

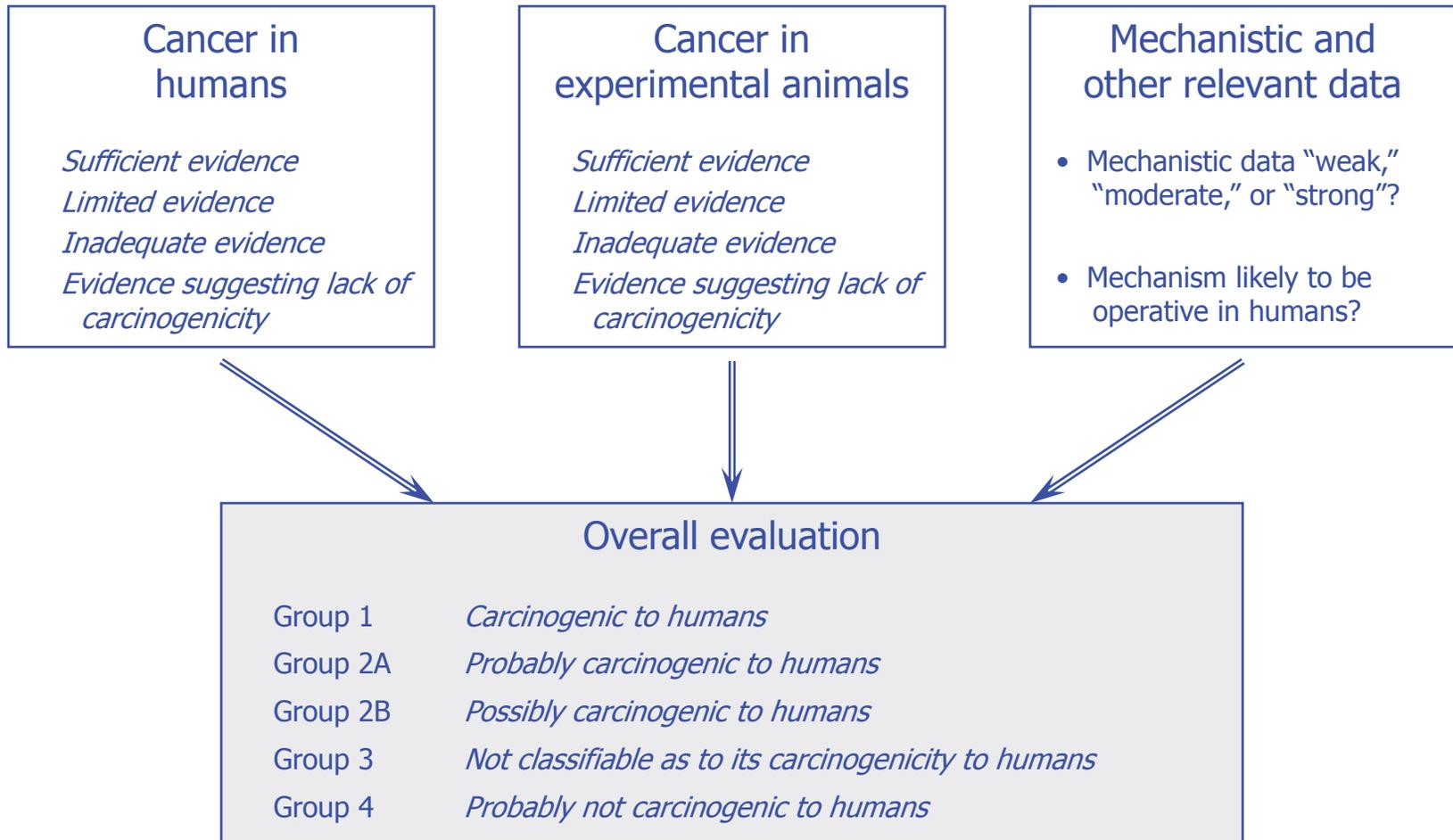


IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

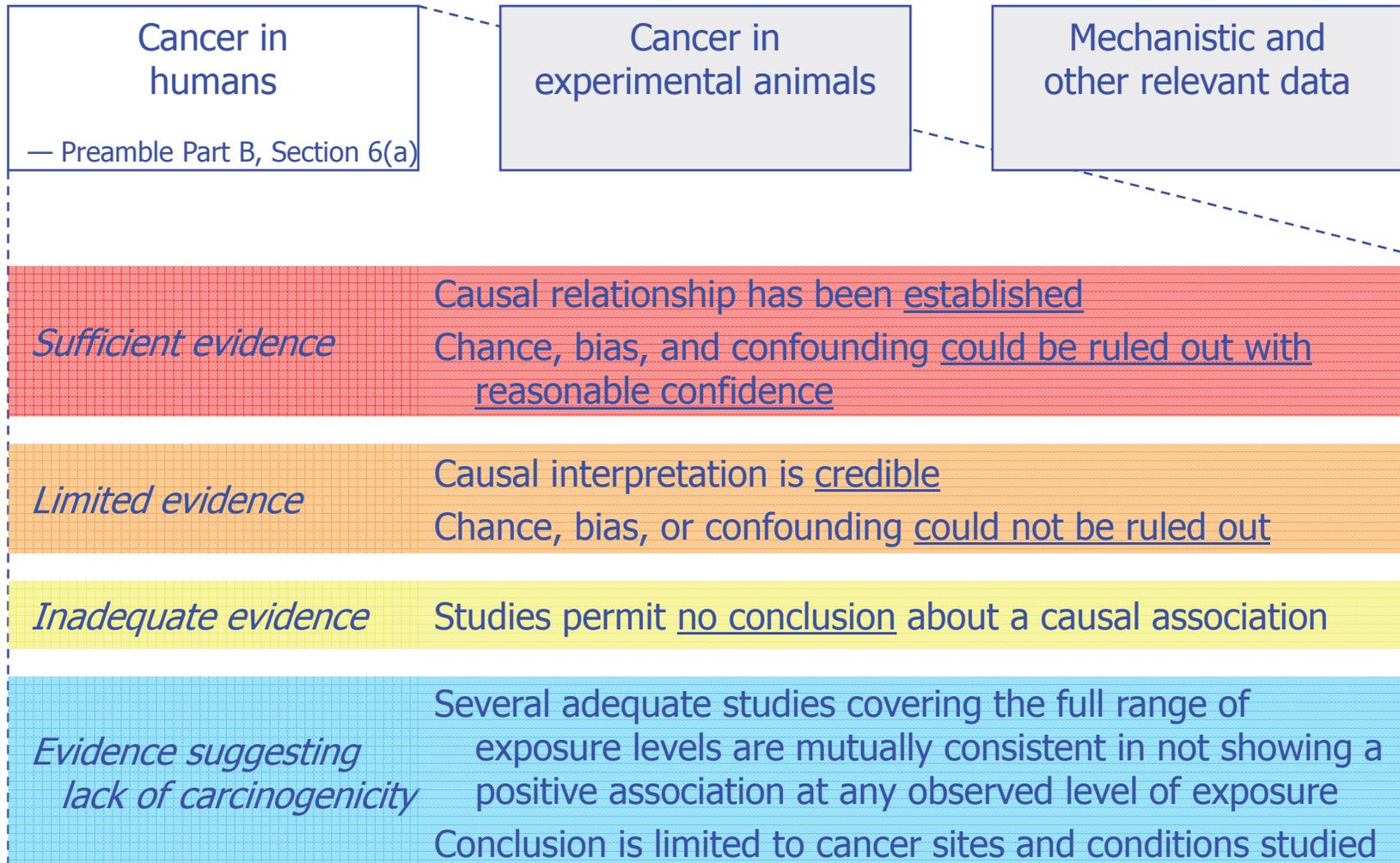
IARC Monograph Evaluations

International Agency for Research on Cancer
Lyon, France

Subgroup work



Evaluating human data (Subgroup 2)



Identifying human tumour sites

Sufficient evidence

- There is *sufficient evidence* in humans for the carcinogenicity of tobacco smoking. Tobacco smoking causes cancer of the lung, oral cavity, naso-, oro- and hypopharynx,...

Sufficient evidence and ESLC

- There is *sufficient evidence* in humans for the carcinogenicity of tamoxifen. Tamoxifen causes cancer of the endometrium. An inverse relationship has been established between exposure to tamoxifen and cancer of the female breast.

Limited evidence

- There is *limited evidence* in humans for the carcinogenicity of Ethylene Oxide. A positive association has been observed between exposure to Ethylene Oxide and cancers of the breast and lymphatic and haematopoietic malignancies.

Evaluating experimental animal data (Subgroup 3)



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

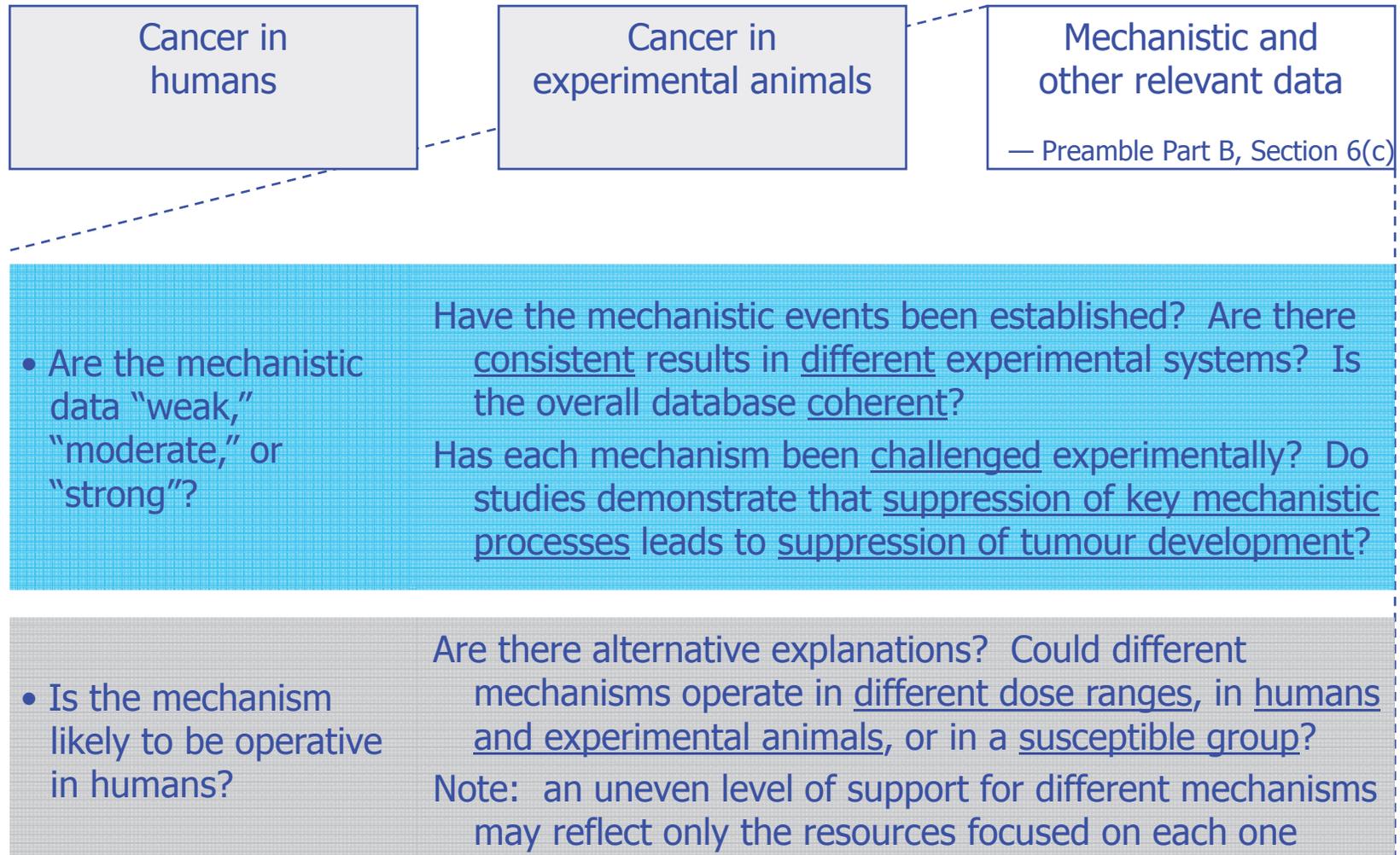
Adequate studies in at least two species show that the agent is not carcinogenic
Conclusion is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied

Identifying animal tumour sites

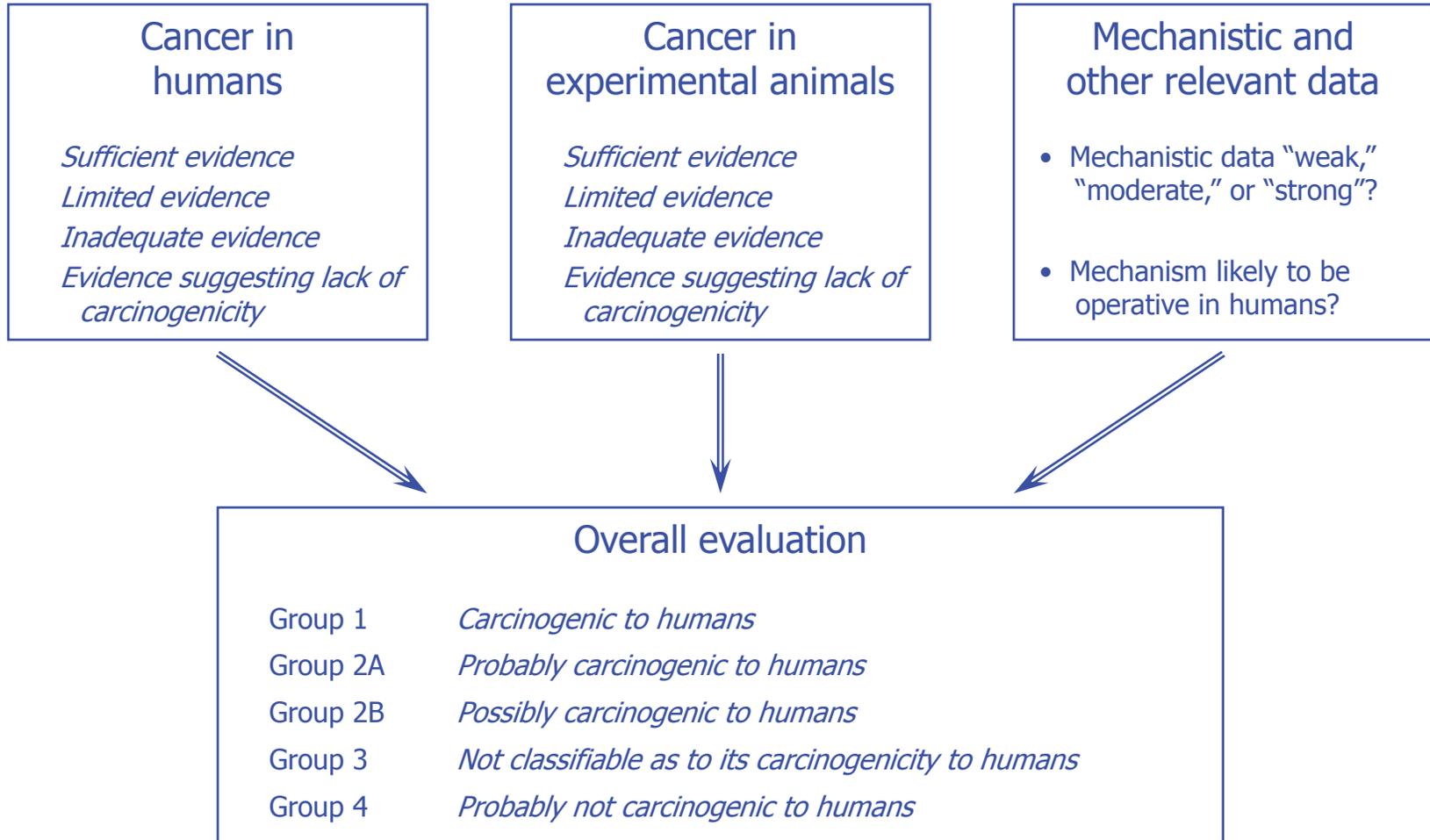
- The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms originating from the same organ in two or more independent studies in **one species** carried out at different times or in different laboratories or under different protocols.
- An increased incidence of tumours originating from the same organ in **both sexes of a single species** in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.
- A single study in one species and sex might be considered to provide sufficient evidence to identify tumour sites when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset

Applying these criteria for the evaluation of carcinogenicity to a species and target site-specific level, the WG identifies sites established as causally related.

Evaluating mechanistic and other data (Subgroup 4)



Plenary session



The plenary sessions will 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>	↓ <u>3 strong evidence ... mechanism does not operate in humans</u>	Group 3		Group 4

Diesel engine exhaust (V 105)

The Working Group concluded that there was “sufficient evidence” in humans for the carcinogenicity of diesel-engine exhaust.

“sufficient evidence” in experimental animals for the carcinogenicity of whole diesel-engine exhaust, of diesel-engine exhaust particles and of extracts of diesel-engine exhaust particles.

“strong evidence” for the ability of whole diesel-engine exhaust to induce cancer in humans through genotoxicity.

Overall evaluation

Diesel engine exhaust is carcinogenic to humans (Group 1)

Polychlorinated biphenyls (V 107)

The Working Group concluded that there was “sufficient evidence” in humans for the carcinogenicity of polychlorinated biphenyls.

“sufficient evidence” in experimental animals for the carcinogenicity of PCB126, PCB118, Aroclor 1260, Aroclor 1254, and Kanechlor 500.

Strong evidence of an AhR-mediated mechanism of carcinogenesis identical to that of 2,3,7,8-TCDD.

Overall evaluation

Polychlorinated biphenyls are carcinogenic to humans (Group 1)
Dioxin-like polychlorinated biphenyls are carcinogenic to humans (Group 1).

Shift-work, Overall Evaluation Vol. 98

6.1 Cancer in humans

- There is *limited evidence* in humans for the carcinogenicity of shiftwork that involves night work.

6.2 Cancer in experimental animals

- There is *sufficient evidence* in experimental animals for the carcinogenicity of light during the daily dark period (biological night).

6.3 Overall evaluation

- Shiftwork that involves circadian disruption is *probably carcinogenic to humans (Group 2A)*

Arsenic, Vol 84, Section 3

There is *limited evidence* in experimental animals for the carcinogenicity of sodium arsenite, calcium arsenate and arsenic trioxide.

There is *inadequate evidence* in experimental animals for the carcinogenicity of sodium arsenate and arsenic trisulfide.

Taken together, the studies on inorganic arsenic provide *limited evidence* for carcinogenicity in experimental animals.

Lead, Vol. 97, Section 3

There is *sufficient evidence* in experimental animals for the carcinogenicity of lead acetate, lead subacetate, lead chromate, and lead phosphate.

There is *inadequate evidence* in experimental animals for the carcinogenicity of lead oxide and lead arsenate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic lead compounds.

“The categorization of an agent is a matter of scientific judgement . . .”

“It is recognized that the criteria for these evaluations cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.”

“These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency).”

— Preamble Part B, Section 6

“The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.”

— Preamble Part A, Section 2

You may apply an evaluation to a broad grouping of agents or to one specific agent

“When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of degree of evidence.”

— Preamble Part B, Section 6

“In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents . . .”

— Preamble Part B, Section 6(d)

“When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.”

— Preamble Part B, Section 6(a)

Guidance can be found in the Preamble

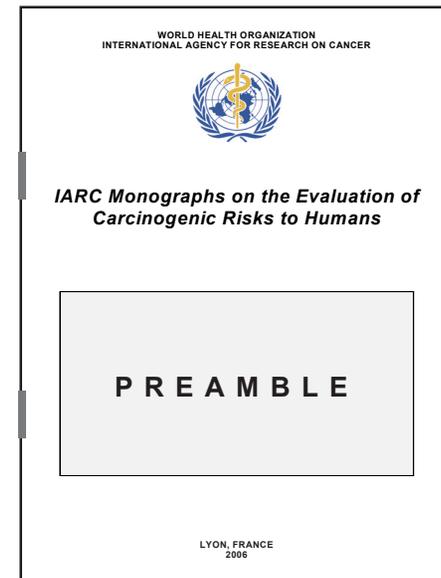
“The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered, and the scientific criteria that guide the evaluations.”

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background
2. Objective and scope
3. Selection of agents for review
4. Data for the *Monographs*
5. Meeting participants
6. Working procedures

B. SCIENTIFIC REVIEW AND EVALUATION

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale



The text should present the Working Group's reasoning

Concise statements of the principal line(s) of argument that emerge

Conclusions of the Working Group on the strength of the evidence for each group of studies

Citations to indicate which studies were pivotal to these conclusions

Explanation of the reasoning of the Working Group in weighing data and making evaluations

— Preamble Part B, Section 6(e)

Plenary session

