Using the Key Characteristics of Carcinogens in Carcinogen Hazard Identification

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Mechanistic Data: Challenges

- 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?

What are the key characteristics?

- Chemical and biological properties of IARC Group 1 human carcinogens (see Smith et al., 2016)
- Distinct from the hallmarks of cancer, the properties of tumours and cancer cells
- Used to assemble data relevant to mechanisms of carcinogens– without needing an a priori hypothesis of the mechanism

Key characteristics in the *IARC Monographs* Preamble

Step 1: Identification of relevant information

Step 2: Screening, selection, organization of studies

Steps 3 & 4: Evaluation of study quality & reporting of results

Step 5: Evidence Synthesis

Exposure characterization

Human cancer study synthesis

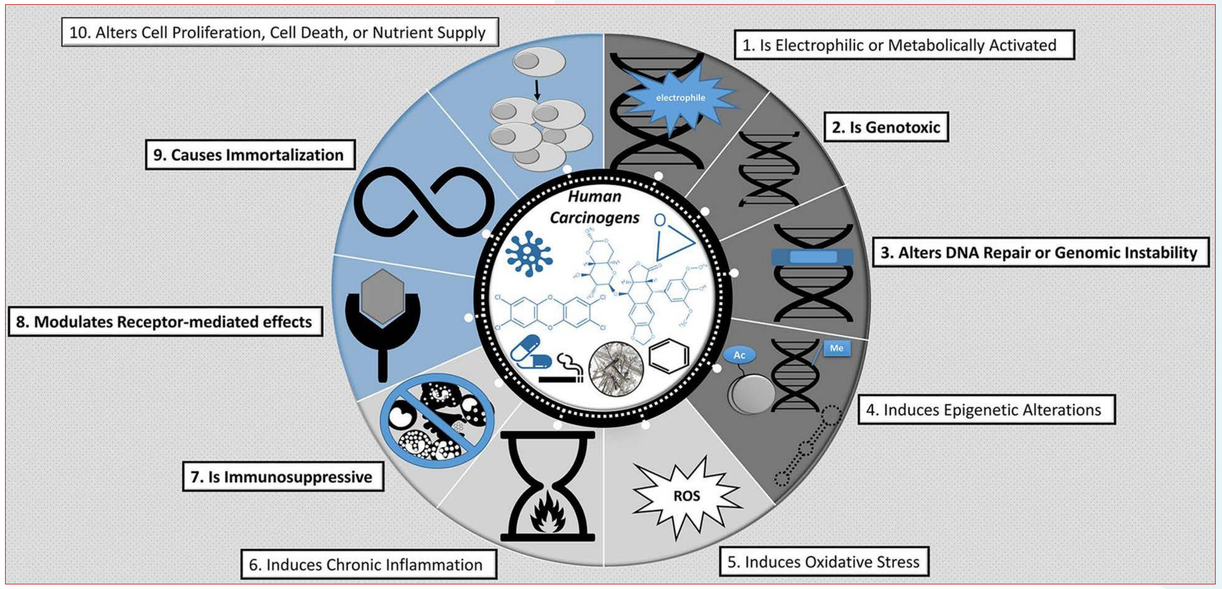
- Causal inference for body of evidence, accounting for study quality & informativeness
- Increased attention to quality of exposure assessment

Cancer bioassay study synthesis

- Evidence of dose-related increases in tumour frequency in high-quality studies

Mechanistic data synthesis

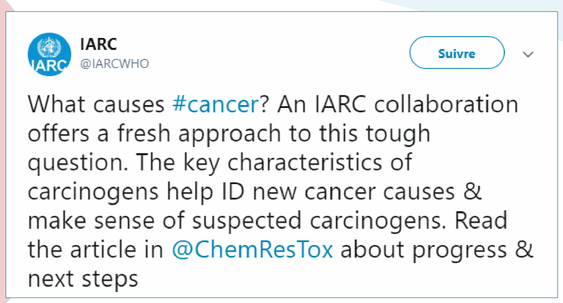
- Strength of evidence: mechanistic class; **key characteristics of carcinogens**; and relevance of mechanism for humans
- Study quality considerations



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		
		Strong (experimental systems)	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

What next for the key characteristics?

- Refine searches for literature and other databases to focus on most informative studies
- Develop and map toxicological and biomarker endpoints to the key characteristics
- Develop key characteristics for other toxicological hazards (e.g., endocrine disruptors)



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