



Application of the Key Characteristics of Carcinogens in the IARC *Monographs*

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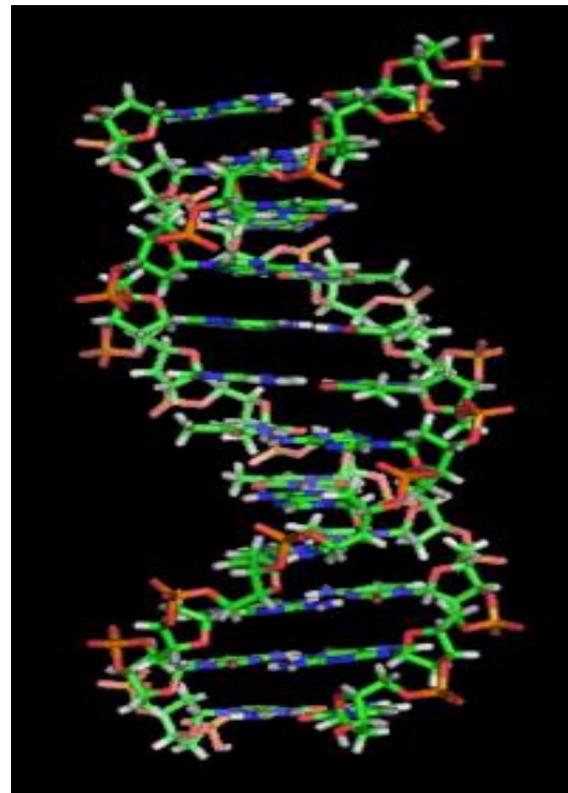
International Agency for Research on Cancer

Conflict of Interest Statement

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

IARC: Two Strands Intertwined

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



How Are the IARC Monograph Evaluations Conducted?



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



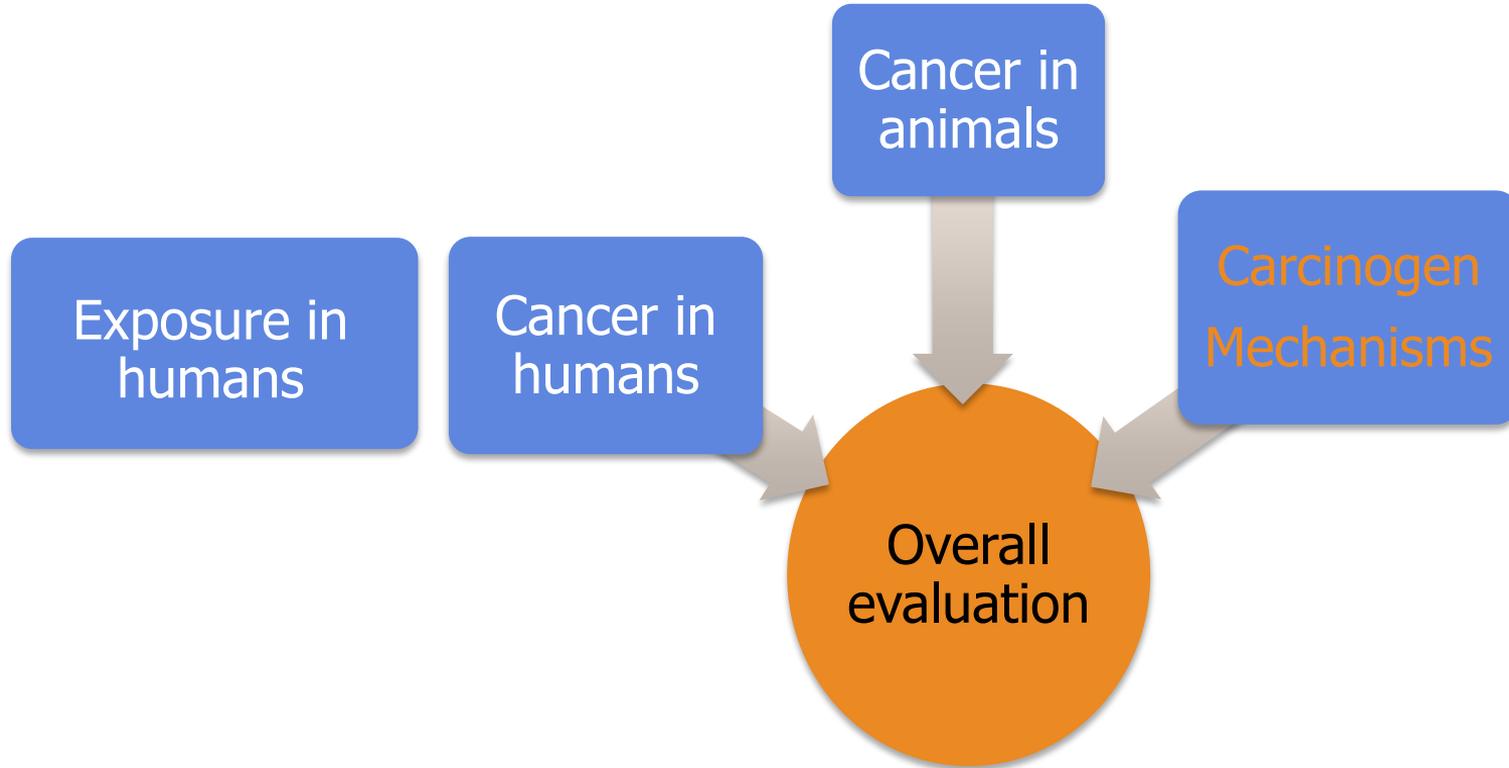
IARC Monographs on the Identification of Carcinogenic Hazards to Humans

PREAMBLE

- 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)):
<https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf>

What Evidence is Considered?



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

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?

IARC Monographs
Volume 100

The 10 Key Characteristics of Human Carcinogens

Key characteristic:

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

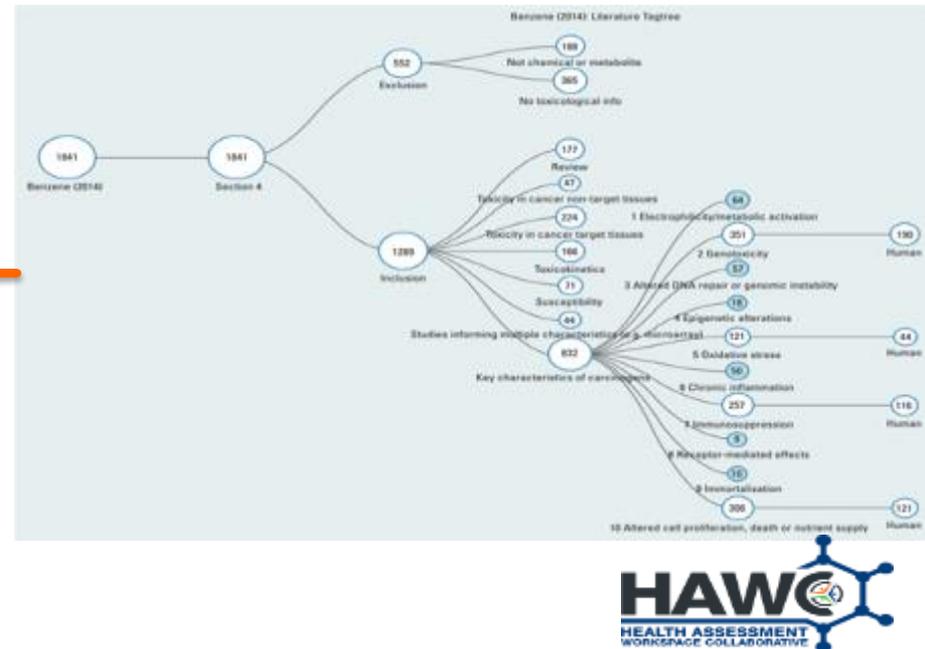
- Chemical and biological properties of established human carcinogens
- Distinct from the hallmarks of cancer, the properties of tumors and cancer cells
- Used to assemble data relevant to mechanisms of carcinogens– without needing an *a priori* hypothesis of the mechanism

Systematic Approach Using Key Characteristics of Carcinogens

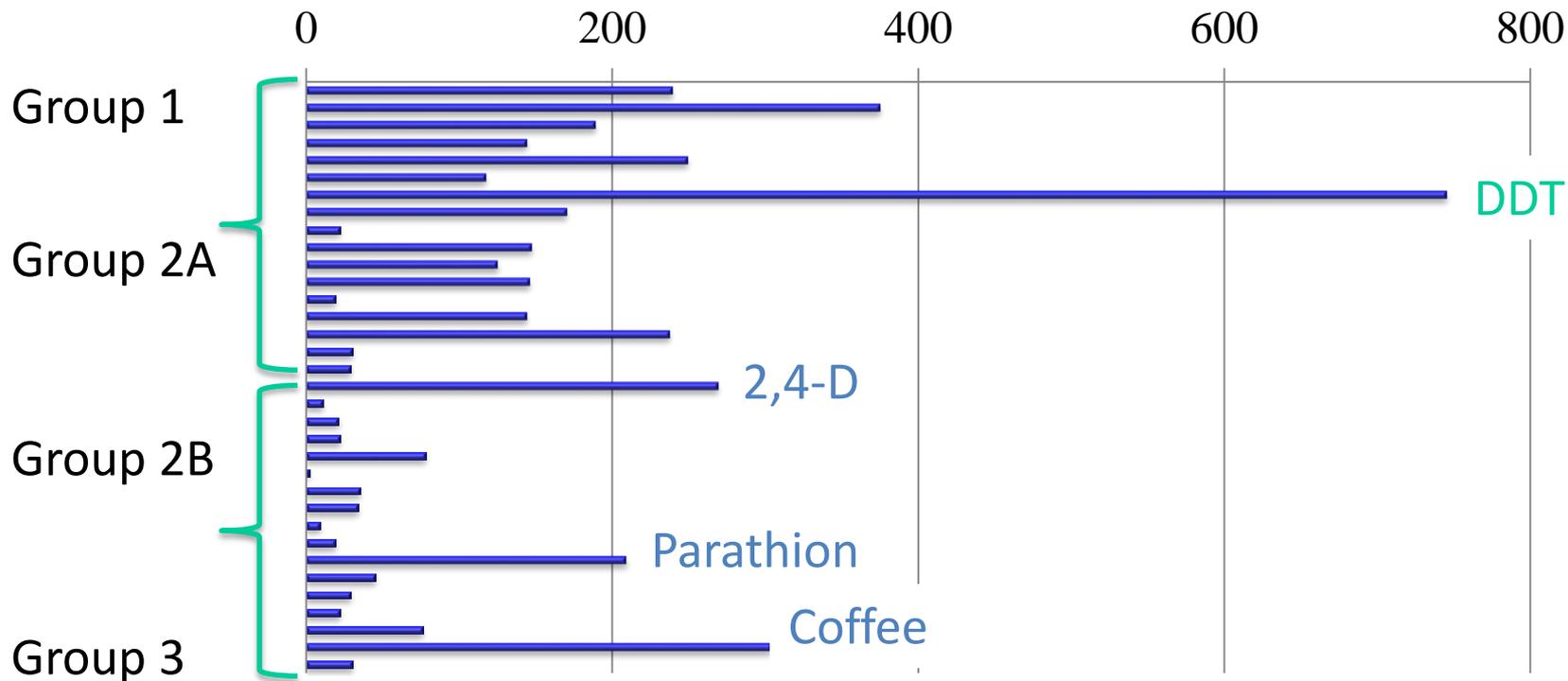
Targeted searches for each key characteristic

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 "chromosome" OR "clastogen" OR "genetic toxicology" OR "strand break" OR "unscheduled DNA synthesis" OR "DNA damage" OR "DNA adducts" OR "SCE" OR "chromatid" OR "micronuclei" 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 "mma 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")	

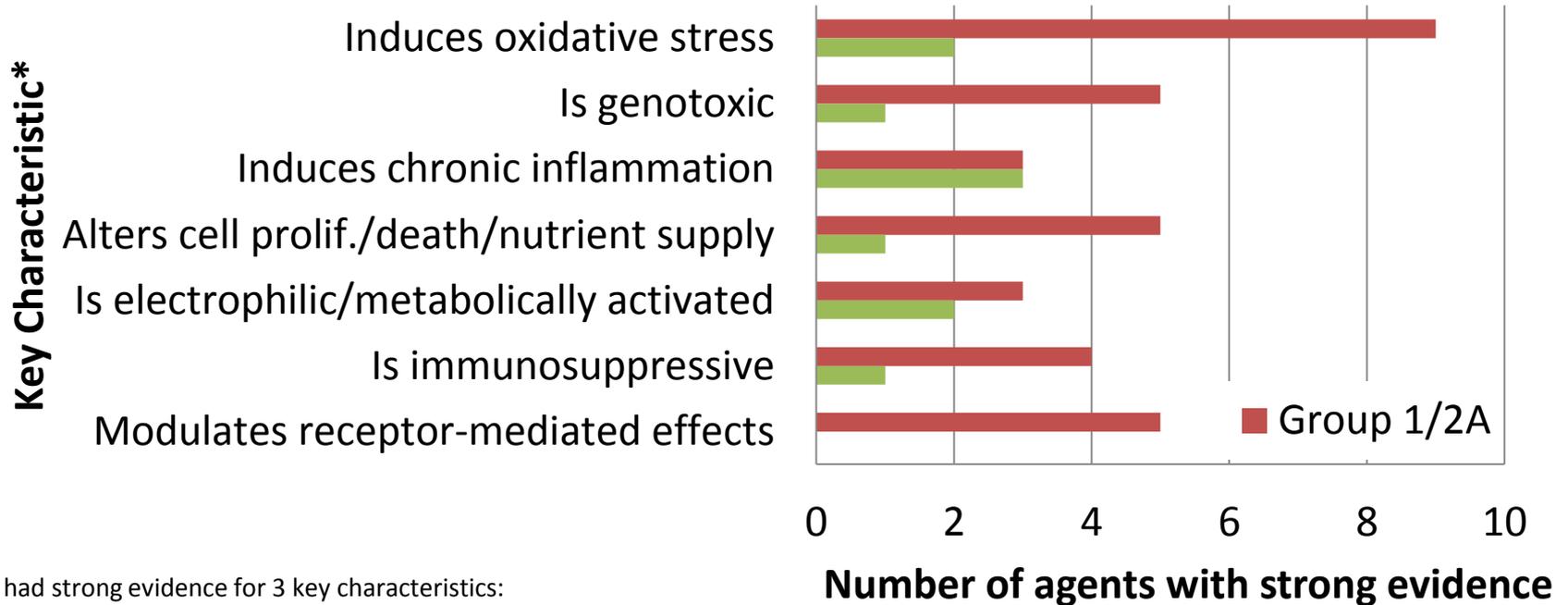
Organize results by key characteristics, species, etc



Applying the Key Characteristics for Group 1, 2 and 3 Agents (Volumes 112-119)



Key Characteristics with Strong Evidence across Multiple Evaluations (Volumes 112-119)



*No agent had strong evidence for 3 key characteristics:

- alters DNA repair or causes genomic instability;
- induces epigenetic alterations
- causes immortalization

Lessons Learned: Volumes 112-119

Agent	Group	Cancer in humans	Cancer in animals	# of Studies (All KCs)	KC 1	KC 2	KC 3	KC 4	KC 5	KC 6	KC 7	KC 8	KC 9	KC 10
Pentachlorophenol (PCP)	1	Sufficient	Sufficient	239	X	X			X			X		X
Lindane	1	Sufficient	Sufficient	375					X		X			
Welding fumes	1	Sufficient	Sufficient	189						X	X			
Consumption of processed meat	1	Sufficient	Inadequate	144*										
Malathion	2A	Limited	Sufficient	249		X			X	X		X		X
Hydrazine	2A	Limited	Sufficient	117	X	X			X					X
Dichlorodiphenyltrichloroethane (DDT)	2A	Limited	Sufficient	745					X		X	X		
N,N-Dimethylformamide (DMF)	2A	Limited	Sufficient	170	X				X					X
Tetrachloroazobenzene (TCAB)	2A	Inadequate	Sufficient	22						X		X		X
Tetrabromobisphenol A	2A	Inadequate	Sufficient	147					X		X	X		
Diazinon	2A	Limited	Limited	125		X			X					
Glyphosate	2A	Limited	Sufficient	146		X			X					
2-Mercaptobenzothiazole	2A	Limited	Sufficient	19										
Consumption of red meat	2A	Limited	Inadequate	144*										
Dieldrin, and aldrin metabolized to dieldrin	2A	Limited	Sufficient	237										
Very hot beverages	2A	Limited	Sufficient	30**										
1-Bromopropane	2B	Inadequate	Sufficient	29	X				X	X	X			X
2,4-Dichlorophenoxyacetic acid (2,4-D)	2B	Inadequate	Limited	269					X					
3-Chloro-2-methylpropene (technical grade)	2B	Inadequate	Sufficient	11		X								
Furfuryl alcohol	2B	Inadequate	Sufficient	21	X									
Indium tin oxide	2B	Inadequate	Sufficient	22						X				
Melamine	2B	Inadequate	Sufficient	78						X				
1-tert-Butoxypropanol	2B	Inadequate	Sufficient	2										
2,4,6-Trichlorophenol	2B	Inadequate	Sufficient	35										
β-Myrcene	2B	Inadequate	Sufficient	34										
Molybdenum trioxide	2B	Inadequate	Sufficient	9										
N,N-Dimethyl-p-toluidine	2B	Inadequate	Sufficient	19										
Parathion	2B	Inadequate	Sufficient	209										
Pyridine	2B	Inadequate	Sufficient	45										
Tetrachlorvinphos	2B	Inadequate	Sufficient	29										
Tetrahydrofuran	2B	Inadequate	Sufficient	22										
Vinylidene chloride	2B	Inadequate	Sufficient	76										
Coffee drinking	3	Inadequate	Inadequate	304						***				
Mate (not very hot)	3	Inadequate	Inadequate	30**										

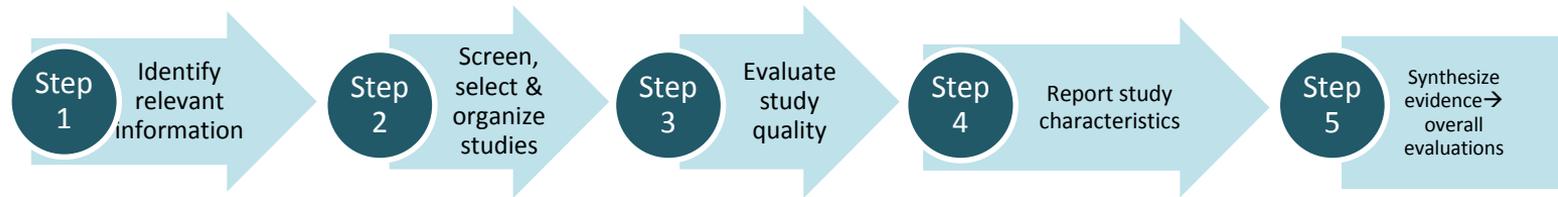
X, Strong evidence; *Number of studies applies to red and processed meat; for red meat, there was strong mechanistic evidence for meat components

Applies to mate and hot beverages; *Antioxidant effects

- Predominance of different KCs in these recent evaluations
- Broad literature on KCs for Group 1/2A agents
- 0-1 KCs for Group 2B or 3 agents
- Few human biomarker studies (except welding)
- Change in overall evaluation for 2/34 agents
- High-throughput data had little overall impact

IARC Monographs Preamble 2019: *What's New for Mechanistic Data?*

- Mechanistic studies identified, screened and evaluated for quality and importance to the evaluation



- New classification categories: *strong, limited, inadequate*
- Single-step evidence integration (vs. up- and down-grade)
 - Harmonized approach to evidence evaluation across scientific disciplines

Three Distinct Mechanistic Topics Can Influence Overall Evaluations

Cancer in
humans

Cancer in
experimental animals

Mechanistic and
other relevant data

—Part B, Section 6(c)

Mechanistic Class

- Belongs, based on mechanistic considerations, to a **class of agents**— one or more of which is probably carcinogenic or carcinogenic to humans

Key Characteristics of Carcinogens

- In exposed **humans**
- In **human primary cells** or tissues
- In **experimental systems**

Mechanism not relevant

- Meets criteria for concluding that mechanism of carcinogenicity in experimental animals is **not relevant to humans**

Overall Evaluations: *What's New?*

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

Single step integration

Overall Evaluations: *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)	Possibly carcinogenic (Group 2B)
Limited			
	Sufficient	Strong (experimental systems)	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)

Strong evidence of KCs- impact on Group 1, 2A and 2B evaluations

Overall Evaluations: *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		
		Strong (experimental systems)	
	Sufficient	St	
All other situations not listed above			

Group 2B based on one stream of evidence

Overall Evaluations: *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		
			Not classifiable (Group 3)

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

Key Characteristics of Carcinogens in Priority Setting

Advisory Group to Recommend Priorities for the IARC, Lyon, France, 25



Advisory Group recommends 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

Agents not previously evaluated by IARC Monographs

Haloacetic acids (and other disinfection byproducts)

Metalworking fluids

Cannabis smoking, fertility treatment, glucocorticoids, *Salmonella typhi*, sedentary behaviour*, tetracyclines and other photosensitising drugs

Cupferron, gasoline oxygenated additives, gentian violet, glycidamide, malachite green and leucomalachite green, oxymetholone, pentabromodiphenyl ethers, vindaolin

Breast implants, dietary salt intake*, neonatal phototherapy*, poor oral hygiene*

Aspartame

Arcoline, carbon disulphide, electronic nicotine delivery systems and nicotine*, human cytomegalovirus, parabens

Agents previously evaluated by IARC Monographs†

Automotive gasoline (leaded and unleaded), carbaryl, malaria

Acrylamide*, acrylonitrile, some anthracyclines, coal dust, combustion of biomass, domestic talc products, firefighting exposure, metallic nickel, some pyrethroids (ie, permethrin, cypermethrin, deltamethrin)

Aniline, acrolein, methyl eugenol and isoeugenol*, multi-walled carbon nanotubes*, non-ionising radiation (radiofrequency)*, some perfluorinated compounds (eg, perfluorooctanoic acid)

Oestrogen: oestradiol and oestrogen-progestogens‡, hydrochlorothiazide, Merkel cell polyomavirus, perchloroethylene, very hot foods and beverages

1,1,1-trichloroethane, weapons-grade alloy (tungsten, nickel, and cobalt)

Acetaldehyde, bisphenol A*, cobalt and cobalt compounds, crotonaldehyde, cyclophosphamide, cyanotoxins, fumonisin B₁, inorganic lead compounds, isoprene, o-anisidine

Rationale

Relevant human cancer, bioassay, and mechanistic evidence

Relevant human cancer and bioassay evidence

Relevant human cancer and mechanistic evidence

Relevant bioassay and mechanistic evidence

Relevant human cancer evidence

Relevant bioassay evidence

Relevant mechanistic evidence

New human cancer, bioassay, and mechanistic evidence to warrant re-evaluation of the classification

New human cancer and mechanistic evidence to warrant re-evaluation of the classification

New bioassay and mechanistic evidence to warrant re-evaluation of the classification

New human cancer evidence to warrant re-evaluation of the classification

New bioassay evidence to warrant re-evaluation of the classification

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[§]).

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

Centre international de Recherche



Organisation mondiale de la Santé

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International Agency for Research on Cancer



Thank you! Merci!

<http://www.iarc.fr>

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