

Perspectives on Common Elements for Evidence Integration

NASEM Workshop on Evidence Integration June 3-4, 2019

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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

1960 1970 1980 1990 2000 2010 2020

Sir Bradford Hill "Criteria" (1965)

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

One-step integration

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First IARC Monographs (1972)

- Human studies of cancer
- Animal bioassays
- Metabolism in animals and humans

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U.S. EPA Cancer Guidelines (1986-2005); IARC Preamble(s) (1991-2006); NTP OHAT (2015)

- Human studies of cancer
- Animal bioassays
- Other supporting information / Mode of Action / Mechanistic data

WHO/IPCS MOA Framework (2001)

 Focused on integrating animal bioassay data and MOA data

One-step integration

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One+Two-step integration (Two-step for WHO/IPCS, animal only)



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IARC Preamble (2019)

- Greater emphasis on mechanistic data

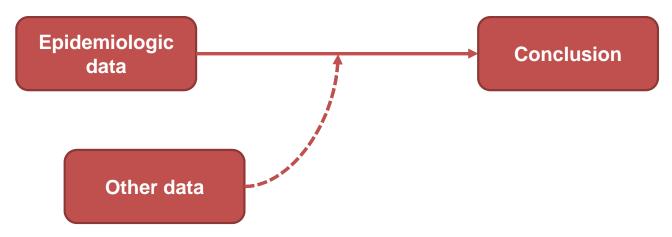
One-step integration

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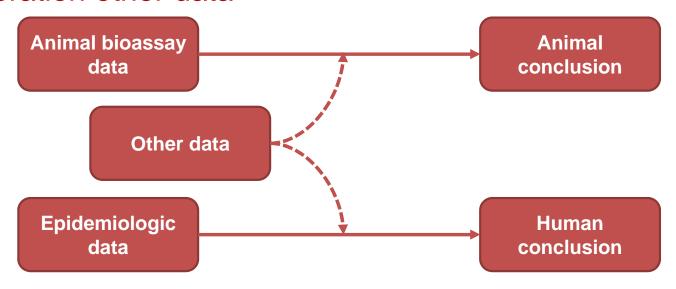
One+Two-step integration (Two-step for WHO/IPCS, animal only)

One+One-step integration

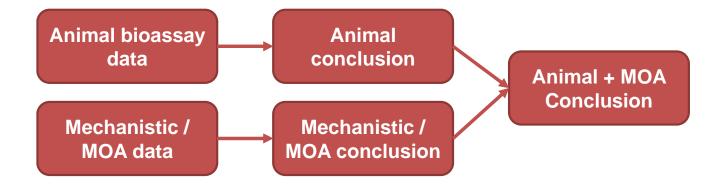
• Sir Bradford Hill: One-step integration focused on epidemiologic data, taking into consideration other data



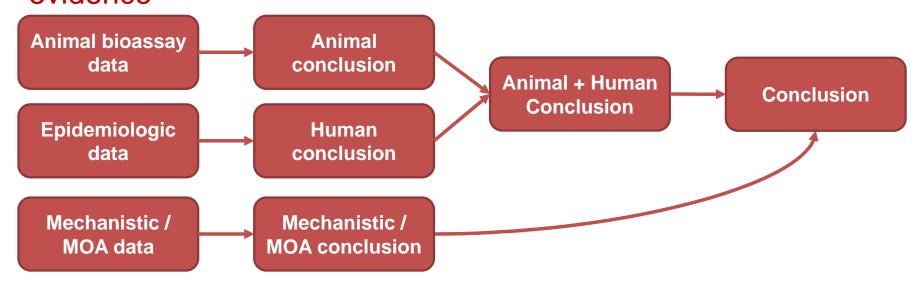
 First IARC Monographs: Parallel one-step integration, separately for animal bioassay and epidemiologic data, taking into consideration other data



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

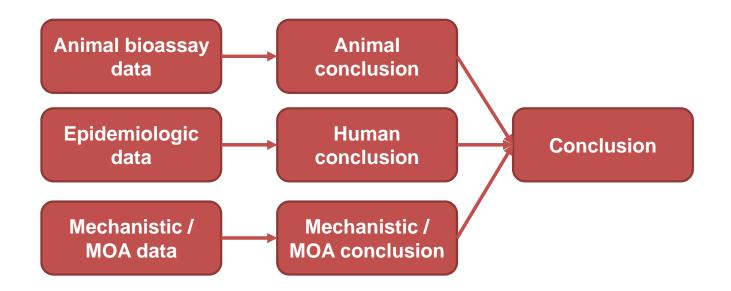


EPA (1996, 2005), IARC (1991, 2006), NTP (2015):
 One+Two-step integration, parallel across three bodies of evidence



• 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

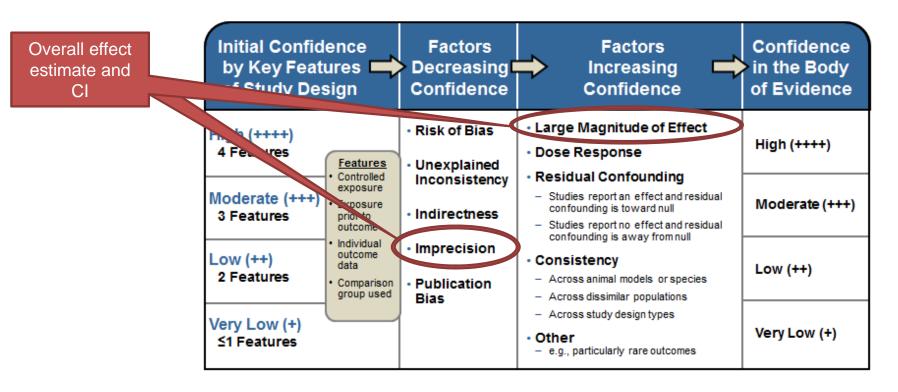
OHAT approach to integrating within a body of evidence



Initial Confidence by Key Features of Study Design		Factors Decreasing Confidence	Factors Increasing Confidence	Confidence in the Body of Evidence
High (++++) 4 Features	<u>Features</u>	Risk of Bias Unexplained	Large Magnitude of Effect Dose Response	High (++++)
Moderate (+++) 3 Features	Controlled exposure Exposure prior to outcome	Inconsistency Indirectness	Residual Confounding Studies report an effect and residual confounding is toward null Studies report no effect and residual	Moderate (+++)
Low (++) 2 Features	Individual outcome data Comparison group used	Imprecision Publication Bias	confounding is away from null Consistency Across animal models or species Across dissimilar populations	Low (++)
Very Low (+) ≤1 Features			Across study design types Other e.g., particularly rare outcomes	Very Low (+)

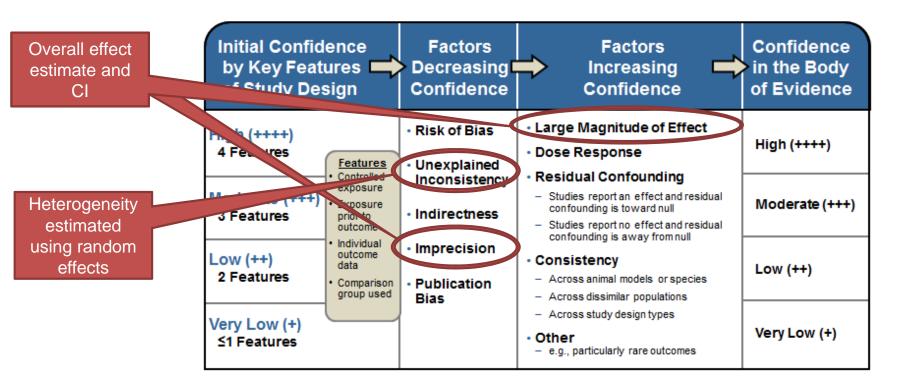
Role of meta-analysis/ meta-regression





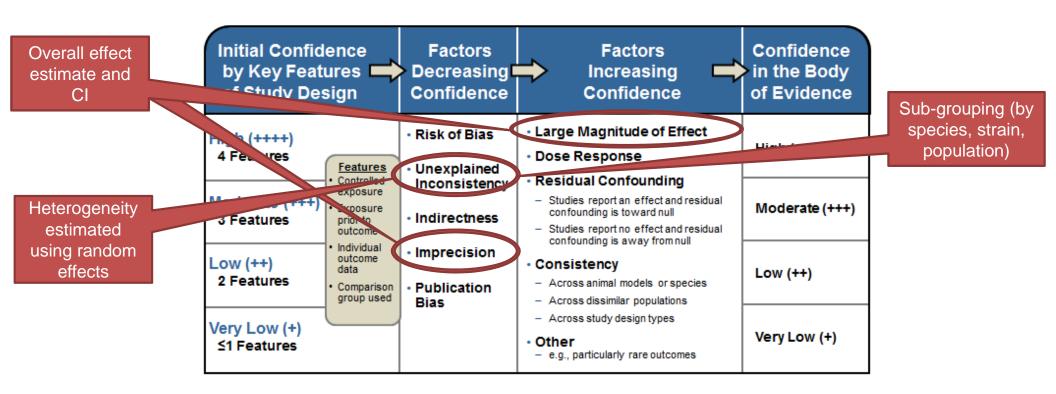
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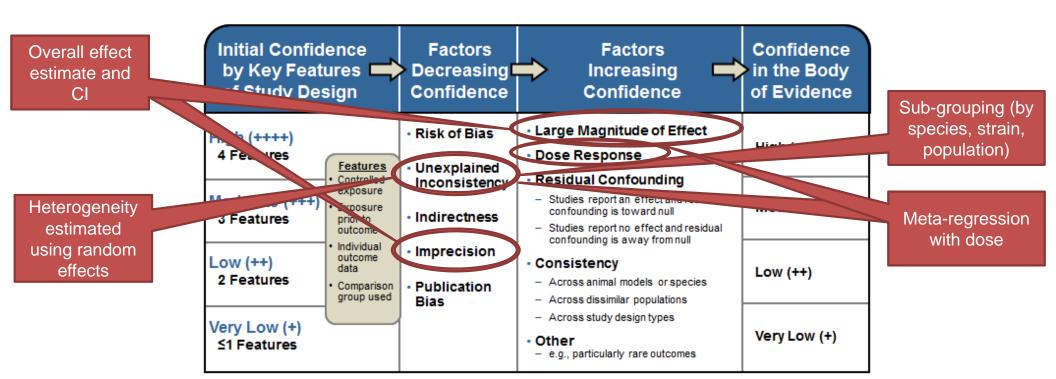
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Emerging Approaches



- Integration within individual bodies of evidence
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Use of Key Characteristics of Carcinogens for Mechanistic data



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		
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)		
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		
 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		
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		
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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

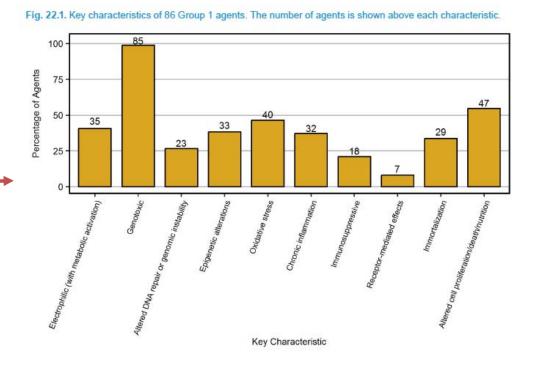
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https://publications.iarc.fr/Book-And-Report-Series/larc-Scientific-Publications/Tumour-Site-Concordance-And-Mechanisms-Of-Carcinogenesis-2019

Use of Key Characteristics of Carcinogens for Mechanistic data



Properties of Cancer <u>Cells /</u>
<u>Microenvironment</u> (what cancer <u>is</u>)

Properties of
Carcinogenic

Agents
(what carcinogens
do)

The Hallmarks of Cancer

- 1. Evasion of Anti-growth Signaling
 - 2. Immune System Evasion
 - 3. Replicative Immortality
 - 4. Inflammation
- 5. Tissue Invasion and Metastasis
 - 6. Angiogenesis
 - 7. Genetic Instability
 - 8. Resistance to Cell Death
- 9. Dysregulated Metabolism
- 10. Sustained Proliferative Signaling

The Key Characteristics of Human Carcinogens

- 1. Is Electrophilic or Can Be Metabolically Activated to Electrophiles
 - 2. Is Genotoxic
- 3. Activates Mutagenic DNA Repair & Promotes Genomic Instability
 - 4. Induces Epigenetic Alterations
 - 5. Induces Oxidative stress
 - 6. Induces Chronic Inflammation
 - 7. Is Immunosuppressive
 - 8. Modulates Receptor-mediated effects
 - 9. Causes Immortalization
 - 10. Alters Cell Proliferation, Cell Death or Nutrient Supply





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



- Integration within individual bodies of evidence
 - Meta-analysis to inform conclusions within an OHAT/GRADE-like framework
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- Integration across bodies of evidence



- Increasing emphasis on mechanistic data

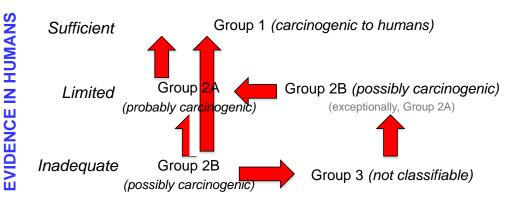
Moving to one-step evidence integration across bodies of evidence



EVIDENCE IN EXPERIMENTAL ANIMALS

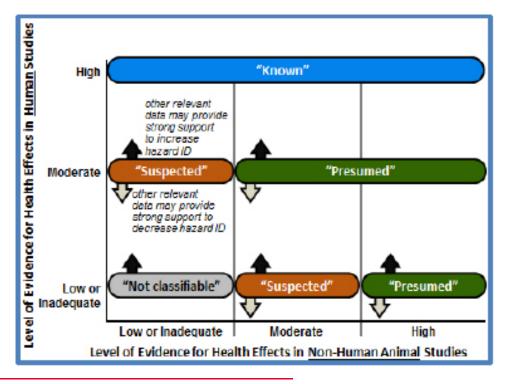
Sufficient Limited

Inadequate



: Possible alterations based on mechanistic 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



- 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 <u>mechanism(s) that does not operate in humans</u>
 - An agent belongs to a <u>mechanistic class of agents causing cancer</u>
 - 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



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



Body of evidence				
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Limited		———	
	Sufficient ———		Possibly carcinogenic
		Strong (experimental systems)	to humans (Group 2B)
	Sufficient	Strong - mechanism in	Not classifiable as to
		experimental animals does not→	its carcinogenicity to
	Any other combin	operate in humans	humans (Group 3)
	Any other combine	nation not listed ————————————————————————————————————	

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