Mechanistic Data Can Play a Pivotal Role in *IARC Monographs* Evaluations When Human Data Are Less Than *Sufficient*

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Overview of Evaluation Process

Integrating Epidemiology, Animal Bioassay, and Mechanistic Evidence

Categorize each stream of evidence using defined terms

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data
• *Sufficient evidence* • *Limited evidence* • *Inadequate evidence*	• *Sufficient evidence* • *Limited evidence* • *Inadequate evidence*	• "strong", "limited", or "inadequate"? • Operative in humans?

Integrate findings in overall evaluations

Overall evaluation

- Group 1 Carcinogenic to humans (119)
- Group 2A Probably carcinogenic to humans (81)
- Group 2B Possibly carcinogenic to humans (292)
- Group 3 Not classifiable as to its carcinogenicity to humans (505)
- Group 4 Probably not carcinogenic to humans (1)

10 "Key Characteristics" of Carcinogens[a]

Key characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with electrophilic structure (e.g. epoxide, quinone, etc.), DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosomal aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g. DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g. ER, PPAR, AhR) or modulation of exogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

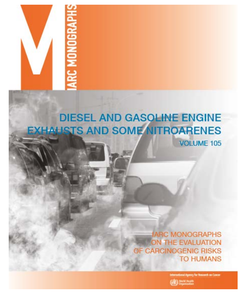
Evaluating Mechanistic Evidence[b]

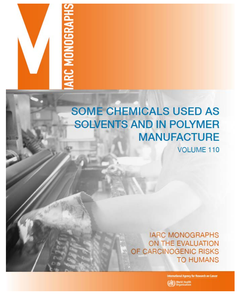
Are the mechanistic data "strong", "limited", or "inadequate"?	• Results in several different experimental systems are consistent • The overall mechanistic database is coherent • Experiments showing that suppression of key mechanistic processes suppresses tumour development can be influential • Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species
"Strong" evidence	• The agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans OR • The agent exhibits key characteristics of carcinogens in exposed humans, in human primary cells or tissue, or in experimental systems OR • The mechanism of carcinogenicity in experimental animals does not operate in humans

Integration of Stream of Evidence in Reaching Overall Classification

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans[a*]	Evidence of cancer in experimental animals	Mechanistic evidence	
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)	
Inadequate	***Sufficient***	***Strong (does not operate in humans)[b*]***	**Not classifiable (Group 3)**
All other situations not listed above			

The evidence in ***bold italic*** represents the basis of the overall evaluation.
[a*] Human cancer(s) with highest evaluation
[b*] The *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* must specifically be for the tumour sites supporting the classification of *sufficient evidence in experimental animals*.





Examples of *IARC Monographs* Classifications Based on Mechanistic Evidence

Agent	Human evidence	Animal evidence	Mechanistic evidence/ key characteristics	Eval.	Publication date Vol.
Simian virus (SV)40	Inadequate	Sufficient	No persuasive evidence that the mechanism of transformation in rodents is operative in humans	**3**	2014 Vol. 104
1-Nitropyrene	Inadequate	Sufficient	Is genotoxic, induces oxidative stress (1,5)	**2A**	2014 Vol. 105
1,3-Propane sultone	Inadequate	Sufficient	Is genotoxic (2)	**2A**	2017 Vol. 110
Tetrabromobisphenol A	Inadequate	Sufficient	Modulates receptor-mediated effects, induces oxidative stress, is immunosuppressive (5, 7, 8)	**2A**	2018 Vol. 115
3,3′,4,4′-Tetrachloro-azobenzene	Inadequate	Sufficient	Belongs to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans	**2A**	2019 Vol. 117
1-*tert*-Butoxypropan-2-ol, β-Myrcene, Pyridine, Tetrahydrofuran	Inadequate	Sufficient	Increased chronic α_{2u}-globulin nephropathy (human relevance could not be ruled out because criteria for α_{2u}-globulin-associated response were not met)*[c]	**2B**	2019 Vol. 119
Ethyl acrylate	Inadequate	Sufficient	Forestomach tumors (human relevance could not be ruled out because genotoxic activity was observed (6, 10))[d]	**2B**	In prep. Vol. 122

*Several of the seven criteria established by IARC for considering the induction of kidney tumours to occur by an α_{2u}-globulin-associated response have not been met.

References
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[a]Smith MT et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Env Health Persp.* 124(6):713–21.
[b]Preamble to the *IARC Monographs* (2019). https://monographs.iarc.fr/preamble-to-the-iarc-monographs/
[c]Capen CC et al. (1999). Species differences in thyroid, kidney and urinary bladder carcinogenesis. IARC Scientific Publication No. 147. Available from: http://publications.iarc.fr/302 PMID:10627184
[d]IARC (2003). Predictive value of rodent forestomach and gastric neuroendocrine tumours in evaluating carcinogenic risks to humans. IARC Technical Publication No. 39. Available from: https://monographs.iarc.fr/iarc-technical-publications-related-to-iarc-monographs-evaluations/

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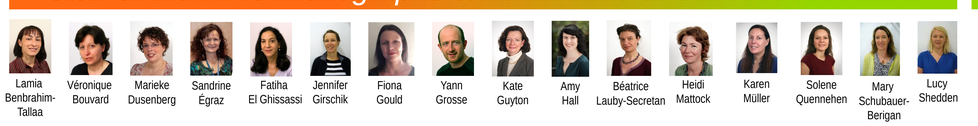
Staff of the *IARC Monographs & Handbooks of Cancer Prevention*



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