night Shift Work (NSW) and Light at Night (LAN)

https://ntp.niehs.nih.gov/go/roc14 https://ntp.niehs.nih.gov/go/rochandbook

Methods

The 10 KCCs provide a framework for identifying, organizing, and evaluating mechanistic data



Methods

Search terms developed for each KCC

Scopus

PubMed

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

Web of Science

Studies screened and tagged

Literature Tagging: Evidence Mapping

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

210
NSW/LAN mechanistic studies

96
Other CD mechanism

98
KCCs

22
Hormone rhythms

40
Epigenetic

25
Immunomodulation or inflammation

15
Oxidative stress

13
Nutrient supply - metabolism

8
Genotoxic or DNA repair

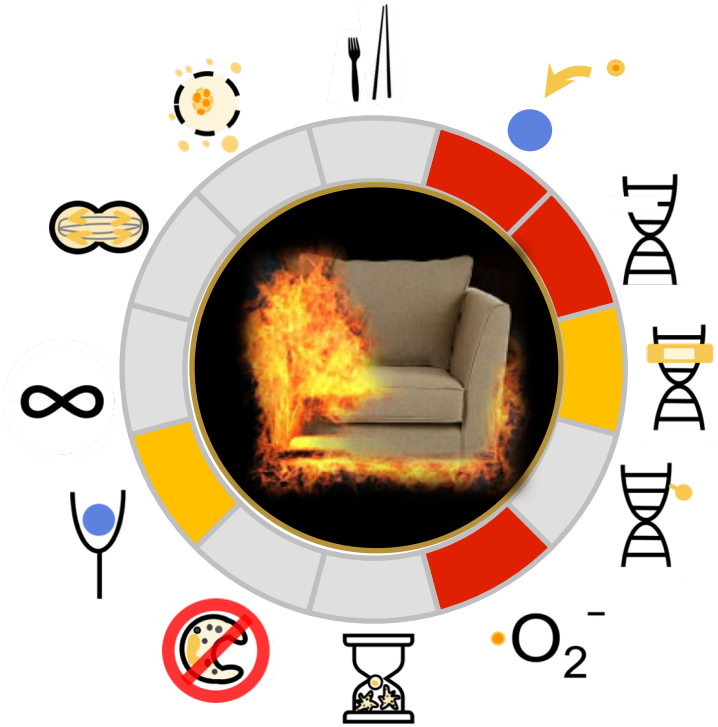
Case Study 1: Antimony Trioxide (Sb_2O_3)

Used as a synergist in flame retardants

Strength of evidence for KCCs

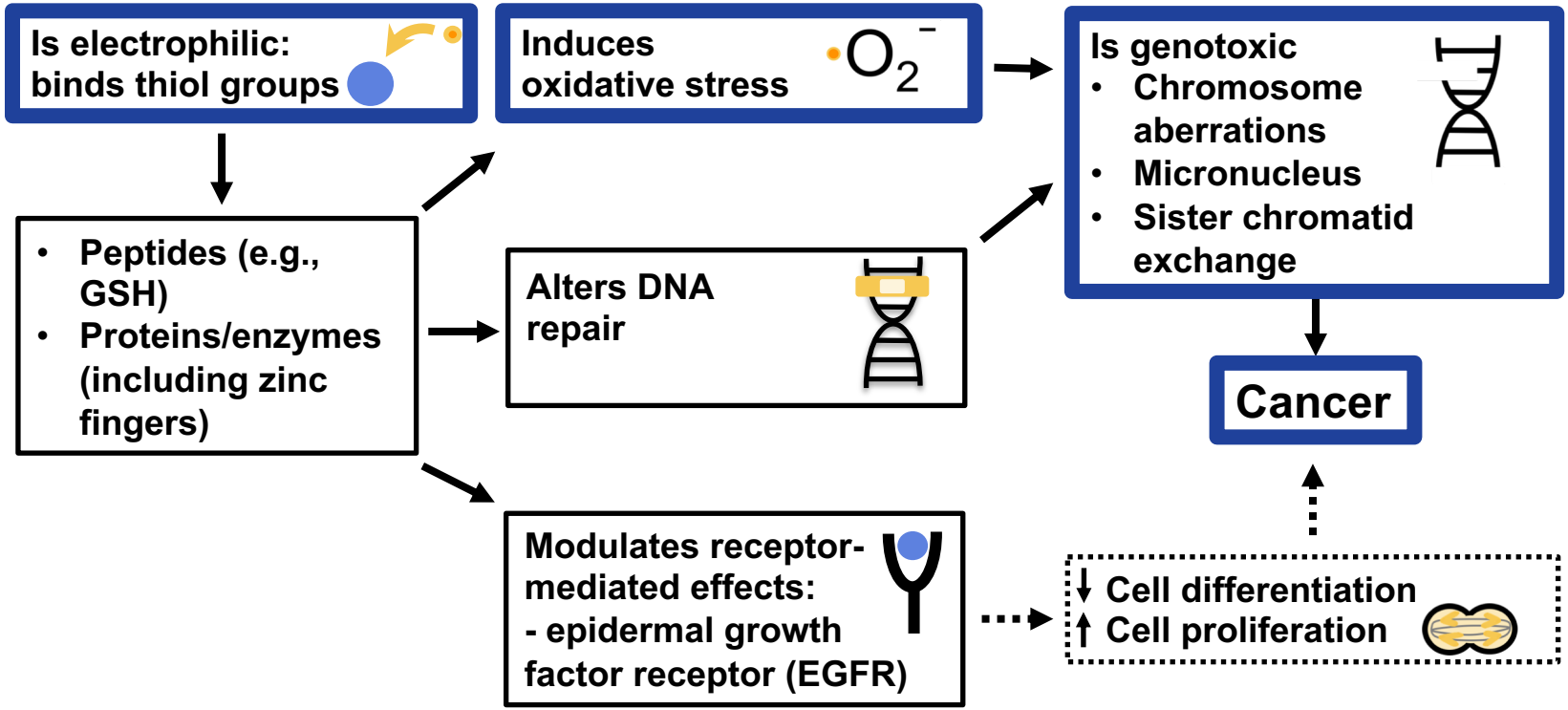
- Strong evidence – Sb_2O_3
- Strong evidence – Other Sb^{III}

- Identify data gaps
- Biological plausibility
- Relevance of animal cancer data
- Inform mechanistic pathways



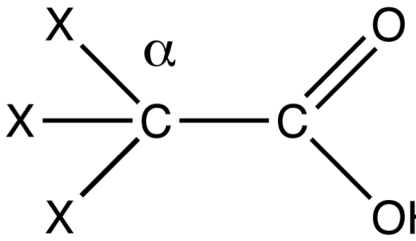
https://ntp.niehs.nih.gov/ntp/roc/monographs/antimony_final20181019_508.pdf

KCCs Informed Possible Mechanistic Pathways

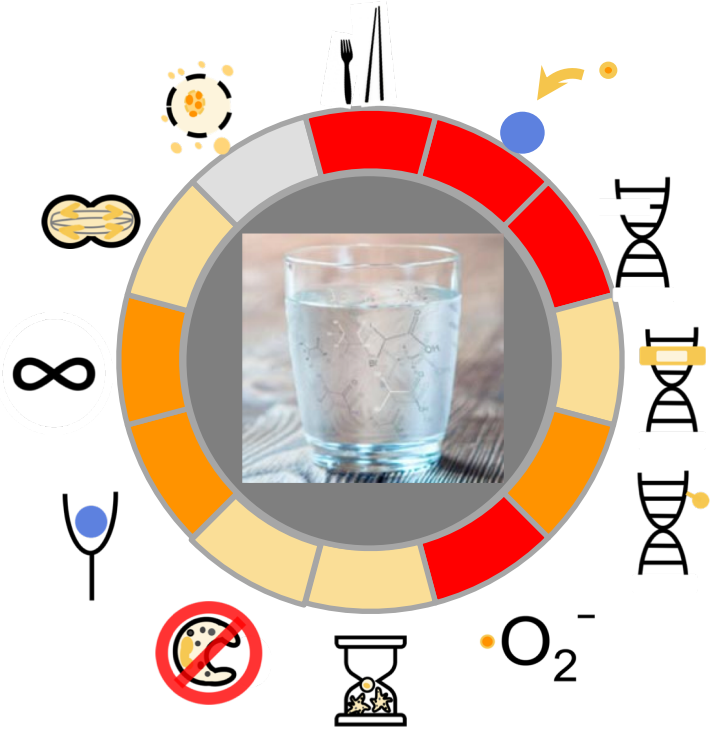


Case Study 2: Haloacetic Acids (HAAs)

Group of 13 HAAs found as water disinfection by-products



X = Cl, Br, I, or H



Strength of evidence for KCCs

- Strong evidence
- Moderate evidence
- Limited evidence

https://ntp.niehs.nih.gov/ntp/roc/monographs/haafinal_508.pdf

KCCs Informed Read-Across for HAAs

Six tested for carcinogenicity but KCC data available for all 13

Endpoint	Mono-HAAs	Di-HAAs		Tri-HAAs	
Rodent bioassay	CA (–) BA IA	DCA (+) DBA (+) DIA	BCA (+) CIA BIA	TCA (+) TBA	BDCA (+) CDBA

KCCs
- Genotoxicity
- Oxidative stress
- Electrophilicity

⬆ Potency with halogen size (Cl << Br < I)

⬇ Potency with the number of halogens (Mono > Di > Tri)

A = acetic acid, B = bromo, C = chloro, I = iodo, D = di, T = tri

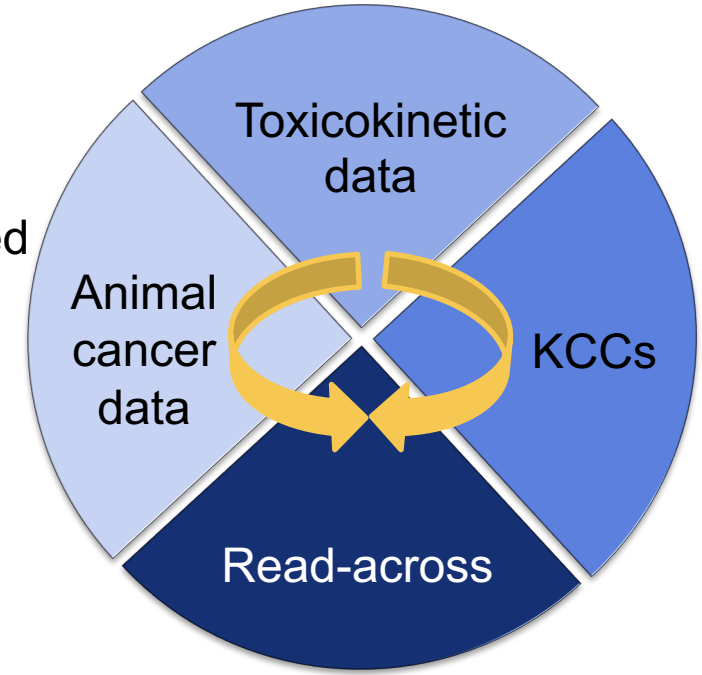
Red = tested for rodent carcinogenicity (+ = rodent carcinogen, – = not carcinogenic)

Black = untested for rodent carcinogenicity

Brominated Di- and Tri-HAAs Selected for Read-Across

- Untested (target) HAAs (CDBA, TBA) are metabolized to source HAAs
- Bromines increase the rate of metabolism of tri-HAAs to di-HAAs

All tested (source) brominated HAAs (DBA, BCA, BDCA) are rodent carcinogens



- Similar effects
- Clear potency trends

CDBA and TBA are predicted to be rodent carcinogens

Case Study 3: Night Shift Work (NSW)

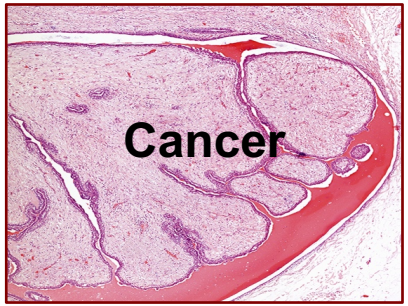
Similar KCCs observed in night shift workers as seen in rodents

Simulated shift work or jet lag

KCCs

- Epigenetic changes
- Receptor-mediated (estrogen levels*)
- Altered DNA repair
- Oxidative stress $\cdot O_2^-$
- Inflammation & immunomodulation

* Observed in rodent studies of exposure to LAN



KCCs also observed in studies of tumor promotion in rodents

https://ntp.niehs.nih.gov/go/717273

Circadian Disruption is Associated with KCCs and Cancer

Circadian disruption

KCCs/other relevant effects

Altered clock gene expression →

- Tumor suppressor genes
- DNA damage checkpoints/repair
- Cell cycle control/cell death
- Cell proliferation/oncogenes
- Cell energy metabolism

Melatonin suppression →

- Oxidative stress response
- Estrogen signaling and biosynthesis
- Cell cycle control/cell death
- Cell proliferation/differentiation
- Cell energy metabolism
- Immunomodulation
- Inflammation
- Metastasis

- Clock gene mutant mice are cancer prone
- Melatonin inhibits tumor growth including LAN-induced tumors

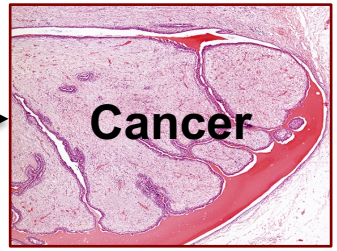
Night Shift Work, Circadian Disruption, KCCs, and Cancer

Simulated shift work or jet lag

Altered clock gene expression

Melatonin suppression

KCCs and other relevant effects



- NSW is associated with circadian disruption and cancer
- Both NSW and circadian disruption are associated with KCCs
- Circadian disruption likely plays a major role in NSW carcinogenicity

Conclusions and Next Steps

KCCs provide an unbiased approach for mechanistic data assessment

- Framework for searching and organizing the generally large and diverse mechanistic database
- Identify potential mechanistic pathways
- Inform biological plausibility and human relevance
- Identify data gaps and inform read-across approaches

Next steps

- Expand and improve framework for mechanistic evaluations
  - Standardize study quality questions
  - Develop guidelines for level of evidence determinations
  - Information will be captured in next version of RoC handbook

Acknowledgments

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