Understanding Chemical and Mechanistic Classes: IARC Approach

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Overview

- Chemical class defined by a single, common agent
- Mechanistic class defined by similar biologic activity
- Mechanistic data alone as the basis for classification

IARC's overall evaluation integrates human, animal, and mechanistic evidence

Evidence in humans

Evidence in animals

Mechanistic evidence

Overall evaluation

- ☐ Group 1 — *Carcinogenic to humans*
- ☐ Group 2A — *Probably carcinogenic to humans*
- ☐ Group 2B — *Possibly carcinogenic to humans*
- ☐ Group 3 — *Not classifiable*

Note: *IARC recognizes, but does not evaluate, differences in potency*

Multiple forms of a single, common agent can define a chemical class

Arsenic & inorganic compounds
Beryllium & compounds
Cadmium & compounds
Chromium(VI) compounds

Nickel compounds
Inorganic lead compounds
Methylmercury compounds
Nitrilotriacetic acid and salts

Dyes metabolized to benzidine
Internally deposited alpha-particle-emitting radionuclides
Internally deposited beta-particle-emitting radionuclides

Most health agencies do this

Biological understanding defines what lies outside the chemical class

Arsenic & inorganic compounds	NOT organic compounds
Beryllium & compounds	
Cadmium & compounds	
Chromium(VI) compounds	NOT chromium(III) compounds
Nickel compounds	NOT nickel metal, nickel alloys
Inorganic lead compounds	NOT organic compounds
Methylmercury compounds	NOT mercury & inorganic compounds
Nitrilotriacetic acid and salts	
Dyes metabolized to benzidine	
Internally deposited alpha-emitters	
Internally deposited beta-emitters	

Most health agencies do this

Dyes metabolized to benzidine
(vol 100F, 2012)

Classification: *carcinogenic to humans* (Group 1)

Common agent: benzidine

Rationale

- *Sufficient evidence* in humans and in experimental animals for the carcinogenicity of benzidine
- Metabolism of benzidine-based dyes results in the release of free benzidine and the induction of chromosomal aberrations in humans and in all experimental animal species studied
- Strong mechanistic evidence that benzidine-based dyes are converted by azo-reduction to benzidine in humans and in experimental animals
- Production of DNA adducts and genotoxic effects similar to those of benzidine

Internalized radionuclides that emit alpha-particles (vol 100D, 2012)

Classification: *carcinogenic to humans* (Group 1)

Common agent: alpha-particles

Rationale

- alpha-particles, irrespective of source, produce the same pattern of secondary ionizations and localized damage to biological molecules, including DNA
- All alpha-particle emitters that have been adequately studied cause cancer in humans and in experimental animals
- alpha-particles, irrespective of source, cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans in vivo
- Similar doses to the same tissues produce the same types of neoplasms and non-neoplastic effects

alpha-Particle emitters also classified as *carcinogenic to humans*

- Rn-222 and its decay products
- Ra-224, Ra-226, Ra-228, Th-232, Pu-239
- Underground hematite mining with exposure to radon

Similar biologic activity can define a mechanistic class

2019 Preamble:

Group 2A (*probably carcinogenic to humans*) "generally applies if there is *strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.*"

2006 Preamble:

"An agent may be assigned to [Group 2A] if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A."

Vinyl halides (vol 97, 2008)

Classifications

- Vinyl bromide: *Probably carcinogenic to humans* (Group 2A)
- Vinyl fluoride: *Probably carcinogenic to humans* (Group 2A)

Analogy: Vinyl chloride, *carcinogenic to humans* (Group 1, vol 97, 2008)

Rationale

- All available studies show a consistently parallel response
- These compounds are activated via a human cytochrome P450 2E1-dependent pathway to their corresponding epoxides
- The covalent binding of these compounds to nucleosides/DNA yields pro-mutagenic etheno adducts
- Positive evidence in studies of genotoxicity, although the number and variety of tests for vinyl bromide/fluoride are fewer

Conclusion: For practical purposes, vinyl bromide/fluoride should be considered to act similarly to the human carcinogen, vinyl chloride

2,3,4,7,8-PeCDF, PCB-126 (vol 100F, 2012)

Classifications

- 2,3,4,7,8-PeCDF: *carcinogenic to humans* (Group 1)
- PCB-126: *carcinogenic to humans* (Group 1)

Analogy: 2,3,7,8-TCDD, *carcinogenic to humans* (Group 1, vol 100F, 2012)

Rationale: similarity to 2,3,7,8-TCDD

- Strong evidence to support a receptor-mediated mechanism for carcinogenesis
- Evidence of carcinogenicity in experimental animals
- Extensive evidence showing activity identical to 2,3,7,8-TCDD for every step of the mechanism described for TCDD-associated carcinogenesis in humans, including:
  - — receptor binding,
  - — gene expression,
  - — protein-activity changes,
  - — cellular replication,
  - — oxidative stress,
  - — promotion in initiation-promotion studies
  - — complete carcinogenesis in animals

Dioxin-like PCBs (vol 107, 2016)

Classifications: Dioxin-like PCBs (those with a WHO-TEF), *carcinogenic to humans* (Group 1)

Analogy: 2,3,7,8-TCDD, *carcinogenic to humans* (Group 1, vol 100F, 2012)

Rationale: similarity to 2,3,7,8-TCDD

- Strong evidence to support a receptor-mediated mechanism for carcinogenesis
- Carcinogenicity in experimental animals for PCB-126 and PCB-118
- Extensive proof of activity identical to 2,3,7,8-TCDD for every step of the mechanism described for TCDD-associated carcinogenesis in humans, including: — receptor binding,
  — gene expression,
  — protein-activity changes,
  — cellular replication,
  — oxidative stress,
  — promotion in initiation-promotion studies
  — complete carcinogenesis in experimental animals

Polybrominated biphenyls (vol 107, 2016)

Classification: *Probably carcinogenic to humans* (Group 2A)

Analogy: Polychlorinated biphenyls, *carcinogenic to humans* (Group 1)

Rationale: mechanistic similarities to PCBs

- PBBs share several chemical and physical characteristics with PCBs
- PBBs are potent, efficacious inducers of xenobiotic-metabolizing enzymes
- PBB congeners inhibit cell-cell communication or metabolic cooperation
- PBB-77, PBB-153, PBB-169 are weak initiators and efficacious promoters of two-stage hepatocarcinogenesis
- Individual PBBs are ligands for several cellular and nuclear receptors
- In acute studies, pathological and biochemical changes in the liver and thymus
- In long-term studies, microscopic changes in rodent liver and in thyroid glands
- Reduced immunocompetence in rodents, birds, cattle, swine and humans
- Perinatal exposure of rats diminished the effect of estradiol on uterine weight and uterine RNA content; PBBs increased the hepatic microsomal metabolism of estradiol, estrone and ethynylestradiol *in vitro*

Human papillomavirus types 30, 34, 69, 85, 97 (vol 100B, 2012)

Classification: *Possibly carcinogenic to humans* (Group 2B)

Analogy

- HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, *carcinogenic to humans* (Group 1)
- HPY type 68, probably carcinogenic to humans (Group 2A)
- HPV types 26, 53, 66, 67, 70, 73, 82, *possibly carcinogenic to humans* (Group 2B)

Rationale: phylogenetic analogy to HPV types with *sufficient* or *limited evidence* in humans

- *Inadequate evidence* in humans
- Based on their phylogenetic analogy to HPV types with sufficient or limited evidence in humans

Mechanistic data alone can be the basis for classification

1999: "In the absence of data from conventional long-term bioassays of carcinogenesis or from assays with neoplasia as the end-point, consistently positive results in several models addressing several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals."

2006: "An agent may be classified in [Group 2B, *possibly carcinogenic to humans*] solely on the basis of strong evidence from mechanistic and other relevant data."

2019: [Group 2B] "may be based on strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens."

IARC (1999) The Use of Short- and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation, Consensus Report, IARC Scientific Publication 146
IARC (2006) Preamble to the IARC Monographs, https://monographs.iarc.fr/previous-preamble/
IARC (2019) Preamble to the IARC Monographs, https://monographs.iarc.fr/preamble-to-the-iarc-monographs/

IARC has long sought to use mechanistic events to identify carcinogens

First known presentation of this idea in 2009

Table 3
Carcinogens operate via multiple key events representing diverse modes of action for carcinogenesis[a].

	Key events															
	DNA reactivity/ covalent binding	Gene mutations	Chromosomal breakage	Aneuploidy	Enzyme-mediated DNA damage/ repair	Epigenetic	Cell Signaling: Nuclear receptor-mediated	Cell Signaling: other	Immune response modulation	Inflammation	Cytotoxicity/ compensatory cell proliferation	Mitogenicity	Chronic metabolic or physiologic overload	Nutrient deficiency related	Interference with GJIC	Other
IARC Group 1																
Aflatoxin B1	+	+	+	–	+	+	–	–	+	+	+	–	+	–	+	
Arsenic +3	–		+	+	+	+	+	+	+	+	+	+	–	+	+	
Asbestos	+	+	+	–		+		+	+	+						
Benzene	+	+	+	+	+	+		+	+	+	+	–	–	–	+	
DES	+	–	+	+	–	+	+	+	+		–	+	+		+	
Formaldehyde	+	+	+	+	+			+	+	+	+					
TCDD, 2,3,7,8-	–	–	–	–	–	–	+	–	+	–	+	–	–	–	+	+
Vinyl chloride	+	+	+	–	+	–	–	–	–	+		–		+	+	
IARC Group 2A																
Acrylamide	+	+	+	+							–	–	–	–		+
PCBs	+	–	+	–	+		+	+	+	+		–	+		+	
Model Carcinogen																
Diethylnitrosourea	+	+	–	–	–		–	–			–	–	–	–		
Non-Carcinogen																
Toluene			+												+	
Acetaminophen	–	–	+	+	+			+		+	+		+		–	

[a] Blank entry indicates no information, equivocal or conflicting information; +, evidence for; –, evidence against. Classification requires scientific judgment; differences of scientific opinion about individual entries were noted in the literature.

Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, Keshava N, Sandy MS, Sonawane B, Zhang L, Waters MD, Smith MT (2009) Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches. *Mutation Research* 681: 230–240

Database on mechanistic events and key characteristics of human carcinogens

IARC Monographs
Volume 100

2008-09: New *Monographs* on the >100 human carcinogens
— Tumour sites in humans and animals
— Established and likely mechanistic events

2012: Workshops to synthesize this mechanistic information
The key characteristics came out of these workshops

Key characteristics of carcinogens
1. 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

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) *Environmental Health Perspectives* 124(6): 713–721

IARC continues to use mechanistic data in hazard identification

Table 3.

Summary of mechanistic evaluations in IARC Monograph Meetings 112–119

Agent	Group	Cancer in humans	Cancer in animals	Number of Studies (All KCs)	KC 1	KC 2	KC 3	KC 4	KC 5	KC 6	KC 7	KC 8	KC 9	KC 10
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[a]										
Malathion	2A	Limited	Sufficient	249		X			X	X		X		X
Hydrazine	2A	Limited	Sufficient	117	X	X			X					X
DDT	2A	Limited	Sufficient	745					X		X	X		
N,N-DMF	2A	Limited	Sufficient	170	X				X					X
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[a]										
Dieldrin and aldrin metabolized to dieldrin	2A	Limited	Sufficient	237										
Very hot beverages	2A	Limited	Sufficient	30[b]										
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										

X represents strong evidence; Bold indicates agent upgraded from Group 2B to Group 2A.

[a]Number of studies applies to red and processed meat; for red meat, there was strong mechanistic evidence for meat components.

[b]Applies to mate and hot beverages.

[c]Antioxidant effects.

Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, Christiani DC, Beland FA, Smith MT (2018) Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis* 39(4): 614–622

In Review

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- Mechanistic class defined by similar biologic activity
- Mechanistic data alone as the basis for classification

Merci de votre attention !