Identifying Carcinogens: The Essential Role of Independent Scientific Experts

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Conflict of Interest Statement

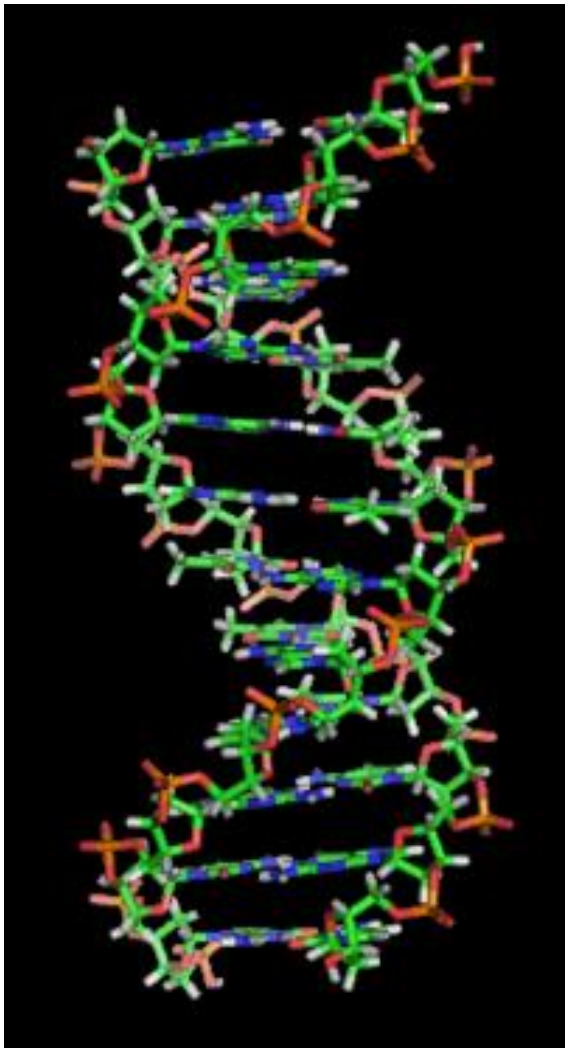
I declare no financial interests related to the subject matter of my presentation.

Outline of Today's Talk

- The role of independent experts in ***IARC Monographs*** evaluations
- The **key characteristics of carcinogens** and their application in cancer hazard identification
- Evidence synthesis & **carcinogen classification**

IARC: Two Strands Intertwined

- Generate data from inter-disciplinary research
- Evaluate data through independent expert review
  - WHO Classification of Tumours
  - *IARC Handbooks of Cancer Prevention*
  - IARC Working Group Reports
  - Global Cancer Statistics
  - *IARC Monographs – since 1971*



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How are the IARC Monograph Evaluations Conducted?

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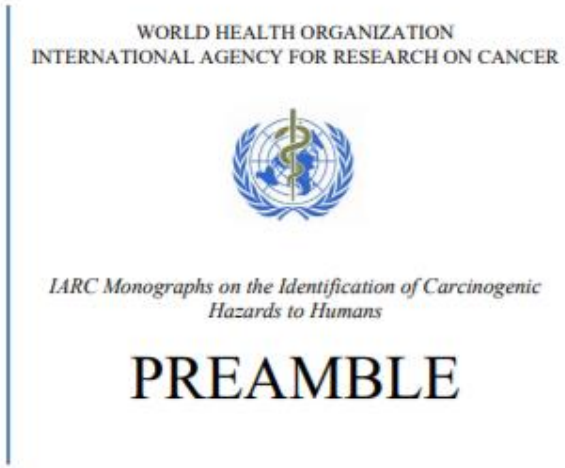

- Procedural guidelines for participant selection, conflict of interest, stakeholder involvement & meeting conduct
- Separate criteria for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

Preamble to the IARC Monographs (amended January 2019):
https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

Who Does the Evaluation?

Attend meetings but do not draft text or contribute to evaluations

IARC Secretariat
Coordinates all aspects of the evaluation

Working Group
Independent scientists without conflict of interest
Review science and develop evaluations

Invited Specialists
Scientists with relevant knowledge but a competing interest

Representatives of governments and health agencies

Observers
Scientists with a competing interest: observe but do not influence outcomes

Preamble to the IARC Monographs (amended January 2019):
https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

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What Are the Steps Involved?

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Step 1 Identify relevant information

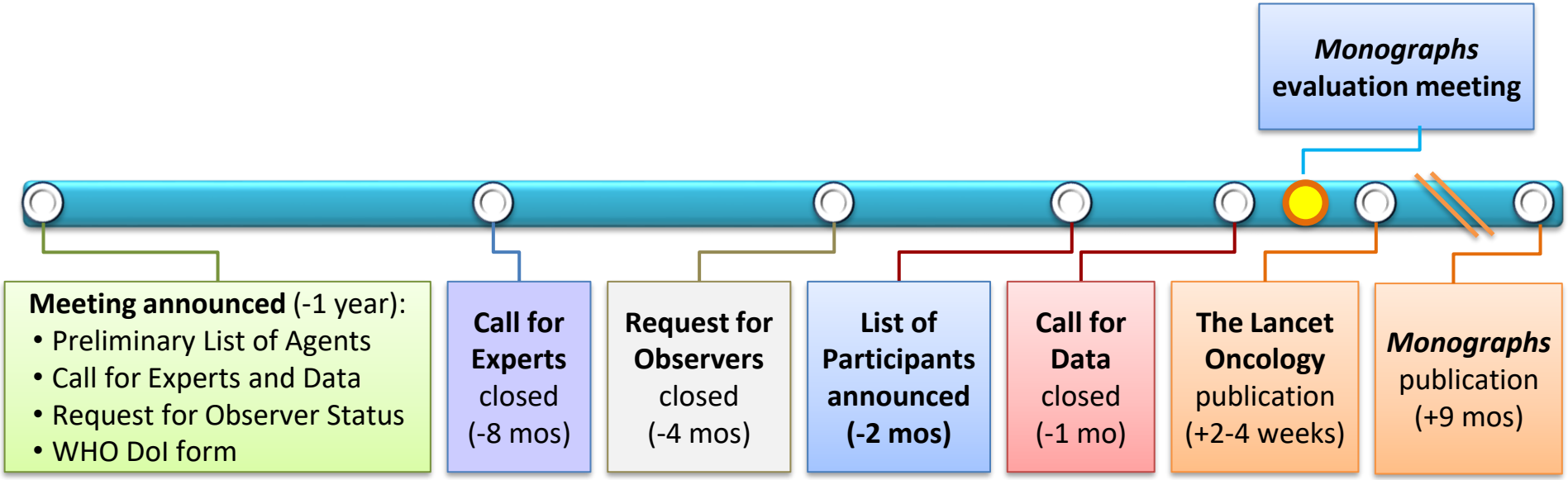
Step 2 Screen, select & organize studies

Step 3 Evaluate study quality

Step 4 Report study characteristics

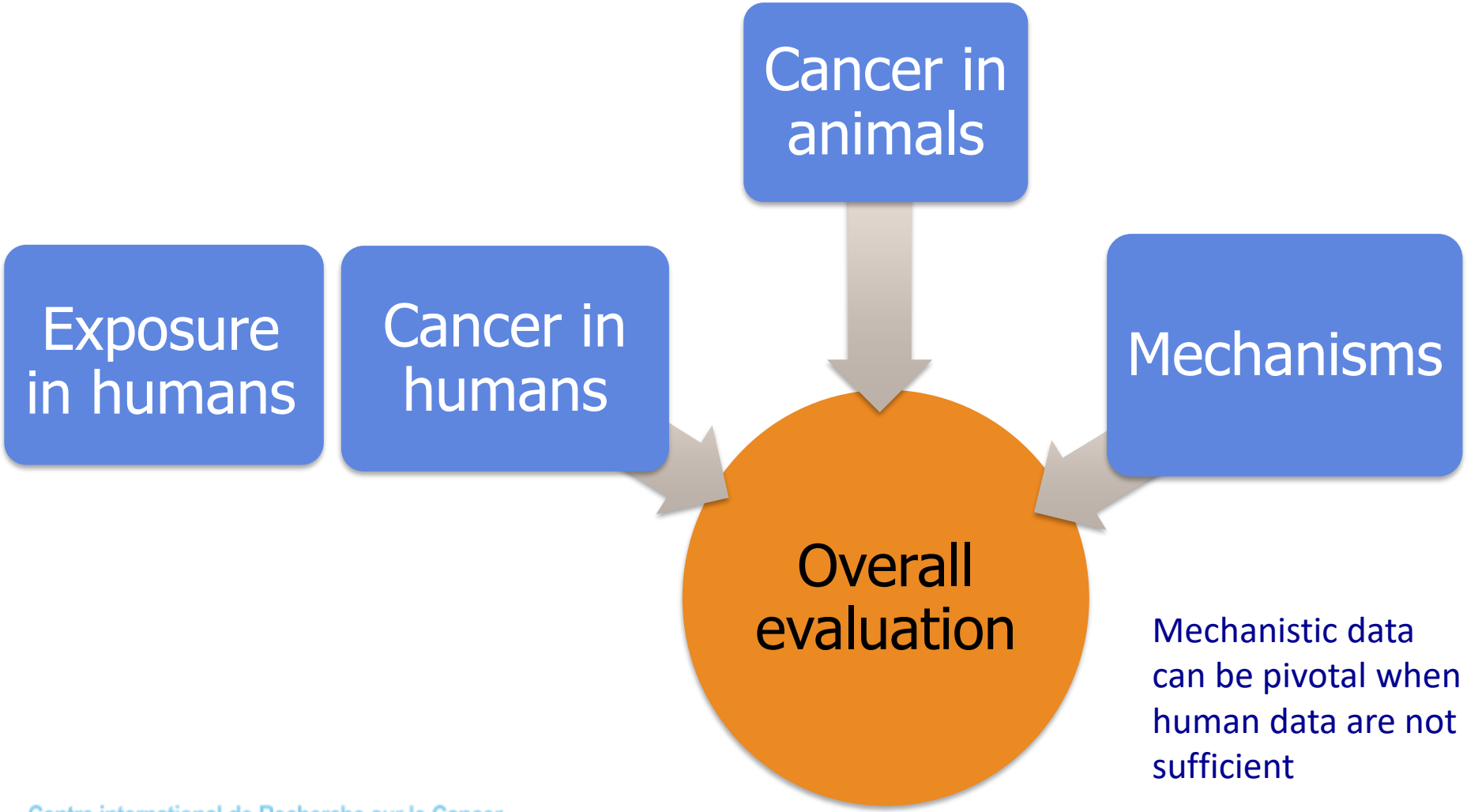
Step 5 Synthesize evidence→ overall evaluations

What Is the Overall Timeline?



- IARC meetings are open and follow transparent, published methods
- All meeting participants have full access to the data being evaluated
- Fully referenced *Monographs* published on-line for free download

What Evidence is Considered?



Mechanistic data can be pivotal when human data are not sufficient

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Mechanistic Data: *Challenges*

IARC Monographs
Volume 100

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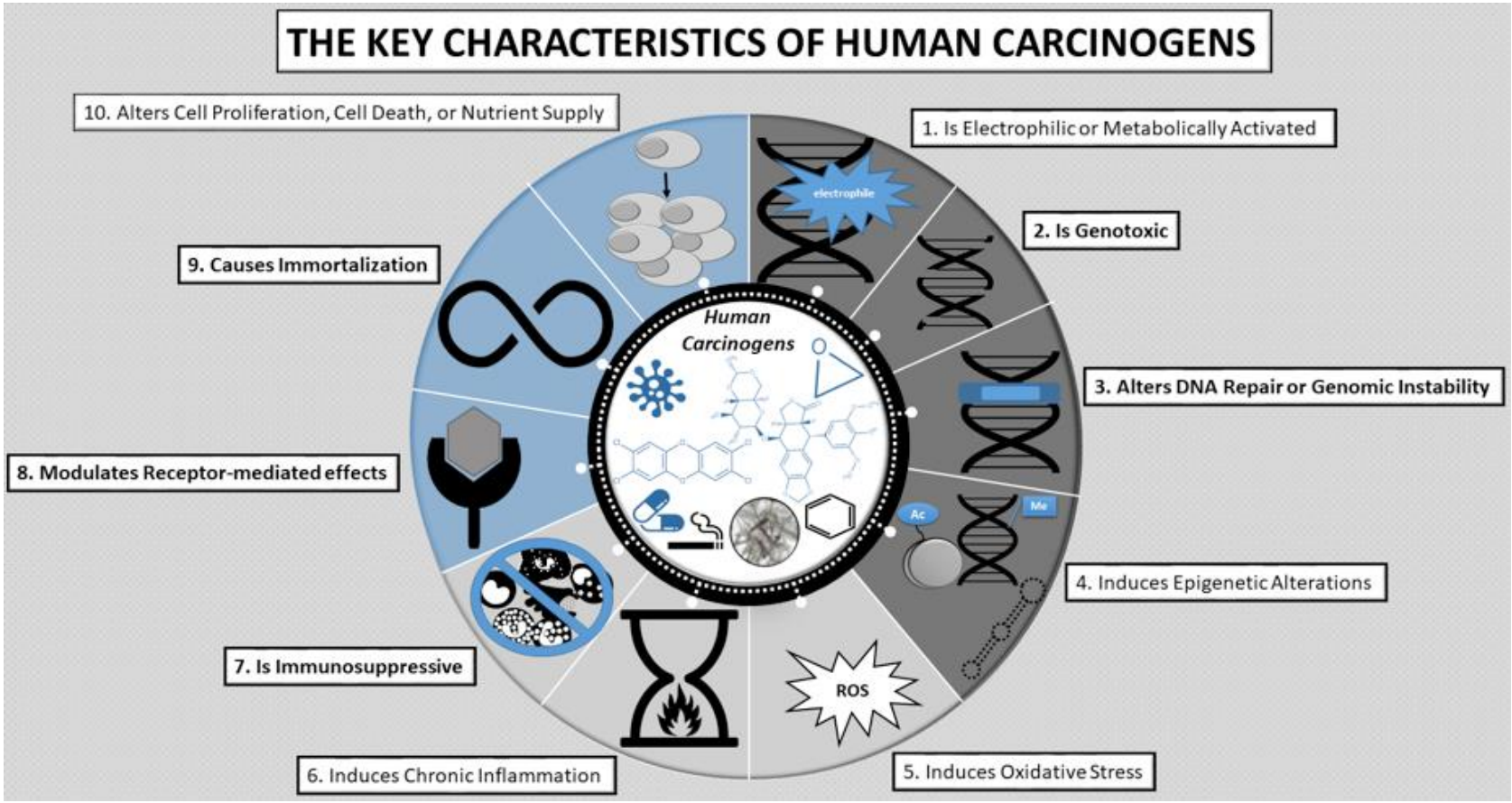
- How to search systematically for relevant mechanisms?
- How to bring uniformity across assessments?
- How to analyze the voluminous mechanistic database efficiently?
- How to avoid bias towards favored mechanisms?

10 Key Characteristics of Human Carcinogens

Key characteristics:
1. Is electrophilic or can be metabolically activated
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

- Chemical and biological properties of established human carcinogens
- Data on key characteristics can provide evidence of carcinogenicity
- Used to assemble data relevant to mechanisms of carcinogens– without needing an *a priori* hypothesis of the mechanism

- Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K (2016); Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Env Health Persp.*, 124(6):713-21.
- Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg, M, Ross, M, Christiani DC, Beland FA, Smith MT (2018); Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis*, 39(4):614.
- IARC Scientific Publication No. 165: Tumour Site Concordance and Mechanisms of Carcinogenesis (2019). https://publications.iarc.fr/578.
- Smith MT, Guyton KZ (2020). Identifying carcinogens from 10 key characteristics: a new approach based on mechanisms. In: Wild CP, Weiderpass E, Stewart BW, editors. World Cancer Report: Cancer Research for Cancer Prevention. http://publications.iarc.fr/586.



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What causes #cancer? An IARC collaboration offers a fresh approach to this tough question. The key characteristics of carcinogens help ID new cancer causes & make sense of suspected carcinogens. Read the article in @ChemResTox about progress & next steps

- Guyton KZ, Rieswijk L, Wang A, Chiu WA, Smith MT (2018); Key characteristics approach to carcinogenic hazard identification. *Chemical Research in Toxicology,* 31(12): 1290-1292.
- Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, Felsher DW, Gibbons CF, Goodson WH, Houck KA, Kane A, La Merrill MA, Lebrec H, Lowe L, McHale CM, Minocherhomji S, Rieswijk L, Sandy MS, Sone H, Wang A, Zhang L, Zeise L, Fielden M (2020). The key characteristics of carcinogens: relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them. *Cancer Epidemiol Biomarkers Prev*. 29(10):1887-1903.
- For more on the key characteristics of hazardous exposures, see: https://keycharacteristics.org/

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Systematic Approach
Using Key Characteristics of Carcinogens

Targeted searches for agent + each key characteristic

Is Genotoxic (#2)

Actions

Description	First three characteristics
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Mutagens"[Mesh] OR "Oncogenes"[Mesh] OR "Genetic Processes"[Mesh] OR "genomic instability"[Mesh] OR chromosom* OR clastogen* OR "genetic toxicology" OR "strand break" OR "unscheduled DNA synthesis" OR "DNA damage" OR "DNA adducts" OR "SCE" OR "chromatid" OR micronucle* OR mutagen* OR "DNA repair" OR "UDS" OR "DNA fragmentation" OR "DNA cleavage")

Induces Epigenetic Alterations (#4)

Actions

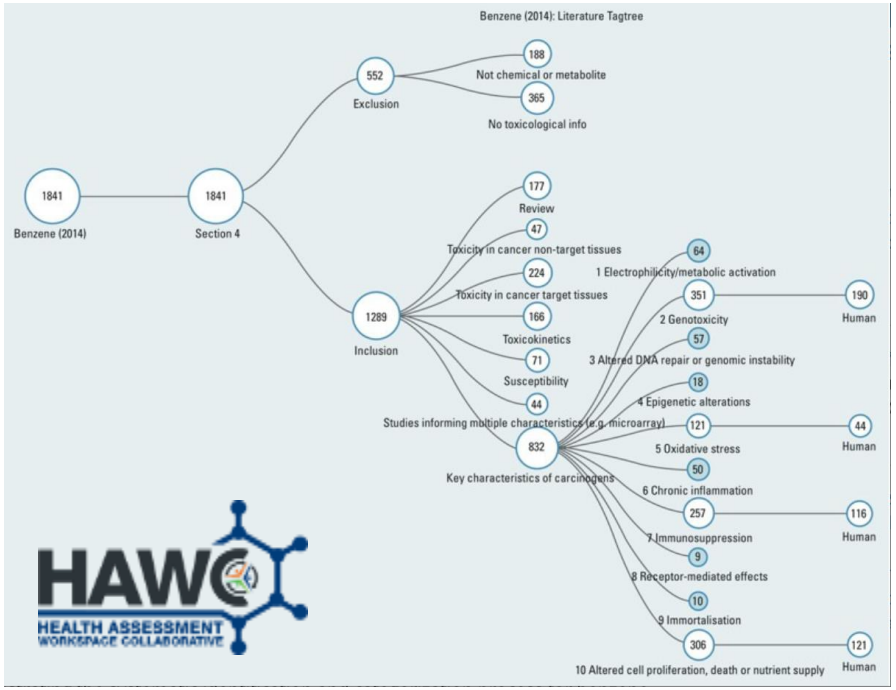
Description	Epigenetics
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("rna"[MeSH] OR "epigenesis, genetic"[MeSH] OR rna OR "rna, messenger"[MeSH] OR "rna" OR "messenger rna" OR mrna OR "histones"[MeSH] OR histones OR epigenetic OR miRNA OR methylation)

Induces oxidative stress (#5)

Actions

Description	Oxidative stress
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("reactive oxygen species"[MeSH] OR "reactive nitrogen species"[MeSH] OR "reactive oxygen species" OR "oxygen radicals" OR "oxidative stress"[MeSH] OR oxidative OR "oxidative stress" OR "free radicals")

Organize results by key characteristics, species, etc



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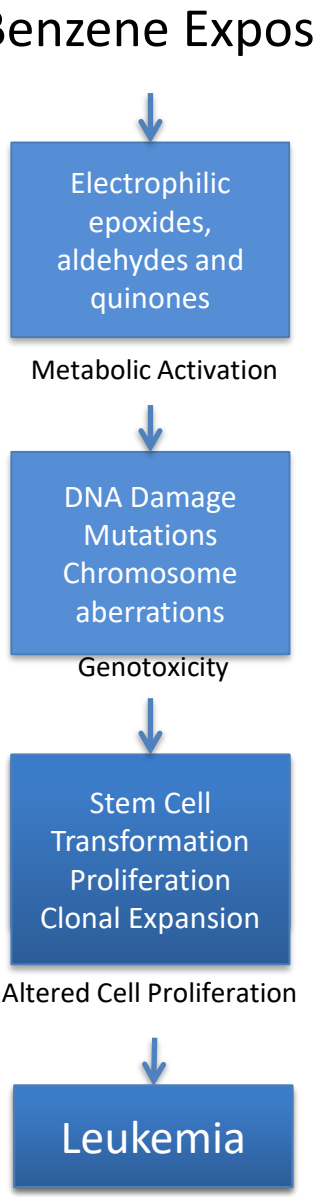
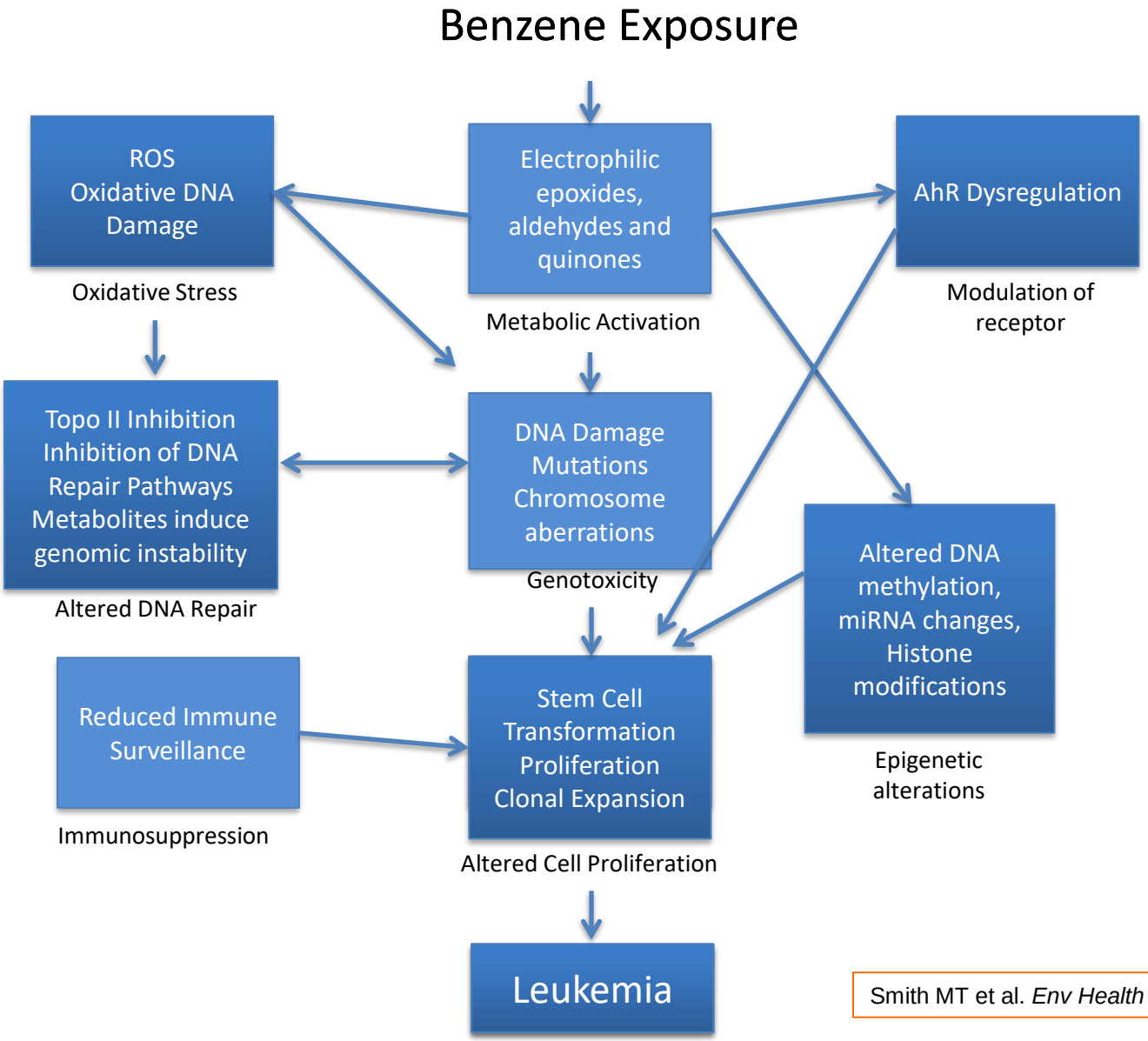
Smith MT et al. *Env Health Persp.*, *124(6):713-21*

Key Characteristics of Benzene: An Adverse Outcome Pathway?



Source: MT Smith

An Adverse Outcome Network Involving 8 Key Characteristics



Smith MT et al. *Env Health Persp.*, *124(6):713-21*

Outline of Today's Talk

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- Evidence synthesis & **carcinogen classification**

Evidence Synthesis and Classification

Step 1 Identify relevant information

Step 2 Screen, select & organize studies

Step 3 Evaluate study quality

Step 4 Report study characteristics

Step 5 Synthesize evidence→ overall evaluations

Synthesis: Categorize each line of evidence using defined terms

Cancer in humans

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
- *Evidence suggesting lack of carcinogenicity*

Cancer in experimental animals

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
- *Evidence suggesting lack of carcinogenicity*

Mechanistic and other relevant data

- *Strong evidence*
  - *Mechanistic class*
  - *Key characteristics*
  - *Mechanism not relevant*
- *Limited evidence*
- *Inadequate evidence*

Overall evaluations: Integrate findings in 3 evidence streams

Overall evaluation

- Group 1 *Carcinogenic to humans (121)*
- Group 2A *Probably carcinogenic to humans (88)*
- Group 2B *Possibly carcinogenic to humans (313)*
- Group 3 *Not classifiable as to its carcinogenicity to humans (499)*

Overall Classifications: *What's New?*

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
		ong (exposed humans)	
			Probably carcinogenic (Group 2A)
		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong (experimental systems)	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Single step integration

Overall Classifications: *What's New?*

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Anima	Mechanistic Evidence	Evaluation
Sufficient			ogenic 1)
	Sufficie		
Limited	Sufficie		
Limited			bly ogenic (Group 2A)
	Sufficient	Strong (human cells	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong (experimental systems)	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Group 2B based on one stream of evidence

Overall Classifications: *What's New?*

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
			classifiable (Group 3)
	A		

Group 2A based on 2 streams of evidence, at least one in human cells

Future Priorities for Evaluation

Advisory Group recor
Monographs

An Advisory Group of 29 scientists from 18 countries met in March, 2019, to recommend priorities for the International Agency for Research on Cancer (IARC) Monographs programme during 2020–24. IARC periodically convenes such advisory

	Rationale
Agents not previously evaluated by IARC Monographs	
Haloacetic acids (and other disinfection byproducts)	Relevant human cancer, bioassay, and mechanistic evidence
Metalworking fluids	Relevant human cancer and bioassay evidence
Cannabis smoking, fertility treatment, glucocorticoids, *Salmonella typhi*, sedentary behaviour*, tetracyclines and other photosensitising drugs	Relevant human cancer and mechanistic evidence
Cupferron, gasoline oxygenated additives, gentian violet, glycidamide, malachite green and leucomalachite green, oxymetholone, pentabromodiphenyl ethers, vinclozolin	Relevant bioassay and mechanistic evidence
Breast implants, dietary salt intake*, neonatal phototherapy*, poor oral hygiene*	Relevant human cancer evidence
Aspartame	Relevant bioassay evidence
Arecoline, carbon disulphide, electronic nicotine delivery systems and nicotine*, human cytomegalovirus, parabens	Relevant mechanistic evidence
Agents previously evaluated by IARC Monographs†	
Automotive gasoline (leaded and unleaded), carbaryl, malaria	New human cancer, bioassay, and mechanistic evidence to warrant re-evaluation of the classification
Acrylamide*, acrylonitrile, some anthracyclines, coal dust, combustion of biomass, domestic talc products, firefighting exposure, metallic nickel, some pyrethroids (ie, permethrin, cypermethrin, deltamethrin)	New human cancer and mechanistic evidence to warrant re-evaluation of the classification
Aniline, acrolein, methyl eugenol and isoeugenol*, multi-walled carbon nanotubes*, non-ionising radiation (radiofrequency)*, some perfluorinated compounds (eg, perfluorooctanoic acid)	New bioassay and mechanistic evidence to warrant re-evaluation of the classification
Ostrogen:oestradiol and oestrogen-progestogens‡, hydrochlorothiazide, Merkel cell polyomavirus, perchloroethylene, very hot foods and beverages	New human cancer evidence to warrant re-evaluation of the classification
1,1,1-trichloroethane, weapons-grade alloy (tungsten, nickel, and cobalt)	New bioassay evidence to warrant re-evaluation of the classification
Acetaldehyde, bisphenol A*, cobalt and cobalt compounds, crotonaldehyde, cyclopeptide cyanotoxins, fumonisin B_1, inorganic lead compounds, isoprene, o-anisidine	New mechanistic evidence to warrant re-evaluation of the classification

Evidence of human exposure was identified for all agents. *Advised to conduct in latter half of 5-year period. †See current International Agency for Research on Cancer (IARC) list of classifications, volumes 1–123. ‡Group 1 carcinogen; new evidence of cancer in humans indicates possible causal associations for additional tumour sites (see Section 3 of Preamble to the IARC Monographs[7]).

Table 1: **Agents recommended for evaluation by the IARC Monographs with high priority**

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Acknowledgements

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- U.S. National Cancer Institute (since 1982)
- European Commission, DG Employment, Social Affairs and Inclusion (since 1986)
- U.S. National Institute of Environmental Health Sciences (since 1992)

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Thank *you*! Merci!

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