Evidence Integration in the IARC Monographs

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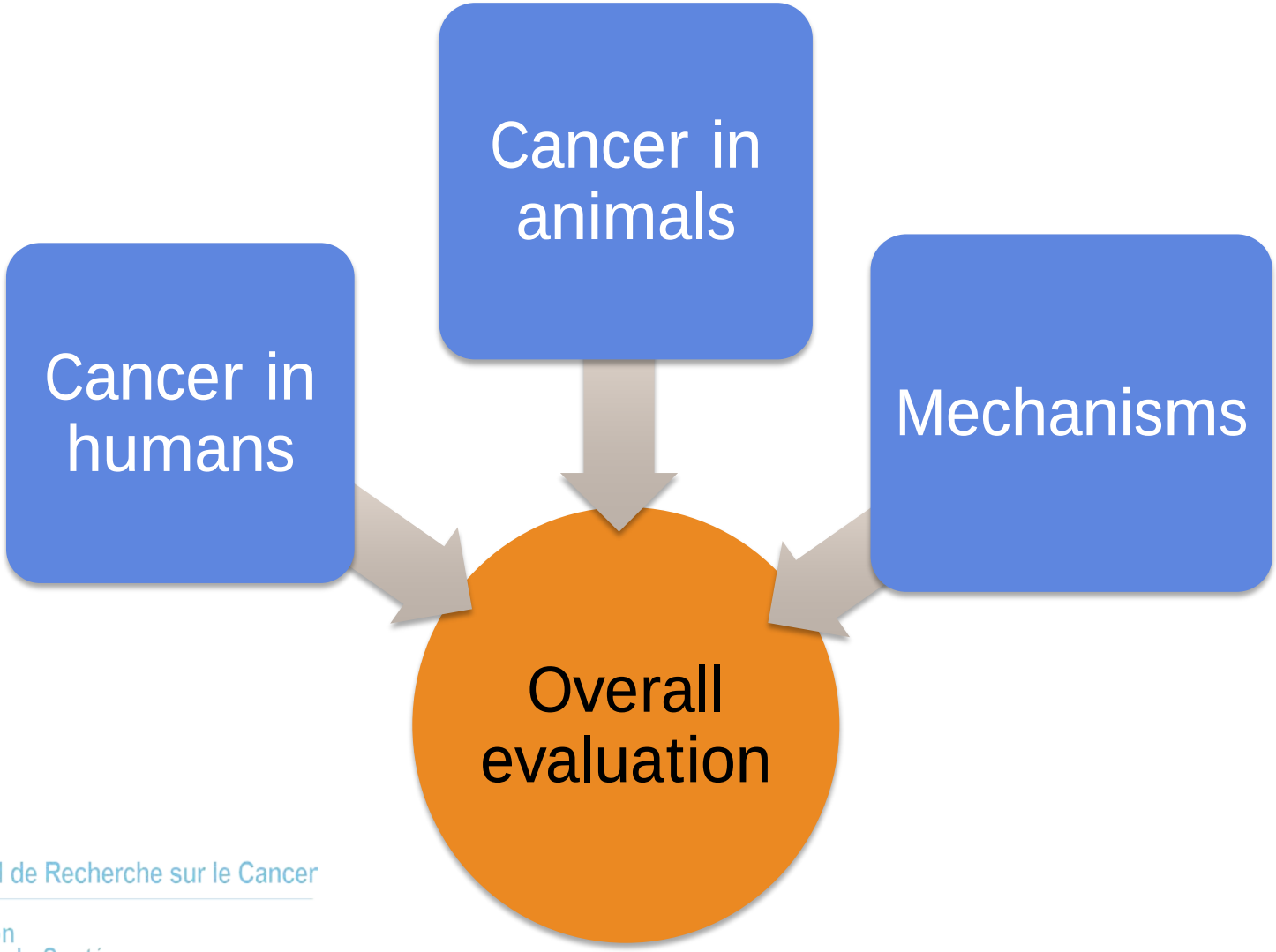
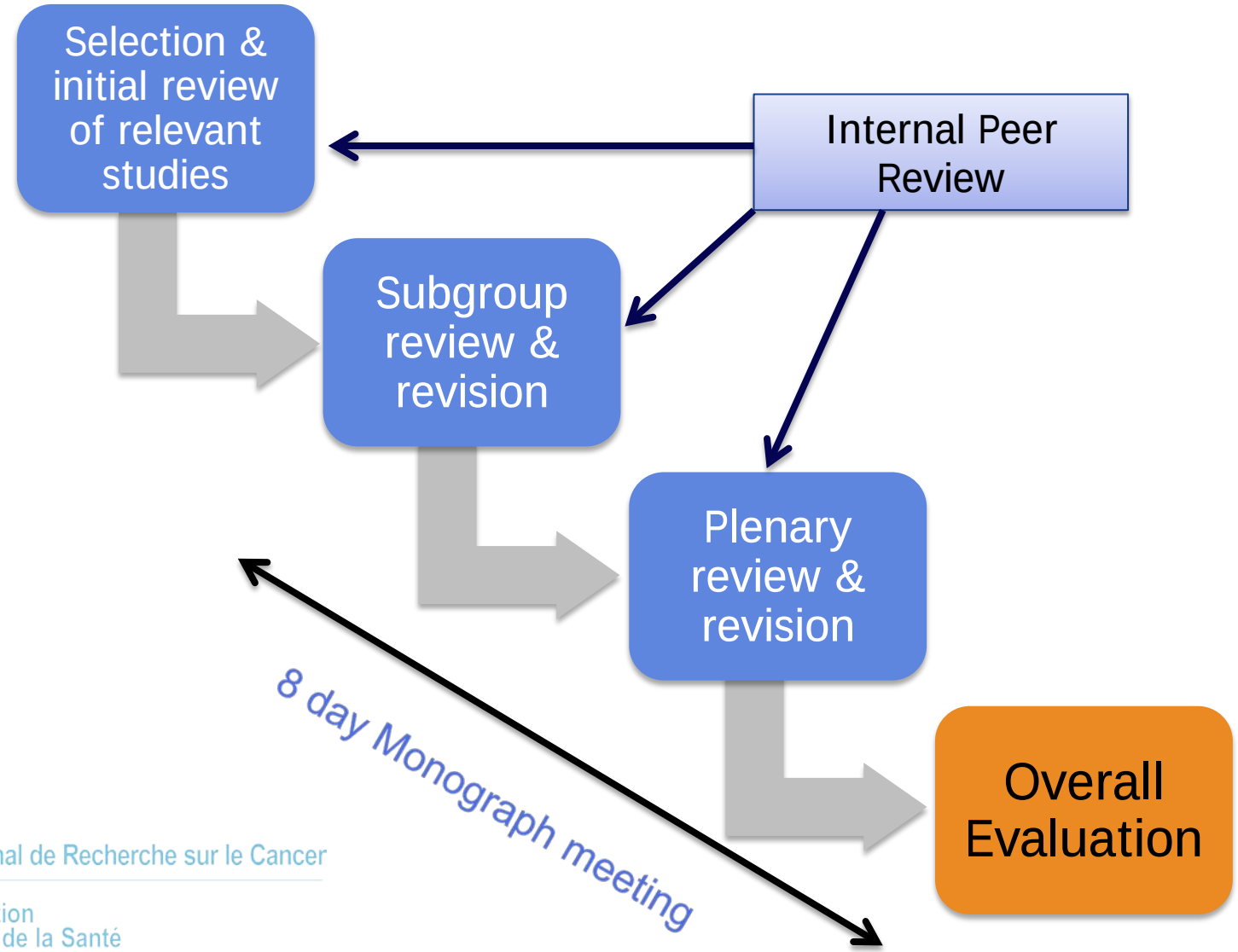
Cancer Hazard Assessment based on 3 lines of evidence



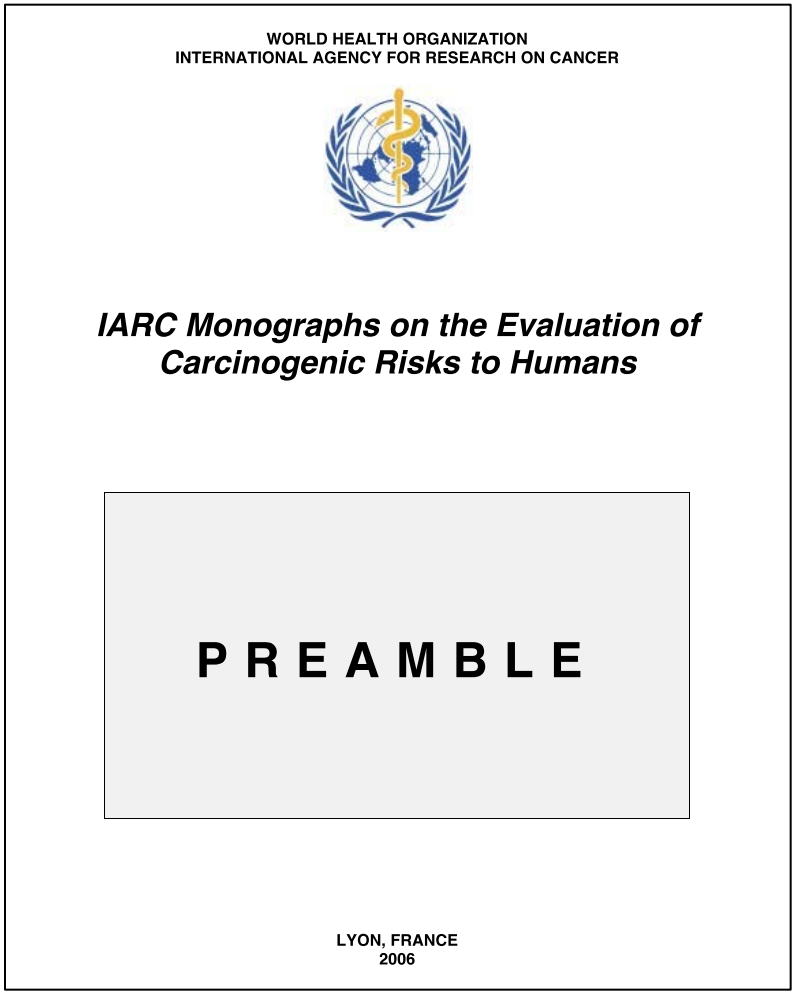
Evaluations are made by working groups of recognised experts. More than 1000 scientists from 50 countries have participated.

Working Group Process



Published Guidance Document

- Guidelines for evaluation are published in the *Preamble* to the Monographs
- Separate criteria for review of human, animal and mechanistic evidence
- Decision process for overall evaluations
- Procedural guidelines for participant selection, conflict of interest, stakeholder involvement & meeting conduct



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http://monographs.iarc.fr/ENG/Preamble/index.php

Ensuring Transparency

- Published process guidelines (Preamble)
- Public nomination of agents for evaluation
- Posted schedule of evaluation topics and dates
- Public calls for data and participants
- Review and evaluation of all relevant human and animal data
- Written rationales for evaluation decisions
- Disclosure of conflicts of interest of all participants

Structured Expert Judgment

- Guidelines are provided for evaluating studies according to the type of data (human, animal, mechanistic) but formal scoring is *not* used.
- Mechanistic evidence can modify the evaluation based on judgments of strength and human relevance.
- Agents with weaker evidence of carcinogenicity may be upgraded based on a judgment that aspect of the evidence are exceptionally compelling.

Evaluating human data

Cancer in humans — Preamble Part B, Section 6(a)	Cancer in experimental animals	Mechanistic and other relevant data

Sufficient evidence	Causal relationship has been established Chance, bias, and confounding could be ruled out with reasonable confidence
Limited evidence	Causal interpretation is credible Chance, bias, or confounding could not be ruled out
Inadequate evidence	Studies permit no conclusion about a causal association
Evidence suggesting lack of carcinogenicity	Several adequate studies covering the full range of exposure levels are mutually consistent in not showing a positive association at any observed level of exposure Conclusion is limited to cancer sites and conditions studied

Evaluating experimental animal data

Cancer in humans	Cancer in experimental animals — Preamble Part B, Section 6(b)	Mechanistic and other relevant 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 mechanistic and other data

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data — Preamble Part B, Section 6(c)

- 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

Integrating Human and Animal Evidence

EVIDENCE IN HUMANS	EVIDENCE IN EXPERIMENTAL ANIMALS: *Sufficient*	*Limited*	*Inadequate*
Sufficient	Group 1 *(carcinogenic to humans)*		
Limited	Group 2A *(probably carcinogenic)*	Group 2B *(possibly carcinogenic)* (exceptionally, Group 2A)	
Inadequate	Group 2B *(possibly carcinogenic)*	Group 3 *(not classifiable)*	

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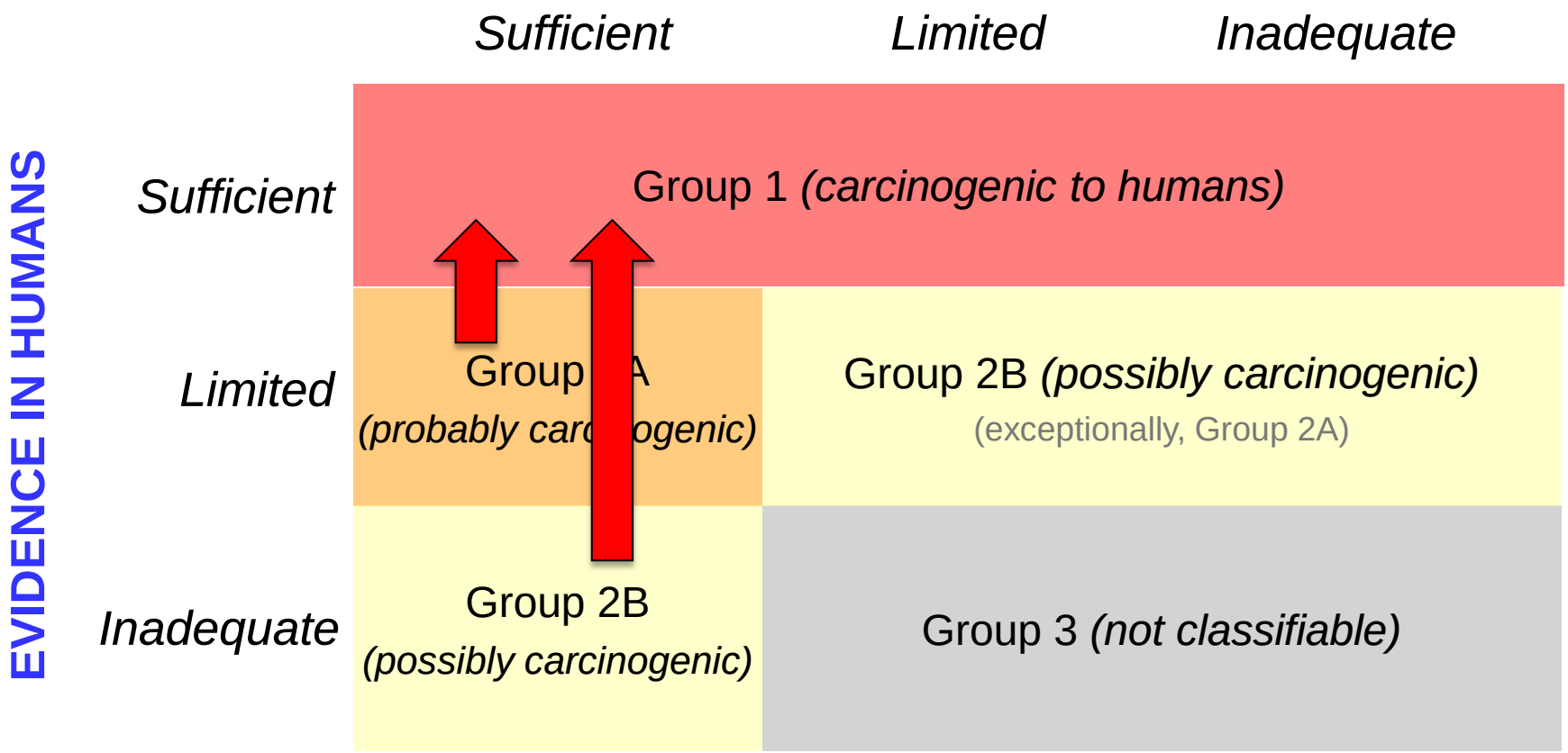
Mechanistic Modifications - when human data are less than sufficient



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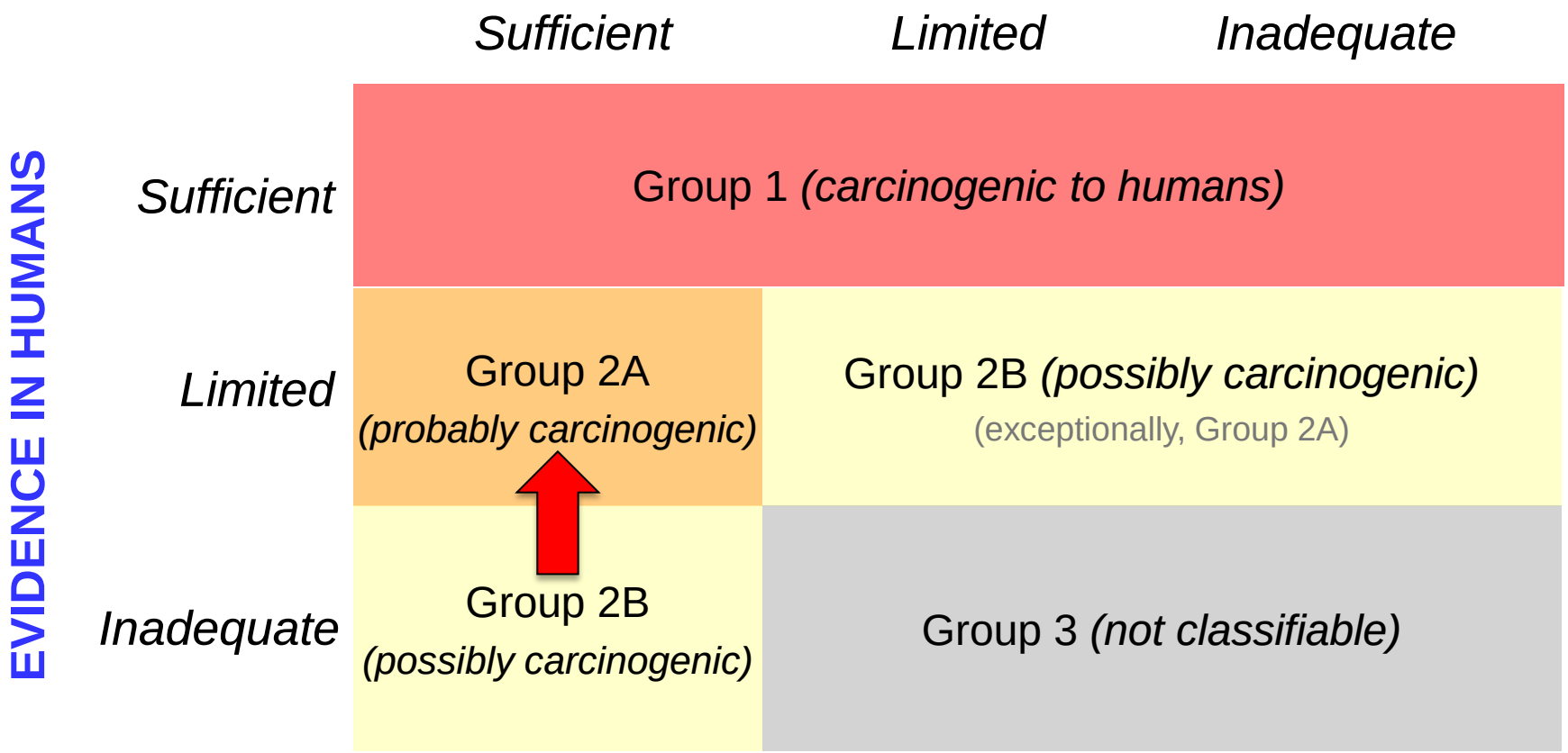
Strong evidence in exposed humans

Mechanistic Modifications - when human data are less than sufficient



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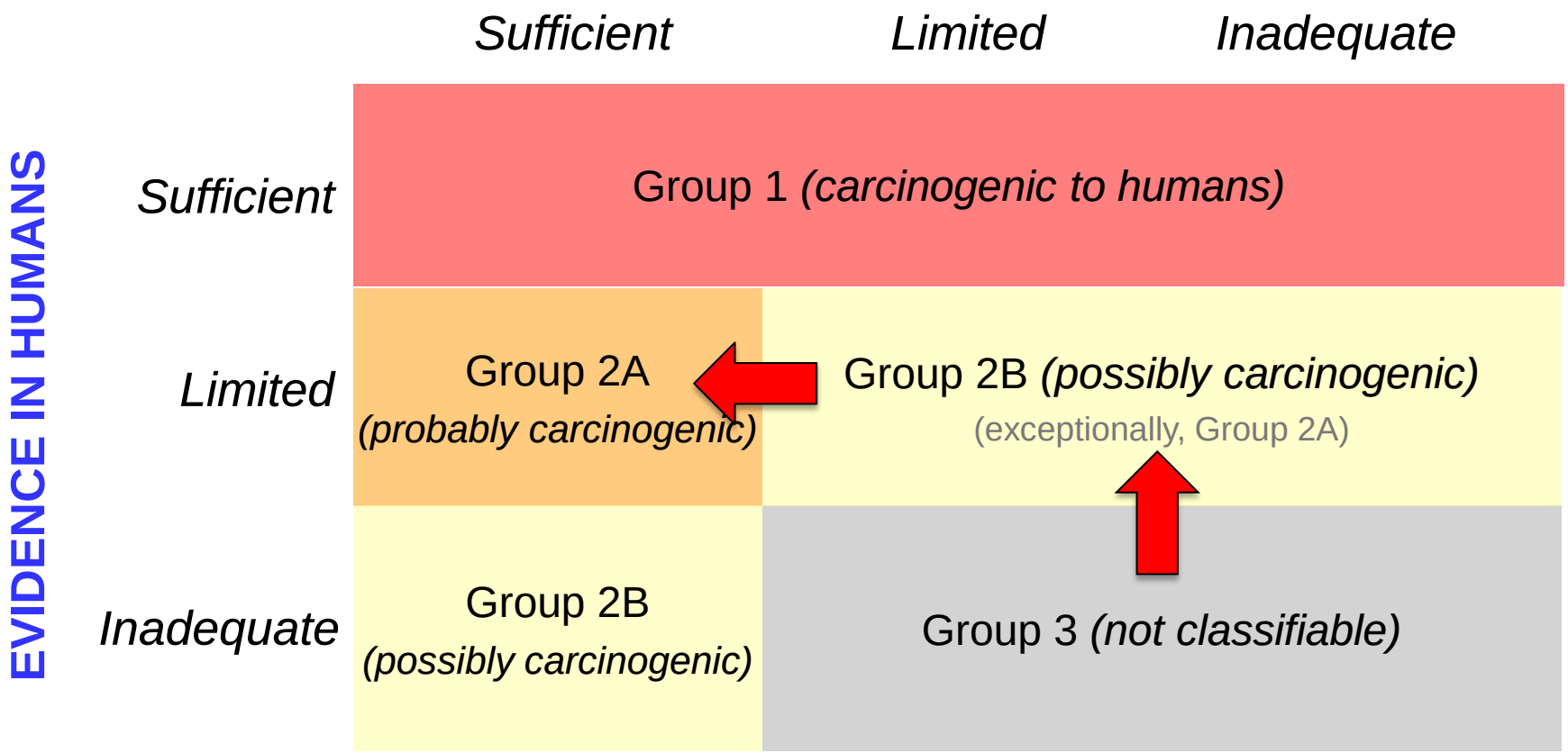
Strong evidence; mechanism also operates in humans

Mechanistic Modifications - when human data are less than sufficient



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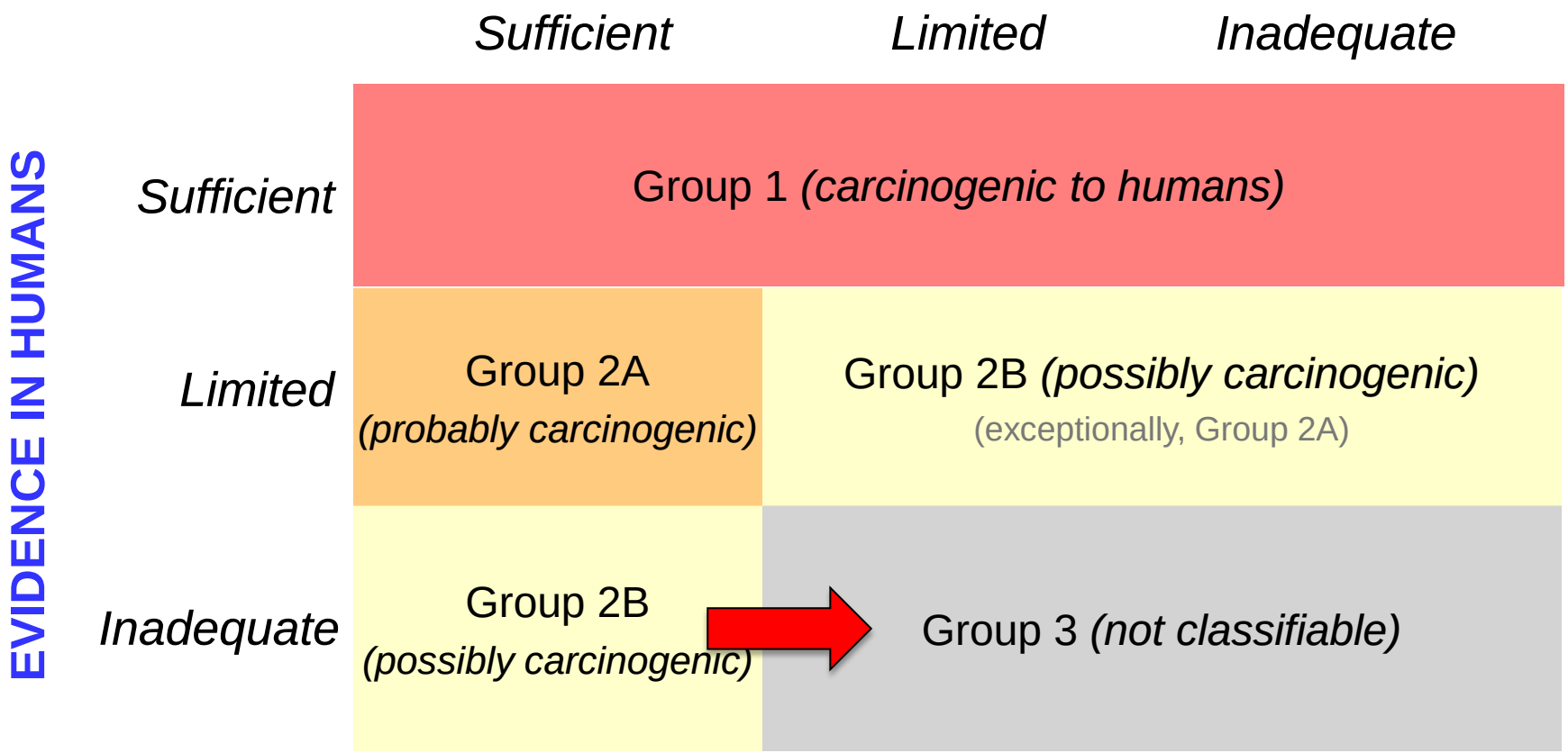
Strong evidence; agent belongs to a mechanistic class with Group 1 or 2A agents

Mechanistic Modifications - when human data are less than sufficient



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Strong evidence; mechanism DOES NOT operate in humans

The Preamble recognizes the need for flexibility

- “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.”