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TOXICOLOGY EXCELLENCE FOR RISK ASSESSMENT

Evidence-Based MoA Frameworks for Carcinogens Should Be Favored for Identification of Carcinogens

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Overview

- Are the **IARC key characteristics** to cancer hazard identification a robust new approach to organizing and evaluating the mechanistic data that avoid the need to identify modes of action and underlying hypotheses?
- From one vantage point, **perhaps**. Because KCCs are based on empirical observations of characteristics associated with known carcinogens, they can assist the organization of the mode of action literature.
- Yet, as much as **50% of carcinogens** classified by IARC **do not exhibit** any key characteristics,* while other chemicals, not known to evoke cancer by both EPA and IARC, often do (perhaps oxygen?).
- Furthermore, many **other toxicities**, unrelated to cancer, may be mediated by similar toxicity pathways and biological responses and **show similar key** characteristics (so specificity to cancer?).

* For example, Becker, Richard A., Michael Dourson, Chijioke Onyema, and Jessica Ryman. 2025. Beyond key characteristics of carcinogens: an archetypal MOA-based evidence system for hypothesis testing to advance carcinogen risk assessment. *Journal Toxicology and Regulatory Policy*. Volume 1:1a-15.



The Key Characteristics of Carcinogens (KCCs) (Smith et al., 2016)*

Ten Key Characteristics of Carcinogens (KCCs)

1. Is electrophilic or can be metabolically activated to an electrophile
2. Is genotoxic
3. Alters DNA repair or causes 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

* Smith, M. T., Guyton, K. Z., Gibbons, C. F., Fritz, J. M., Portier, C. J., Rusyn, I., DeMarini, D. M., Caldwell, J. C., Kavlock, R. J., Lambert, P. F., Hecht, S. S., Bucher, J. R., Stewart, B. W., Baan, R. A., Coglianò, V. J., & Straif, K. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ. Health Perspect.*, 124(6), 713–721.



Agents with IARC Cancer Classifications & KCCs (source: Guyton et al., 2018)*

Agent	IARC Group	Cancer in Humans	Cancer in Animals	# KCCs
PCP	1	Sufficient	Sufficient	5
Lindane	1	Sufficient	Sufficient	2
Welding fumes	1	Sufficient	Sufficient	2
Consumption of processed meat	1	Sufficient	Inadequate	0
Malathion	2A	Limited	Sufficient	5
Hydrazine	2A	Limited	Sufficient	4
DDT	2A	Limited	Sufficient	3
N,N-DMF	2A	Limited	Sufficient	3
TCAB	2A	Inadequate	Sufficient	3
Tetrabromobisphenol A	2A	Inadequate	Sufficient	3
Diazinon	2A	Limited	Limited	2
Glyphosate	2A	Limited	Sufficient	2
2-Mercaptobenzothiazole	2A	Limited	Sufficient	0
Consumption of red meat	2A	Limited	Inadequate	0
Dieldrin and aldrin metabolized to dieldrin	2A	Limited	Sufficient	0
Very hot beverages	2A	Limited	Sufficient	0
1-Bromopropane	2B	Inadequate	Sufficient	5
2,4-Dichlorophenoxyacetic acid (2,4-D)	2B	Inadequate	Limited	1

Agent	IARC Group	Cancer in Humans	Cancer in Animals	# KCCs
3-Chloro-2-methylpropene	2B	Inadequate	Sufficient	1
Furfuryl alcohol	2B	Inadequate	Sufficient	1
Indium tin oxide	2B	Inadequate	Sufficient	1
Melamine	2B	Inadequate	Sufficient	1
1-tert-Butoxypropanol	2B	Inadequate	Sufficient	0
2,4,6-Trichlorophenol	2B	Inadequate	Sufficient	0
β-Myrcene	2B	Inadequate	Sufficient	0
Molybdenum trioxide	2B	Inadequate	Sufficient	0
N,N-Dimethyl-p-toluidine	2B	Inadequate	Sufficient	0
Parathion	2B	Inadequate	Sufficient	0
Pyridine	2B	Inadequate	Sufficient	0
Tetrachlorvinphos	2B	Inadequate	Sufficient	0
Tetrahydrofuran	2B	Inadequate	Sufficient	0
Vinylidene chloride	2B	Inadequate	Sufficient	0

Summary: 1/4 Category 1 had no associated KCCs, 4/12 category 2A had no associated KCCs, and 10/16 category 2B agents had no associated KCCs. **Overall, 15/32 IARC carcinogens had no associated KCCs. (Becker et al., 2025, Table 3)**

* Guyton, K.Z., Rusyn, I., Chiu, W.A., Corpet, D.E., van den Berg, M., Ross, M.K., Christiani, D.C., Beland, F.A., & Smith, M.T. (2018). Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis*, 39(4), 614-622. doi:10.1093/carcin/bgy031. PMID:29562322. PMCID:PMC5888955.



Summary of KCCs for IARC Group 3 and EPA Groups D&E non-carcinogens (Becker et al., 2025, Table 4)

Agent	IARC Group 3 or EPA Group D or E	# of Putative KCCs Identified by Authors from Literature Search
Aldicarb	IARC Group 3	0
Atrazine	IARC Group 3	2
Chloroacetonitrile	IARC Group 3	2
Coal dust	IARC Group 3	2
Decabromodiphenyl ox.	IARC Group 3	3
Dicofol	IARC Group 3	1
Hepatitis D	IARC Group 3	1
Hydroquinone	IARC Group 3	2
Jet fuel	IARC Group 3	4
Pentavalent antimony	IARC Group 3	2
Permethrin	IARC Group 3	3
Simazine	IARC Group 3	2
Sulfur dioxide	IARC Group 3	1
Thiram	IARC Group 3	2
Zineb	IARC Group 3	2
Glyphosate	EPA Group D	2
DEET	EPA Group D	2
Kathon	EPA Group D	2
Chlorpyrifos	EPA Group E	2
Prometryn	EPA Group E	1



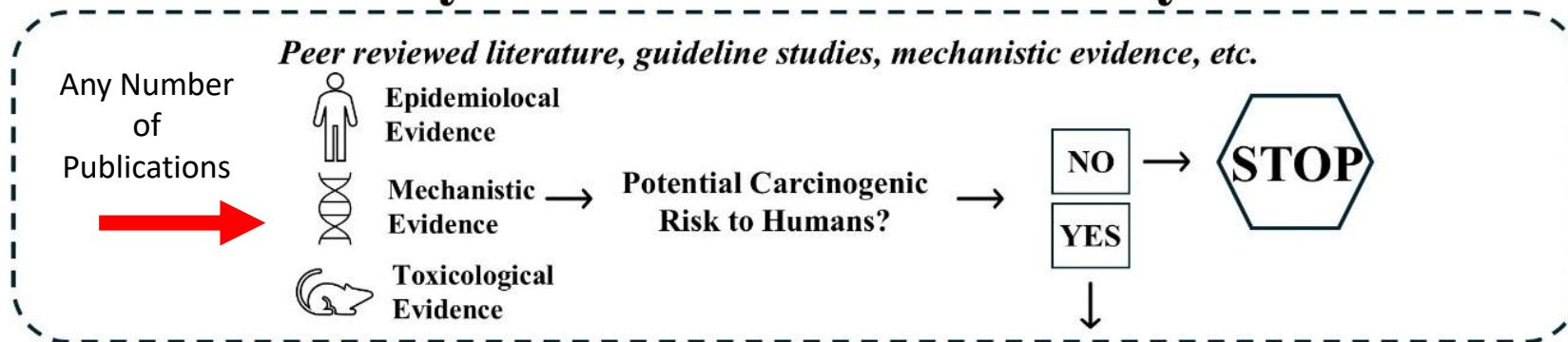
Archetypal Modes of Action (MOA) of Chemical Carcinogenesis (Becker et al., 2025, Table 6)

Modes of Action (MOA)	Unique Key Events			Common Key Events	
Mutagenic (hypothesized non-threshold)	KE #1 - Formation of pro- mutagenic DNA adducts	KE #2 - Insufficient repair of adducts	KE #3 - Early induced critical mutations driving cancer	KE #4 Proliferation, clonal expansion of mutant cells, and progression	KE #5 Cancer
Cytotoxic (threshold)	KE #1 - Direct cytotoxicity	KE #2 - Cytotoxicity in target tissues	KE #3 - Regenerative cell proliferation		
Receptor Mediated (threshold)	KE #1 - Direct interaction that binds a receptor	KE #2 - Interaction of the receptor in target tissues / cells	KE #3 - Cell proliferation stimulus		
Immune Suppression (hypothesized threshold)	KE #1 - Reduced humoral or cellular immune response	KE #2 - Reduced detection and destruction of cancer cells	KE #3 - Survival of pre-cancer or cancer cells		
Novel MOA	KE #1 - Interaction with a chemical and biosystem	KE #2 - Response in the cell triggered	KE #3 - cellular or tissue response initiates proliferation		

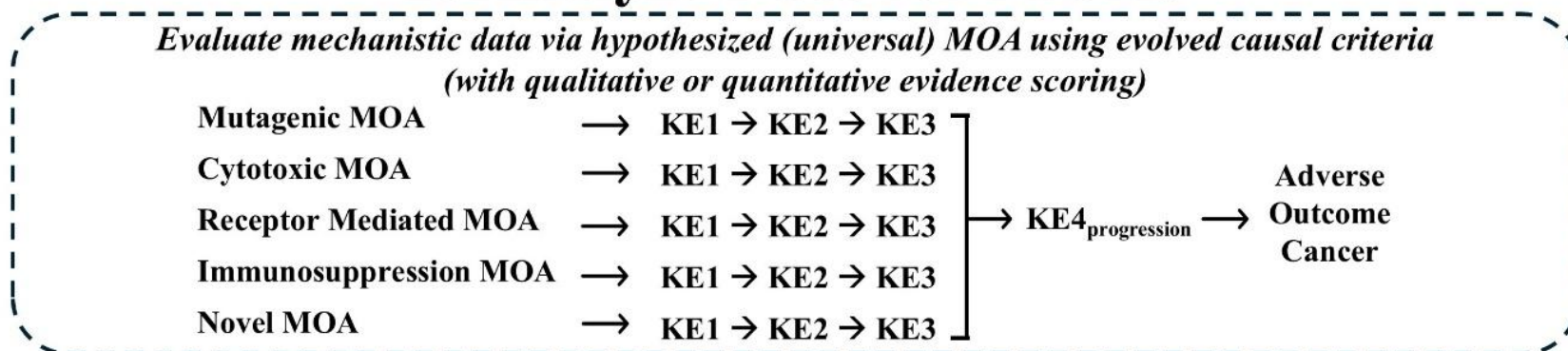


Hypothesis-testing using archetypal cancer MOAs (Becker et al. 2025, Figure 1)

1. Systematic Evidence Analysis

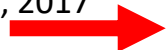


2. Analyze Data for MOAs





Becker et al., 2017



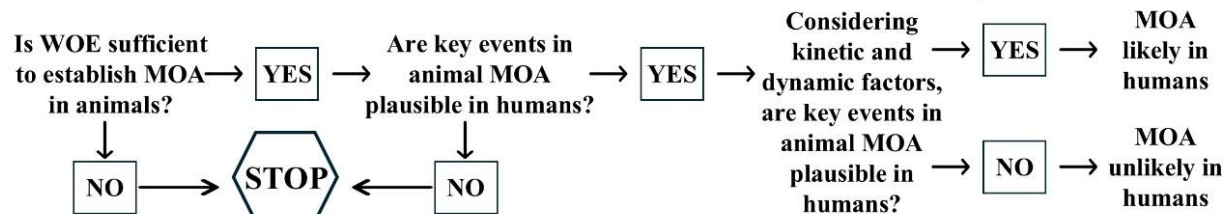
3. Determine Likely Operative MOA

Compare evidence scores to determine most likely MOA (see reference 63 and Supplemental Material)

Mechanistic MOA	→ Evidence Score (-100 to 100)	} Highest Score = Most Likely MOA
Cytotoxic MOA	→ Evidence Score (-100 to 100)	
Receptor Mediated MOA	→ Evidence Score (-100 to 100)	
Immunosuppression MOA	→ Evidence Score (-100 to 100)	
Novel MOA	→ Evidence Score (-100 to 100)	

4. Human Relevance of Likely MOA

Summarize WOE, including human relevance, consistencies/inconsistencies of data sets etc.

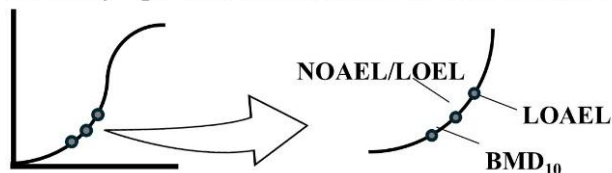


Any Number of Publications



5. Derive POD for Risk Assessment

When relevant to humans, select method for calculating quantitative risks arising from potential exposure based on Likely Operative MOA (threshold or non-threshold models)



Meek and Wikoff,
2023, Figure 4*

1. Systematic Evidence Identification

Peer-reviewed literature, HTS, Existing pathways, etc.

2. Assess information within each characteristic by considering biological level of organization, directionality of activity (and lack of activity), consistency, and plausibility of potential key events and key event relationships in a biological pathway

Electrophilic or ability to undergo metabolic activation

Genotoxic

Altered DNA repair or cause genomic instability

Epigenetic alterations

Oxidative stressor

Alter cell proliferation, cell death and nutrient supply

Immortalization

Modulate receptor-mediated effects

Immunosuppressant

Induce chronic inflammation

3. Integrate evidence in biological pathway construct

Exposure

Initiating Event

Key Event

Key Event

Adverse Outcome

Volume and Specificity >>>

* Meek, M. E., & Wikoff, D. (2023). The need for good practice in the application of mechanistic constructs in hazard and risk assessment. *Toxicol. Sciences*, 194(1), 13–22. <https://doi.org/10.1093/toxsci/kfad039>



Conclusions

- IARC's use of its Key Characteristics (KCCs) for carcinogens is not inappropriate for **data organization**---its original intent.
- However, IARC's use of its KCCs should not **replace critical thinking**, exemplified by over 20 years of development of Mode of Action (MOA) understanding of carcinogenicity. Evaluation of potential human cancer from any particular chemical **is not a checklist** undertaking.
- The use of KCCs for carcinogenicity by IARC or for this or other toxicities by some authorities, other than for its original intent, **is misguided**.