Perspectives on Common Elements for Evidence Integration

NASEM Workshop on Evidence Integration
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Outline

- **Milestones in evidence integration**
- **Common elements of evidence integration**
  - Three bodies of evidence: human, experimental animal, mechanistic
  - Integration within a body of evidence
  - Integration across bodies of evidence
- **Emerging approaches**

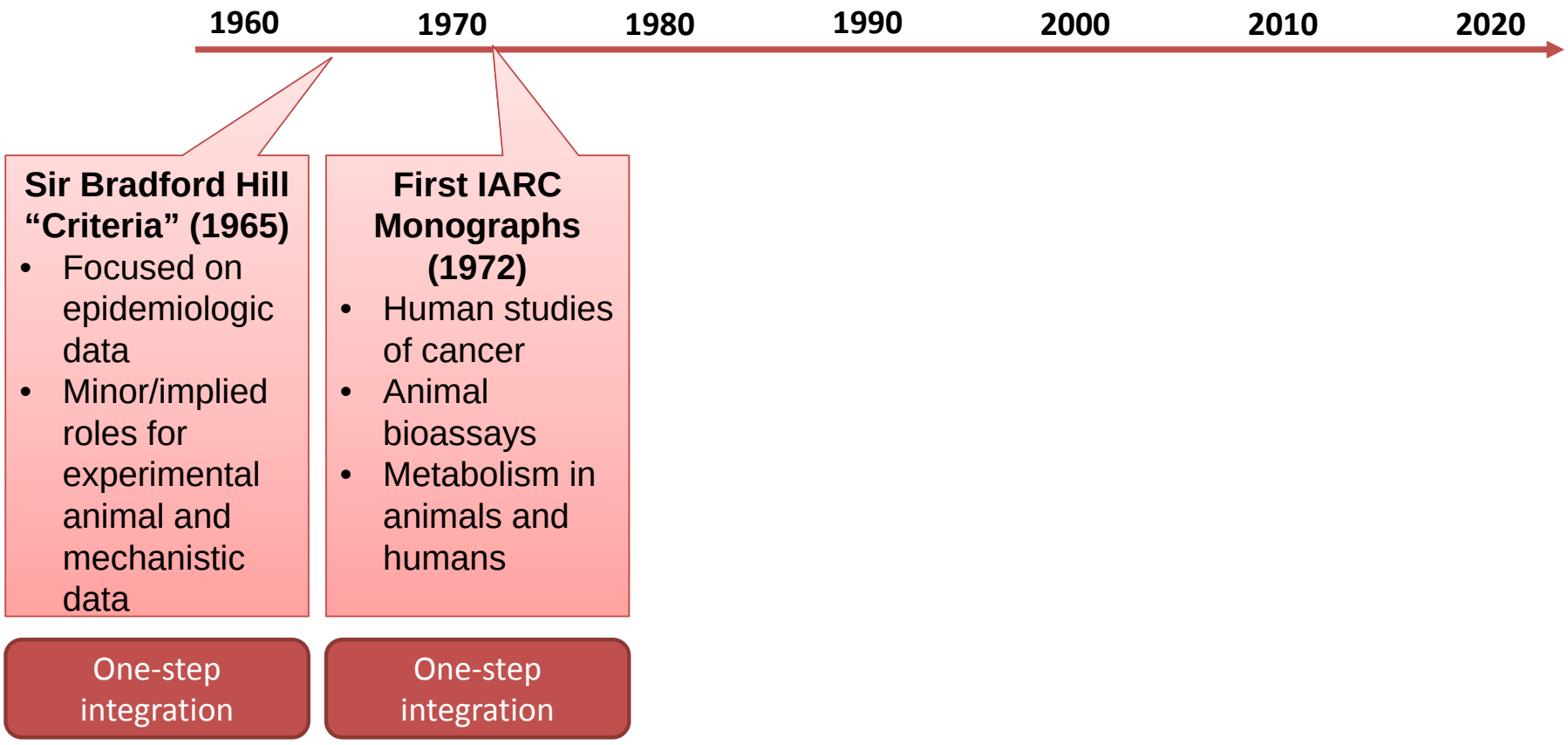
Milestones in evidence integration

Sir Bradford Hill "Criteria" (1965)

- Focused on epidemiologic data
- Minor/implied roles for experimental animal and mechanistic data

One-step integration

Milestones in evidence integration



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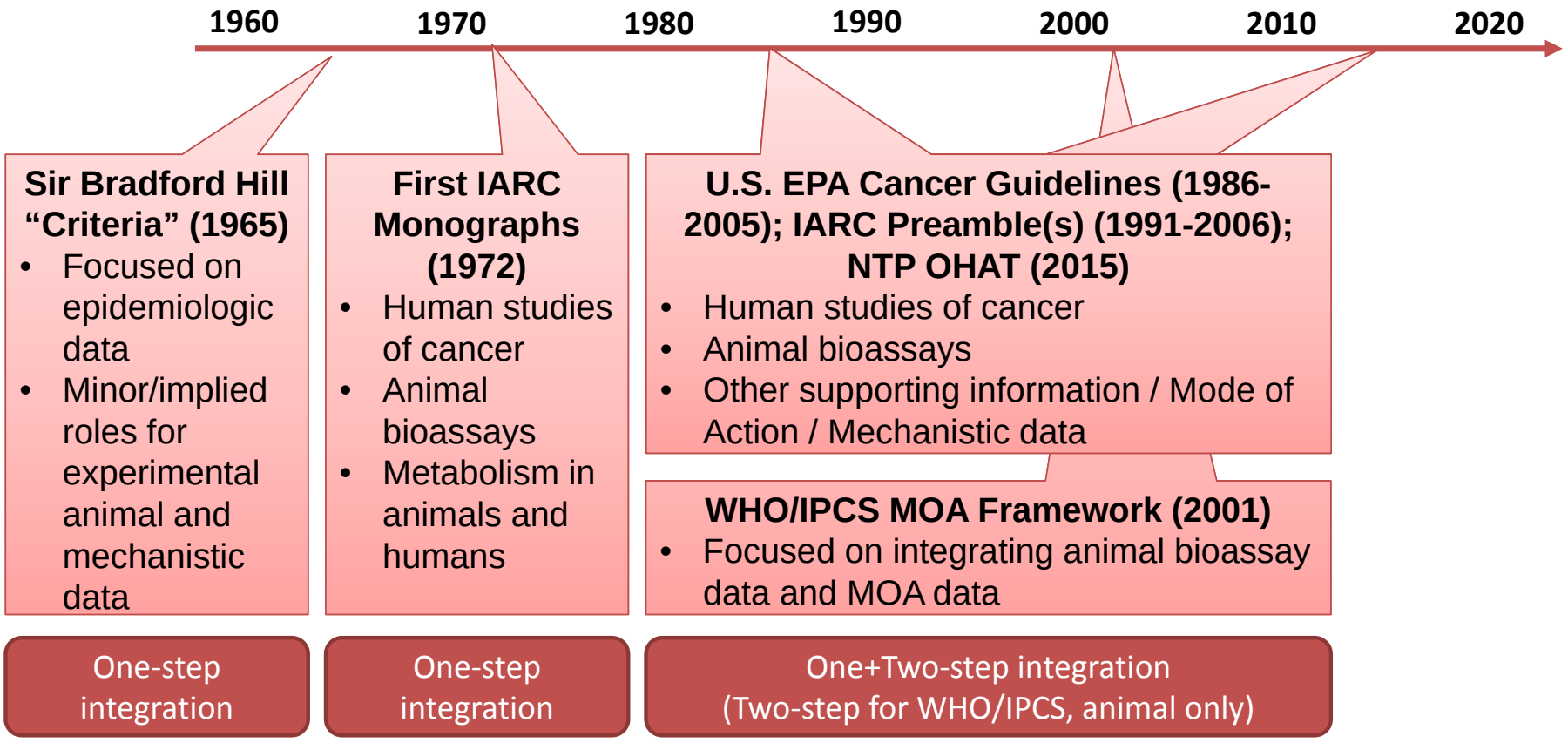

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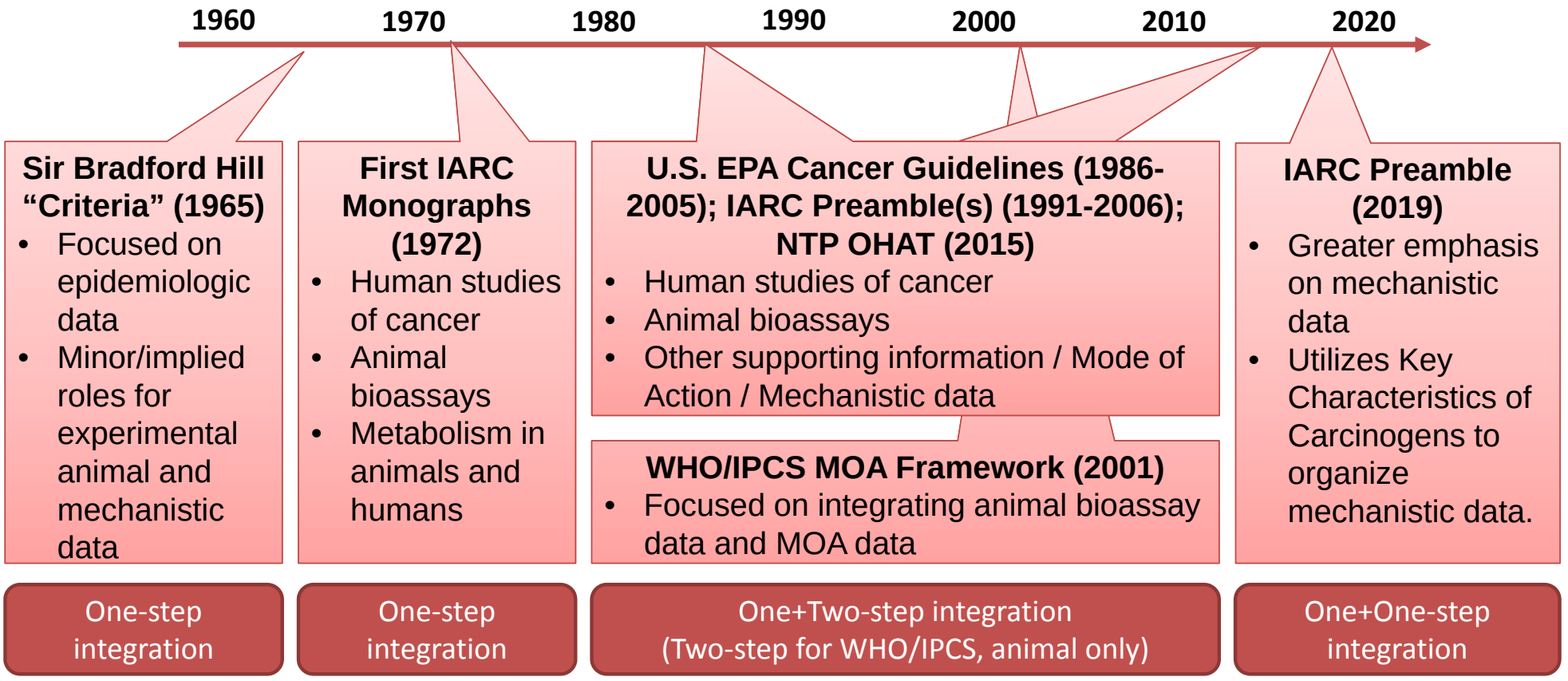
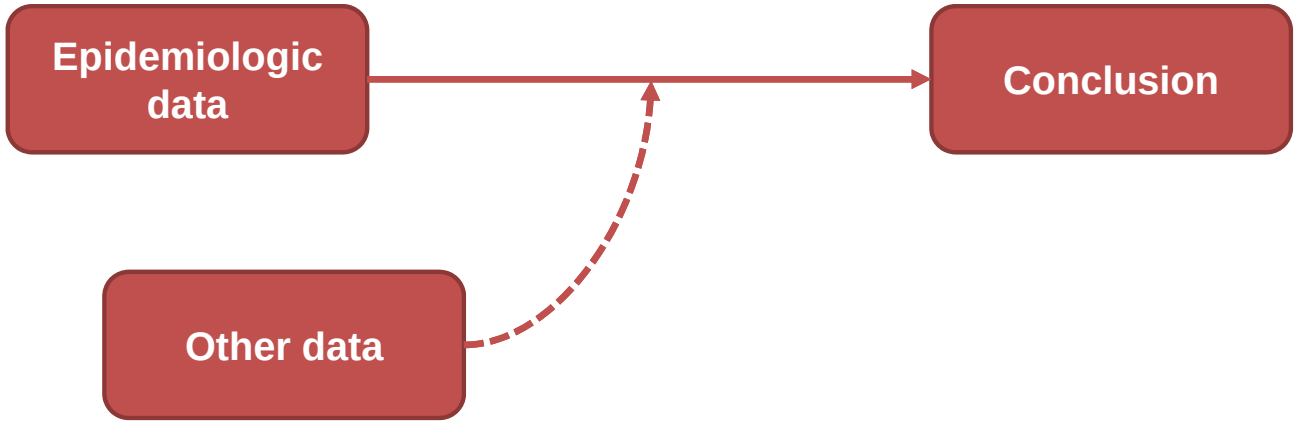


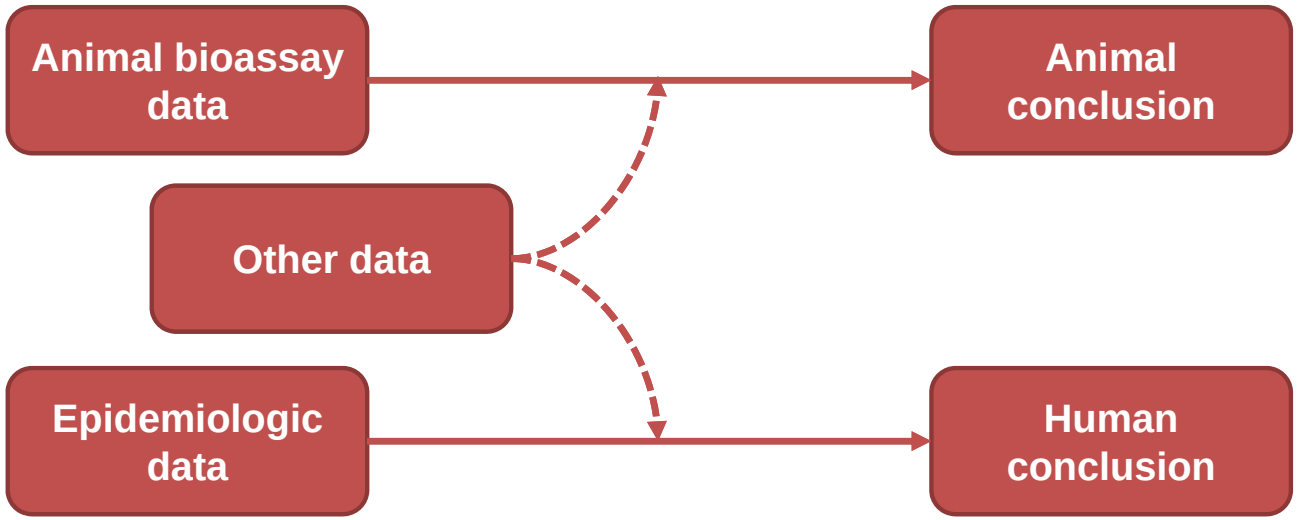
Milestones in evidence integration

- **Sir Bradford Hill:** One-step integration focused on epidemiologic data, taking into consideration other data



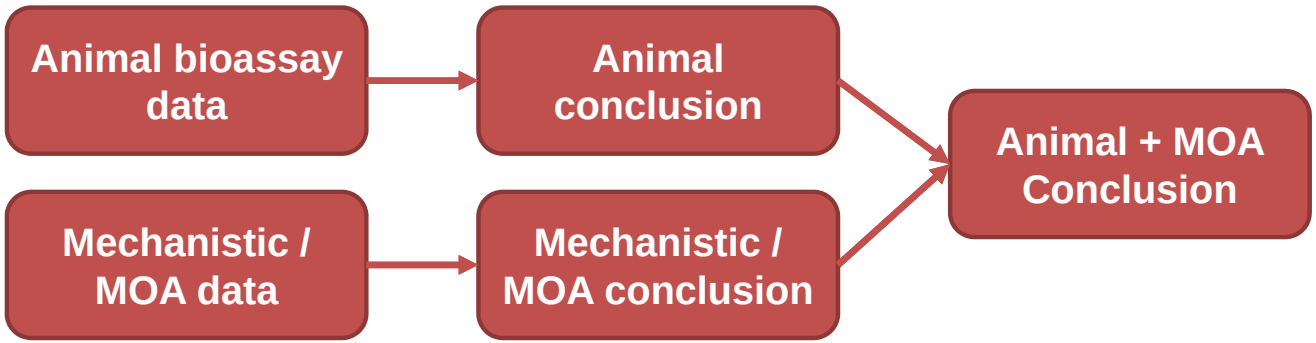
Milestones in evidence integration

- **First IARC Monographs:** Parallel one-step integration, separately for animal bioassay and epidemiologic data, taking into consideration other data



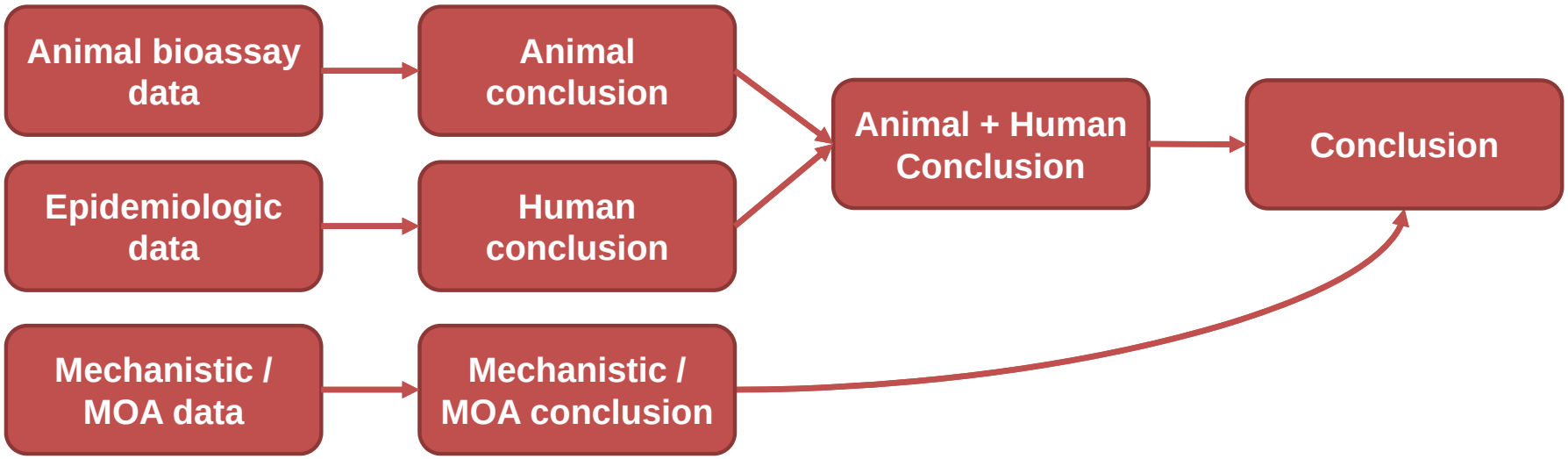
Milestones in evidence integration

- **WHO/IPCS (2001):** One+One-step integration focused on human relevance of animal bioassay data



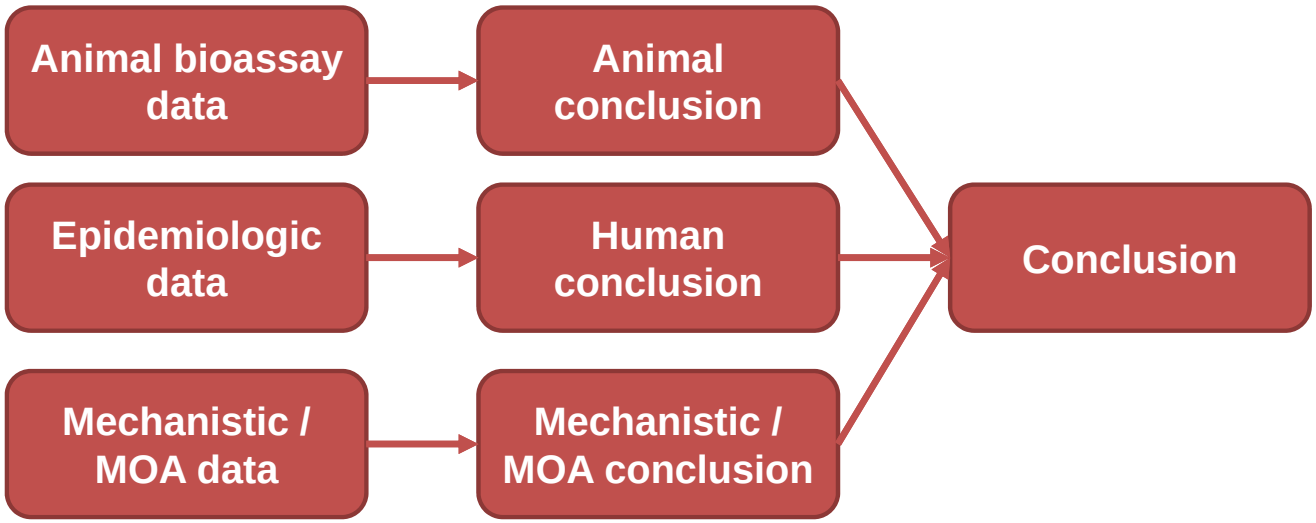
Milestones in evidence integration

- **EPA (1996, 2005), IARC (1991, 2006), NTP (2015):** One+Two-step integration, parallel across three bodies of evidence



Milestones in evidence integration

- **IARC (2019):**
  One+One-step integration, parallel, and then together all at once.



Common Elements

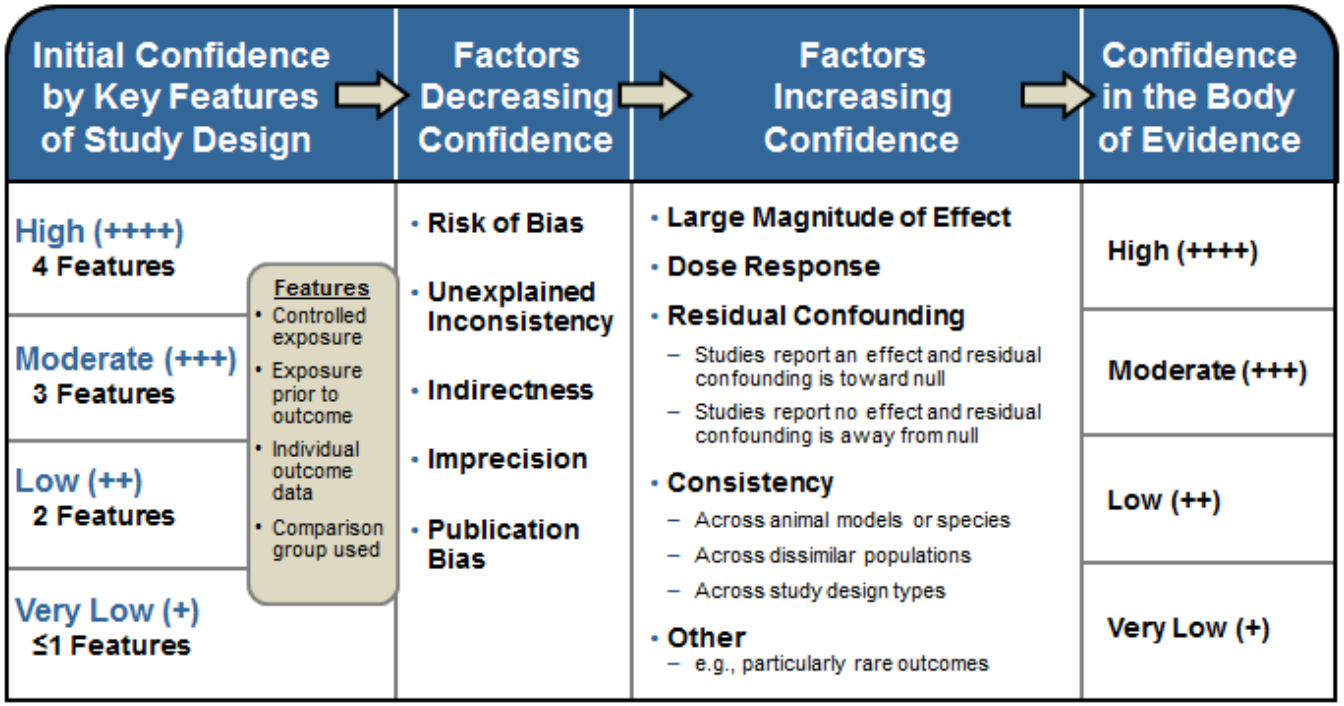
- **Three "bodies of evidence"**
  - Human epidemiologic data
  - Experimental animal data
  - Mechanistic / MOA data
- **First step** is always integration **within individual bodies of evidence**
  - Conceptually, performed "in parallel"
  - In practice, some cross-talk is needed (e.g., toxicokinetics/metabolism, target tissues, etc.)
- **Subsequent step(s)** involve integration **across bodies of evidence**
  - Most use a two-step approach (animal + human, then add mechanistic data)
  - IARC (2019) recently moved to a one-step approach (all bodies of evidence together)

Emerging Approaches

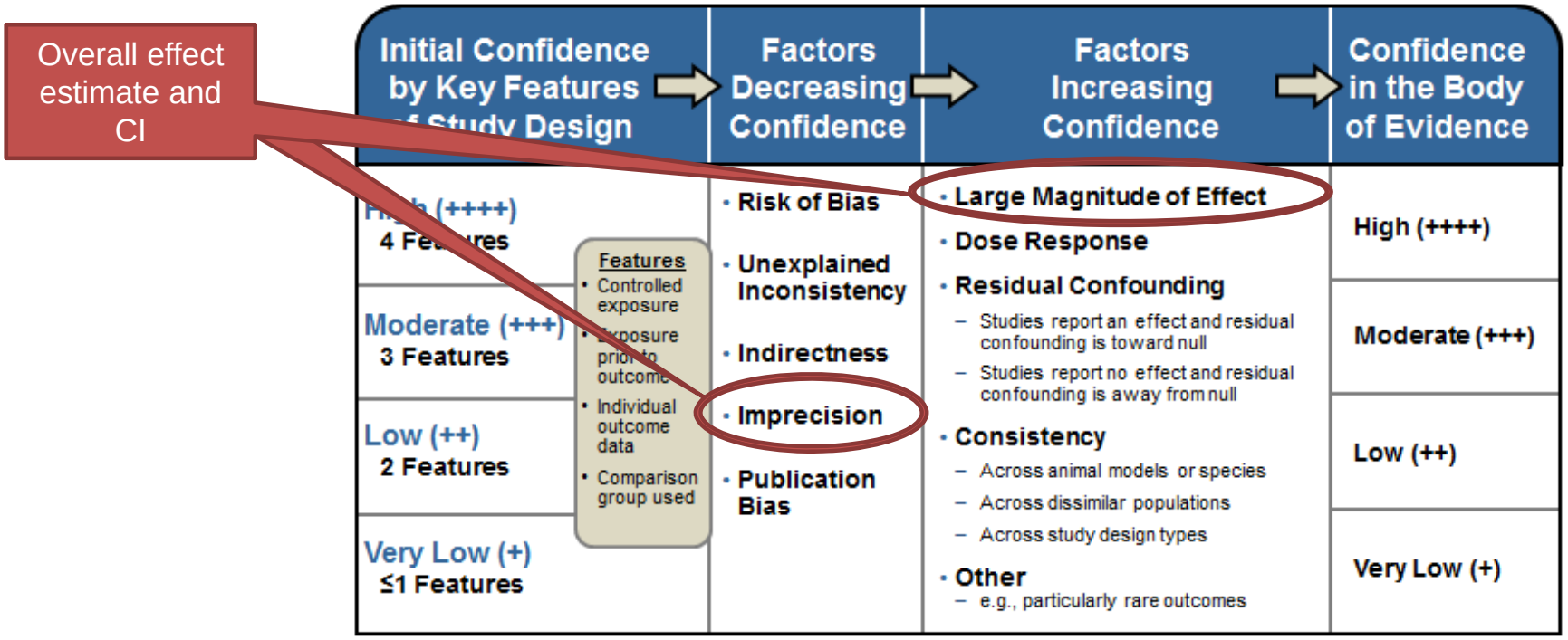
- **Integration *within* individual bodies of evidence**
  - Meta-analysis to inform conclusions within an OHAT/GRADE-like framework
  - Use of Key Characteristics of Carcinogens (or other “-icities”) to identify and organize mechanistic data

- **Integration *across* bodies of evidence**
  - Increasing emphasis on mechanistic data

OHAT approach to integrating *within* a body of evidence



Role of meta-analysis/ meta-regression

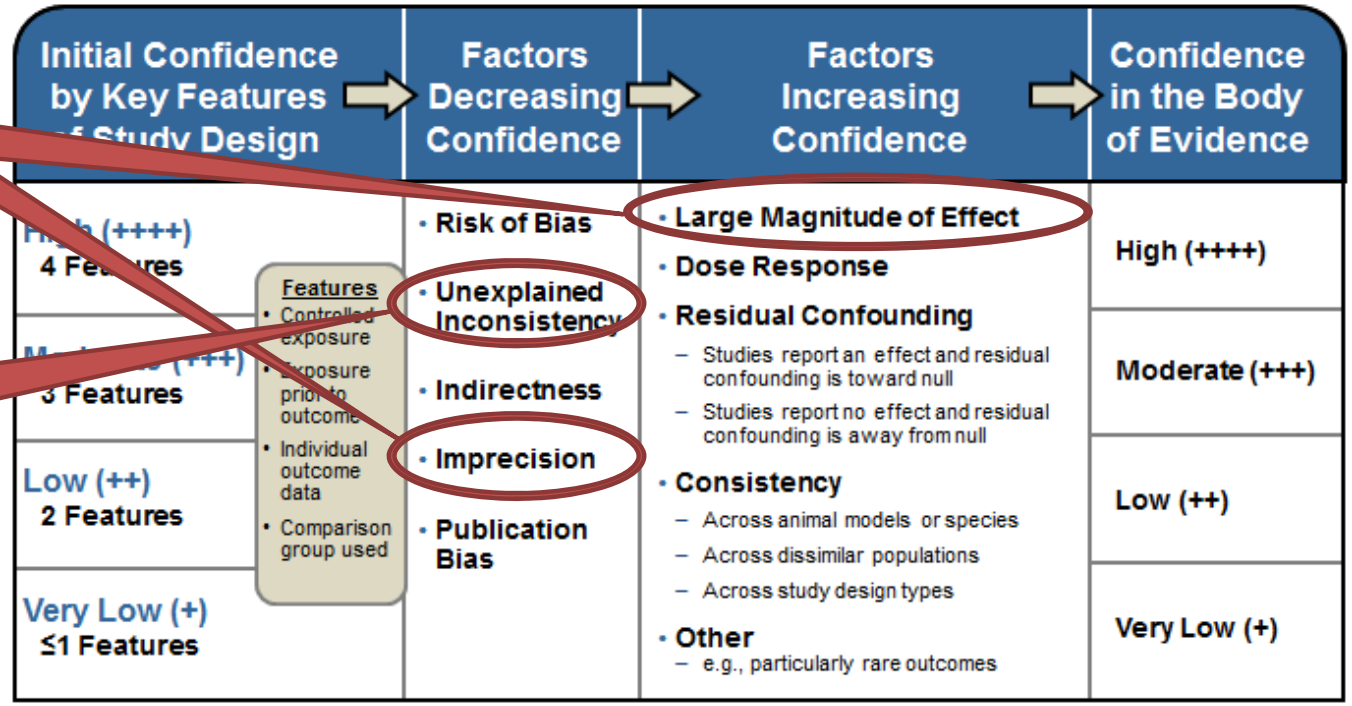


See NASEM (2017) low dose endocrine report for more details
https://www.nap.edu/catalog/24758/

Role of meta-analysis/ meta-regression

Overall effect estimate and CI

Heterogeneity estimated using random effects



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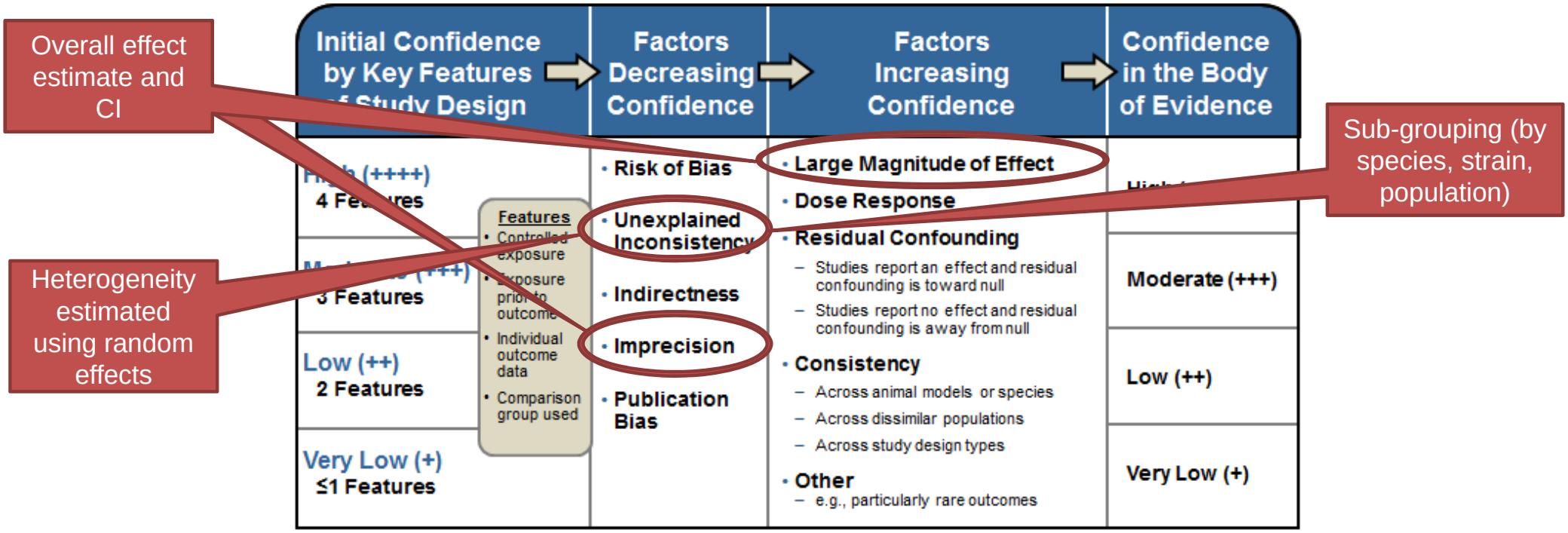

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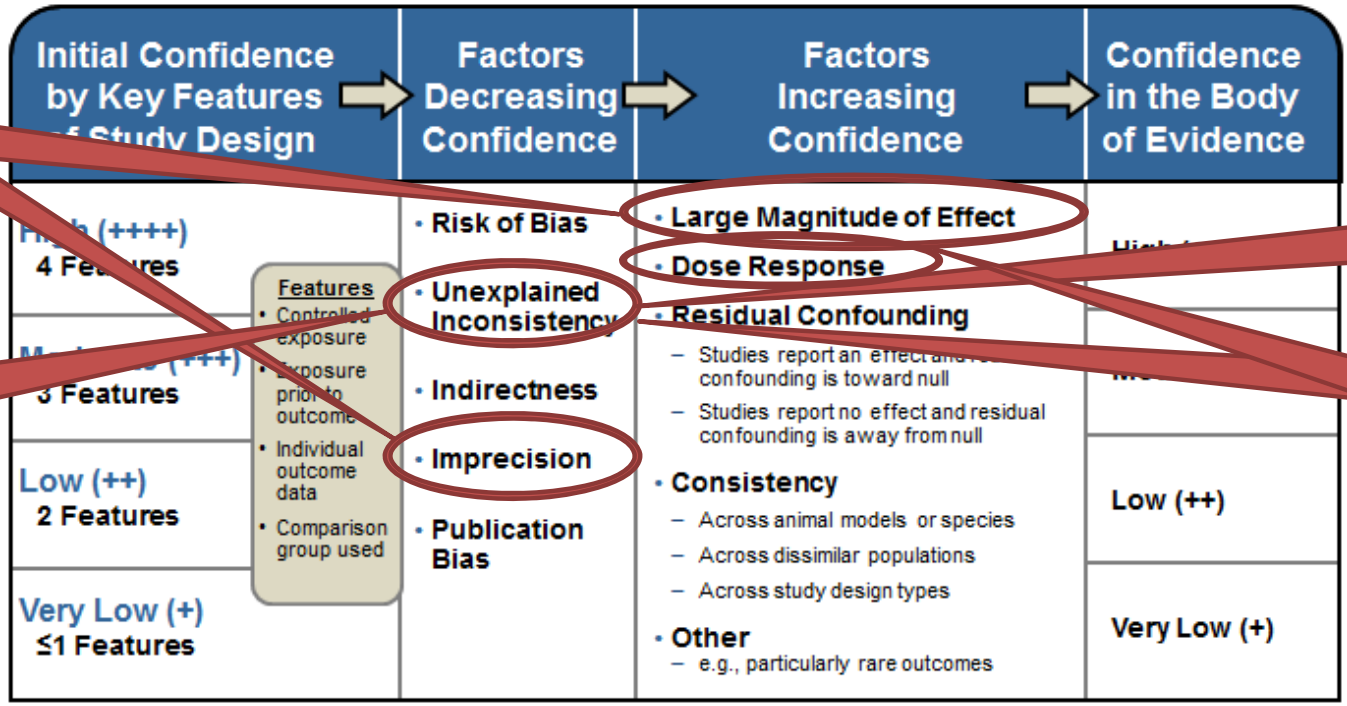

Sub-grouping (by species, strain, population)

Meta-regression with dose

See NASEM (2017) low dose endocrine report for more details
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Emerging Approaches

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- **Integration *across* bodies of evidence**
  - Increasing emphasis on mechanistic data

Use of Key Characteristics of Carcinogens for Mechanistic data

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What ***are*** the "Key Characteristics of Carcinogens?"

Known human carcinogens (IARC Group 1)

↓

Mechanistic data on known human carcinogents →

Table 1. Key characteristics of carcinogens.

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

KCCs are a set of properties common among known human carcinogens, and that are believed to contribute to their carcinogenic effects.

Smith et al. (2016) https://dx.doi.org/10.1289%2Fehp.1509912

Use of Key Characteristics of Carcinogens for Mechanistic data

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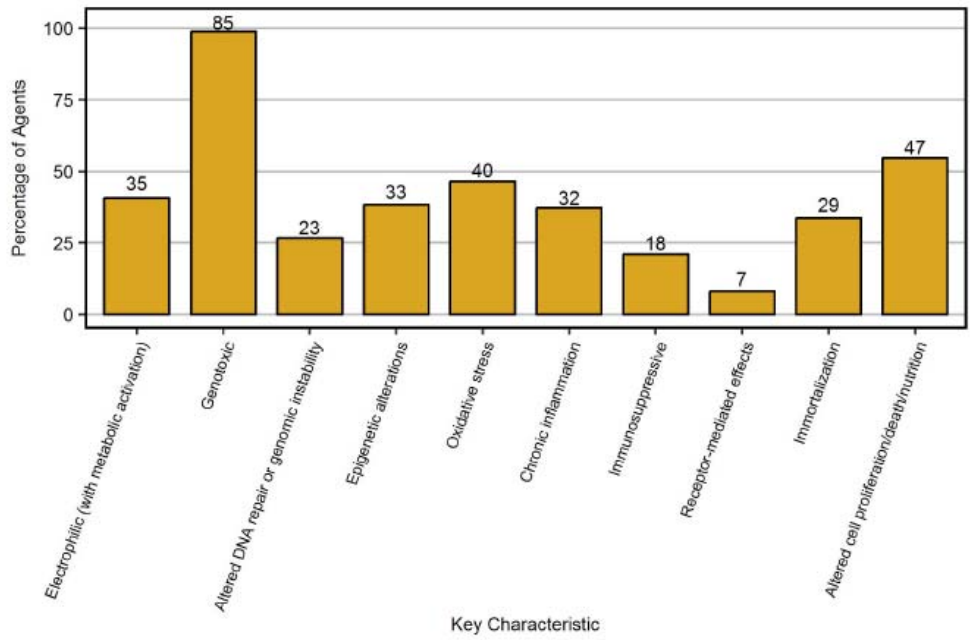
Fig. 22.1. Key characteristics of 86 Group 1 agents. The number of agents is shown above each characteristic.



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https://publications.iarc.fr/Book-And-Report-Series/Iarc-Scientific-Publications/Tumour-Site-Concordance-And-Mechanisms-Of-Carcinogenesis-2019

Use of Key Characteristics of Carcinogens for Mechanistic data

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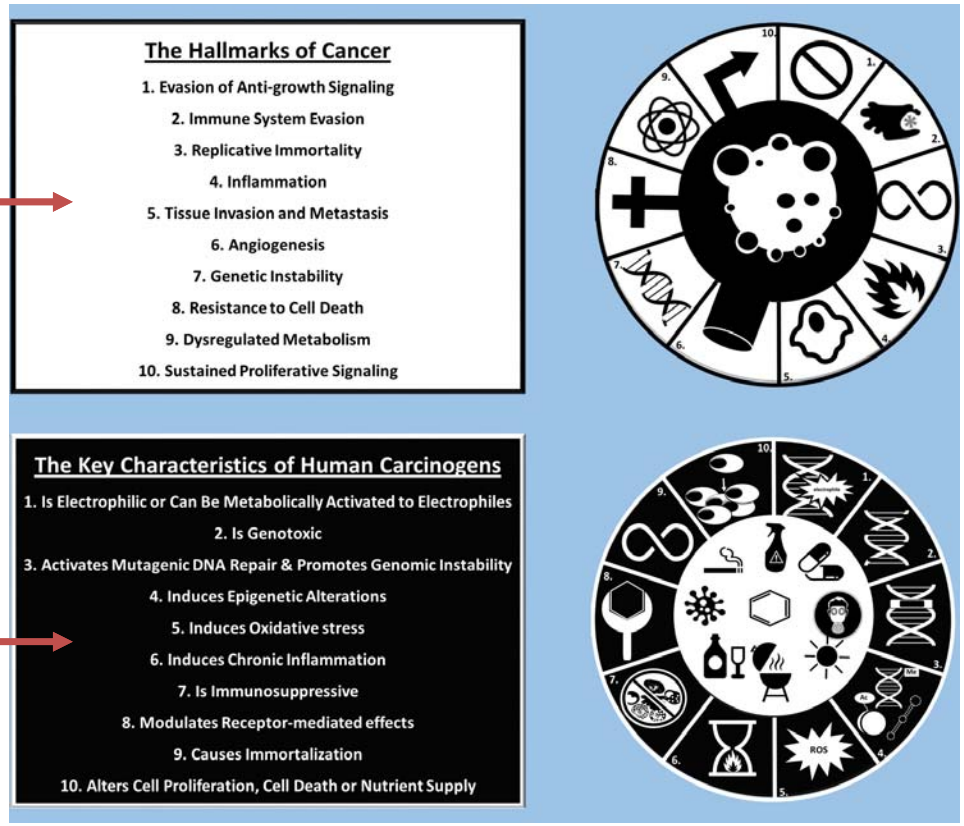
Properties of Cancer Cells / Microenvironment (what cancer is)

Properties of Carcinogenic Agents (what carcinogens do)



Example:

Inflammation is a "hallmark" of the tumor micro-environment.

Some agents cause chronic inflammation, which contributes to their carcinogenicity.

Use of Key Characteristics of Carcinogens for Mechanistic data

- "Key Characteristics of Carcinogens" are
  - **NOT** "Hallmarks of Cancer"
  - **NOT** mechanisms in and of themselves, MOAs, or AOPs.

- KCCs form the "basis for **identifying** and **categorizing** scientific findings relevant to cancer mechanisms when assessing whether an agent is a potential human carcinogen."
  - Enables broad consideration of the mechanistic evidence, encompassing a wide range of end points of known relevance to carcinogenesis.
  - Avoids focusing narrowly on specific mechanistic hypotheses/pathways in isolation
  - Facilitates comparisons across agents.
  - Adopted by IARC, NTP.
  - Key characteristics for other endpoints in development.

- Integration across KCCs still a developing area

Emerging Approaches

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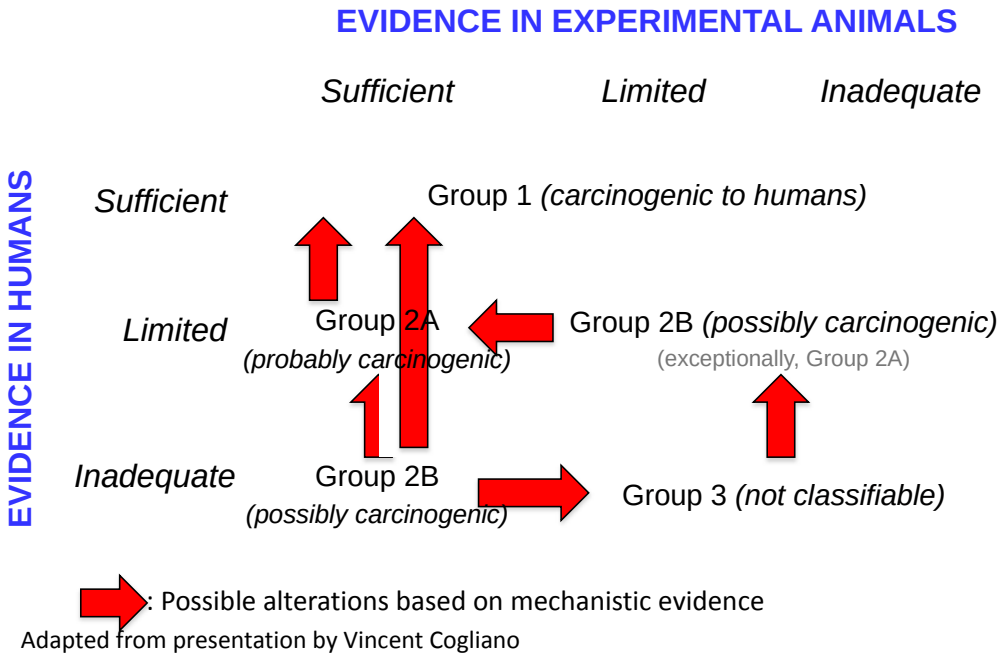
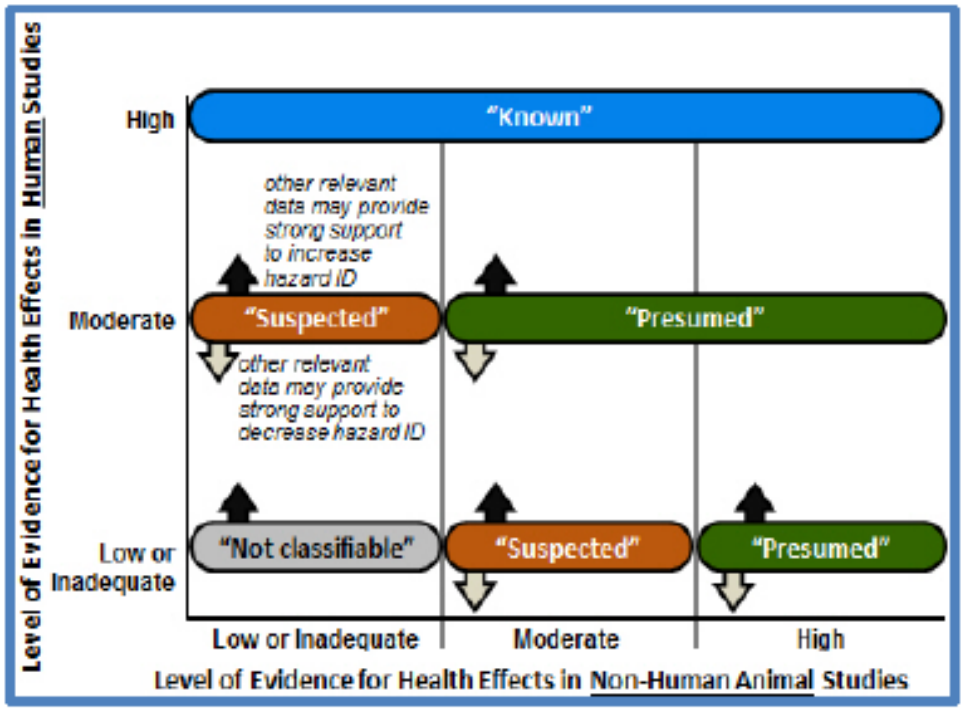
Moving to one-step evidence integration across bodies of evidence



Adapted from presentation by Vincent Cogliano

Two-step approach critiqued for appearing to give less weight to mechanistic data.



Moving to one-step evidence integration across bodies of evidence

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- Downward trends in the production of new human and animal data for most agents
- Rising prominence and complexity of mechanistic data
- Recognition that mechanistic data can play ***multiple roles*** in evidence integration
  - An agent causes cancer in experimental animals via mechanism(s) that does not operate in humans
  - An agent belongs to a mechanistic class of agents causing cancer
  - An agent causes mechanistic events related to cancer
    - In humans exposed to the agent (e.g., biomarkers)
    - In human cells/tissues treated (in vitro) with the agent
    - In non-human test systems treated (in vivo or in vitro) with the agent

IARC (2019) as a prototype for one-step evidence integration

Body of evidence			
Cancer in humans	**Cancer in experimental animals**	**Mechanistic evidence**	**Classification based on strength of evidence**
Sufficient			**Carcinogenic to humans (Group 1)**
	Sufficient	Strong (in exposed humans)	
Limited	Sufficient		**Probably carcinogenic to humans (Group 2A)**
Limited		Strong	
	Sufficient	Strong (in human cells/tissues)	
		Strong - mechanistic class	
Limited			**Possibly carcinogenic to humans (Group 2B)**
	Sufficient		
		Strong (experimental systems)	
	Sufficient	Strong - mechanism in experimental animals does not operate in humans	**Not classifiable as to its carcinogenicity to humans (Group 3)**
Any other combination not listed			

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Clarifies differing roles of different types of mechanistic evidence

Summary

- **Common elements of evidence integration**
  - Three bodies of evidence: human, experimental animal, mechanistic
  - Two types of integration: *within* a body of evidence and *across* bodies of evidence
- **Emerging approaches to evidence integration**
  - Use of meta-analysis for integration of human and experimental animal evidence
  - Use of “Key Characteristics” approach for identifying and organizing mechanistic evidence
  - Treating mechanistic evidence as a “co-equal” body of evidence during final integration