



# IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Hierarchy of evidence, University of Kent, 6 Sept 2012

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The *IARC Monographs* are a series of scientific reviews that identify **environmental factors** that can increase the risk of cancer in humans.

Oldest ongoing program of hazard identification, since 1971 more than 900 agents have been evaluated.

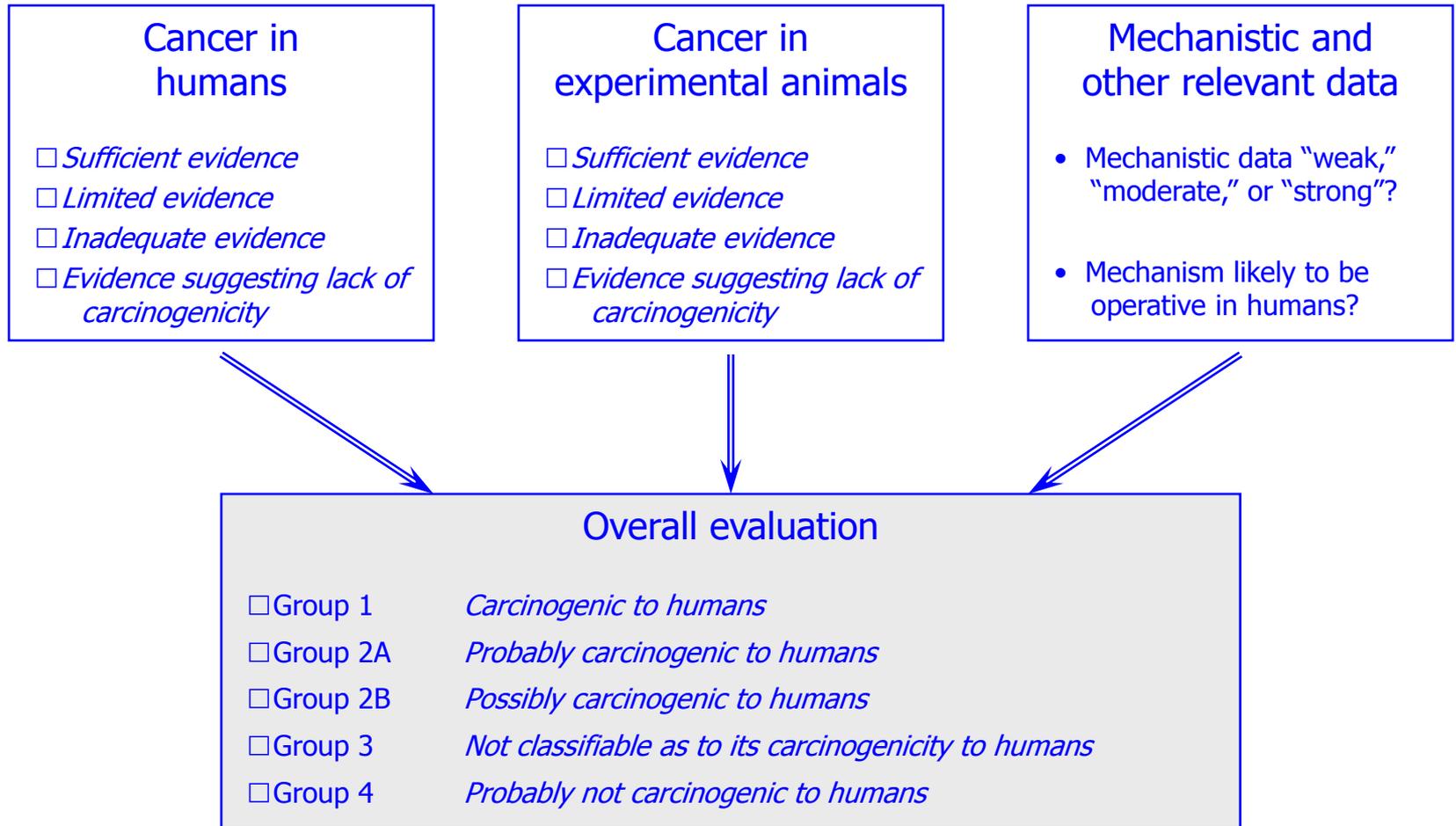
# Evolution of criteria for weight of evidence evaluation in IARC Monographs

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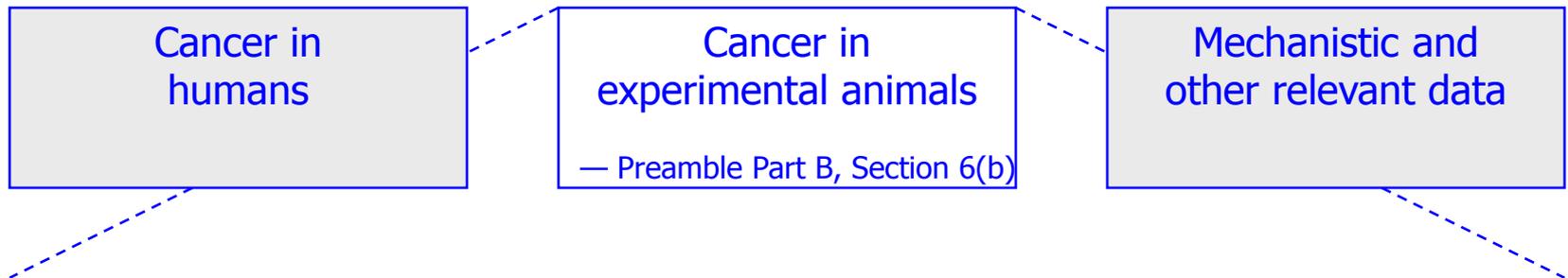
Vol 1, 1971	Evaluation of strength of evidence for carcinogenicity (hazard, not potency)
Vol 17, 1977	Use of standard terms for separate evaluation of human and animal evidence, free wording of overall evaluation
Suppl 1, 1979 (Vol 1-20)	Defined groups for overall evaluation (1, 2 high or low, 3); Annex: listing of target organs
Suppl 4, 1982 (Vol 1- 29)	Results from short-term test used for up-grade Group 1, 2A, 2B, 3
Suppl 7, 1987	Overall evaluation Vol 1-42, Group 4 (probably not carcinogenic to humans)
Vol 43, 1987 Vol 54, 1991	Concurrent overall evaluation Allow data on mechanisms for up/downgrade

# Subgroup work

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# Evaluating experimental animal data



## *Sufficient evidence*

Causal relationship has been established through either:

- Multiple positive results (2 species, studies, sexes of GLP)
- Single unusual result (incidence, site/type, age, multi-site)

## *Limited evidence*

Data suggest a carcinogenic effect but: (*e.g.*) single study, benign tumours only, promoting activity only

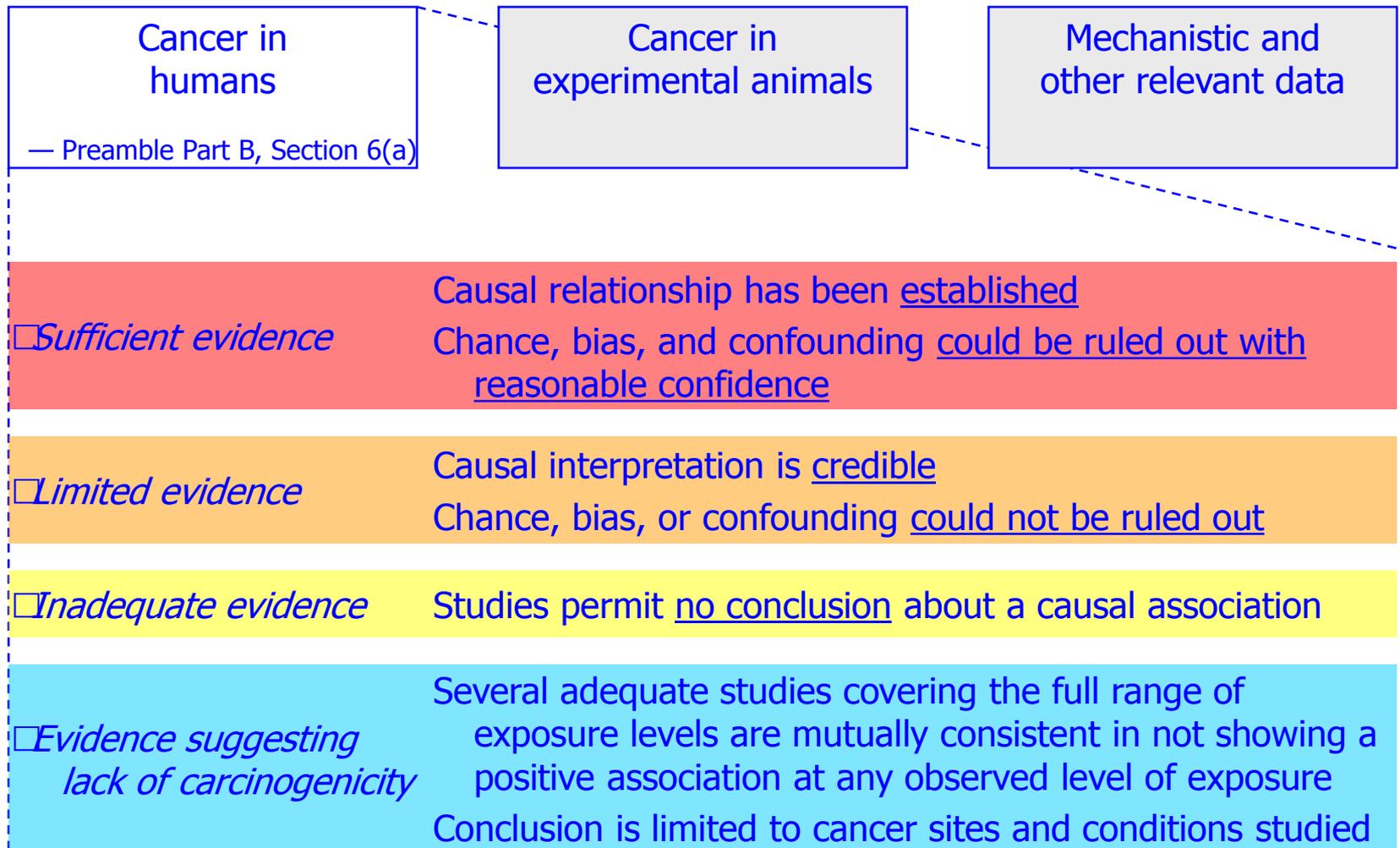
## *Inadequate evidence*

Studies permit no conclusion about a carcinogenic effect

## *Evidence suggesting lack of carcinogenicity*

Adequate studies in at least two species show that the agent is not carcinogenic  
Conclusion is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied

# Evaluating human data



# Hierarchy in epidemiological studies ?

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- RCT, e.g. HBV vaccination studies
  - Contamination of non-treated group
- Analytical epidemiology;  
(including molecular epidemiology)
  - cohort studies
  - case-control studies
- Ecological studies, eg Arsenic in drinking water
- Case series, ege Aristolochic acid and kidney cancer

# Evaluating mechanistic and other data



- Are the mechanistic data “weak,” “moderate,” or “strong”?

Have the mechanistic events been established? Are there consistent results in different experimental systems? Is the overall database coherent?

Has each mechanism been challenged experimentally? Do studies demonstrate that suppression of key mechanistic processes leads to suppression of tumour development?

- Is the mechanism likely to be operative in humans?

Are there alternative explanations? Could different mechanisms operate in different dose ranges, in humans and experimental animals, or in a susceptible group?

Note: an uneven level of support for different mechanisms may reflect only the resources focused on each one

# The plenary sessions combine the human and experimental evaluations

		EVIDENCE IN EXPERIMENTAL ANIMALS			
		<i>Sufficient</i>	<i>Limited</i>	<i>Inadequate</i>	<i>ESLC</i>
EVIDENCE IN HUMANS	<i>Sufficient</i>	Group 1 ( <i>carcinogenic to humans</i> )			
	<i>Limited</i>	Group 2A ( <i>probably carcinogenic</i> )	Group 2B ( <i>possibly carcinogenic</i> ) (exceptionally, Group 2A)		
	<i>Inadequate</i>	Group 2B ( <i>possibly carcinogenic</i> )	Group 3 ( <i>not classifiable</i> )		
	<i>ESLC</i>				Group 4

# Mechanistic data can be pivotal when the human data are not conclusive

		EVIDENCE IN EXPERIMENTAL ANIMALS			
		<i>Sufficient</i>	<i>Limited</i>	<i>Inadequate</i>	<i>ESLC</i>
EVIDENCE IN HUMANS	<i>Sufficient</i>	Group 1			
	<i>Limited</i>	↑ <u>1 strong evidence in exposed humans</u> Group 2A	↑ <u>2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A</u> Group 2B (exceptionally, Group 2A)		
	<i>Inadequate</i>	↑ <u>1 strong evidence in exposed humans</u> ↑ <u>2A strong evidence ... mechanism also operates in humans</u> Group 2B	↑ <u>2A belongs to a mechanistic class</u> ↑ <u>2B with supporting evidence from mechanistic and other relevant data</u> Group 3	↑ <u>2A belongs to a mechanistic class</u> ↑ <u>2B with strong evidence from mechanistic and other relevant data</u> Group 3	Group 3 ↓ <u>4 consistently and strongly supported by a broad range of mechanistic and other relevant data</u>
	<i>ESLC</i>		Group 3		Group 4

# Volume 100 compiled information for subsequent scientific publications

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## *Tumour (Site) Concordance between Humans and Animals*

- Increase understanding of the correspondence across species
- Identify human cancer sites without good animal models

## *Mechanisms Involved in Human Carcinogenesis*

- Organized by mechanism to facilitate joint consideration of agents that act through similar mechanisms
- Identify biomarkers that could be influential in future studies
- Identify susceptible populations and developmental stages
- Promote research that will lead to more confident evaluations