IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Hierarchy of evidence, University of Kent, 6 Sept 2012

Kurt Straif
International Agency for Research on Cancer
Lyon, France

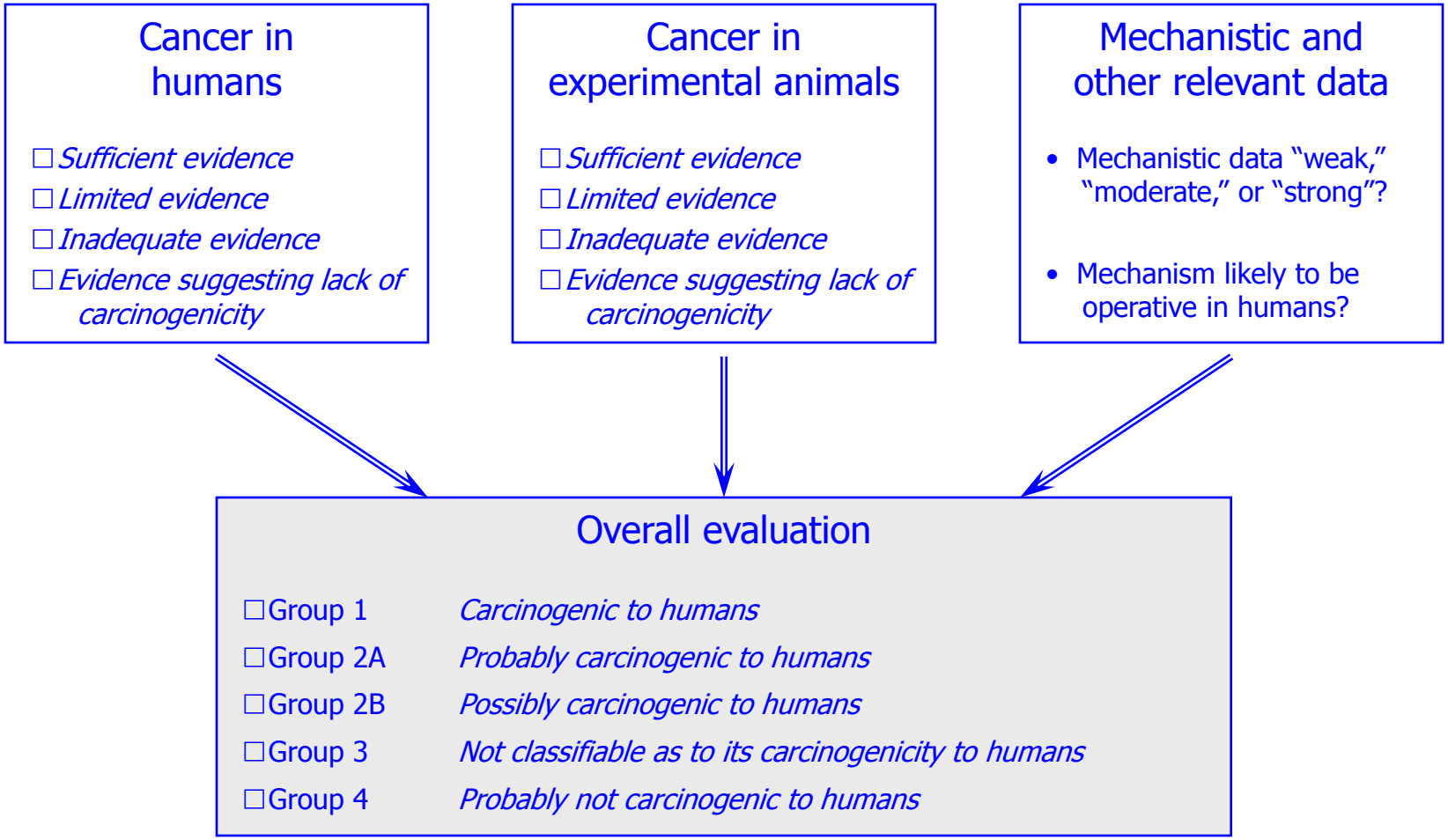
The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of cancer in humans.

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

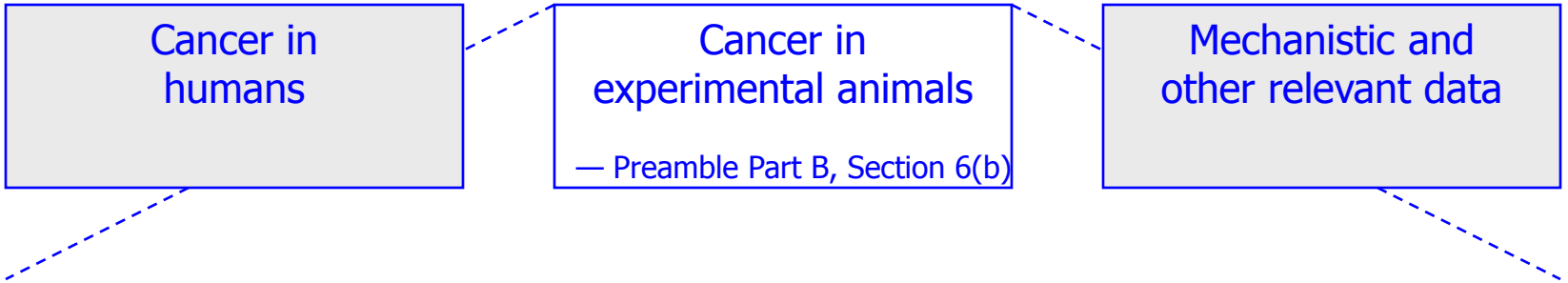
Evolution of criteria for weight of evidence evaluation in IARC Monographs

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



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

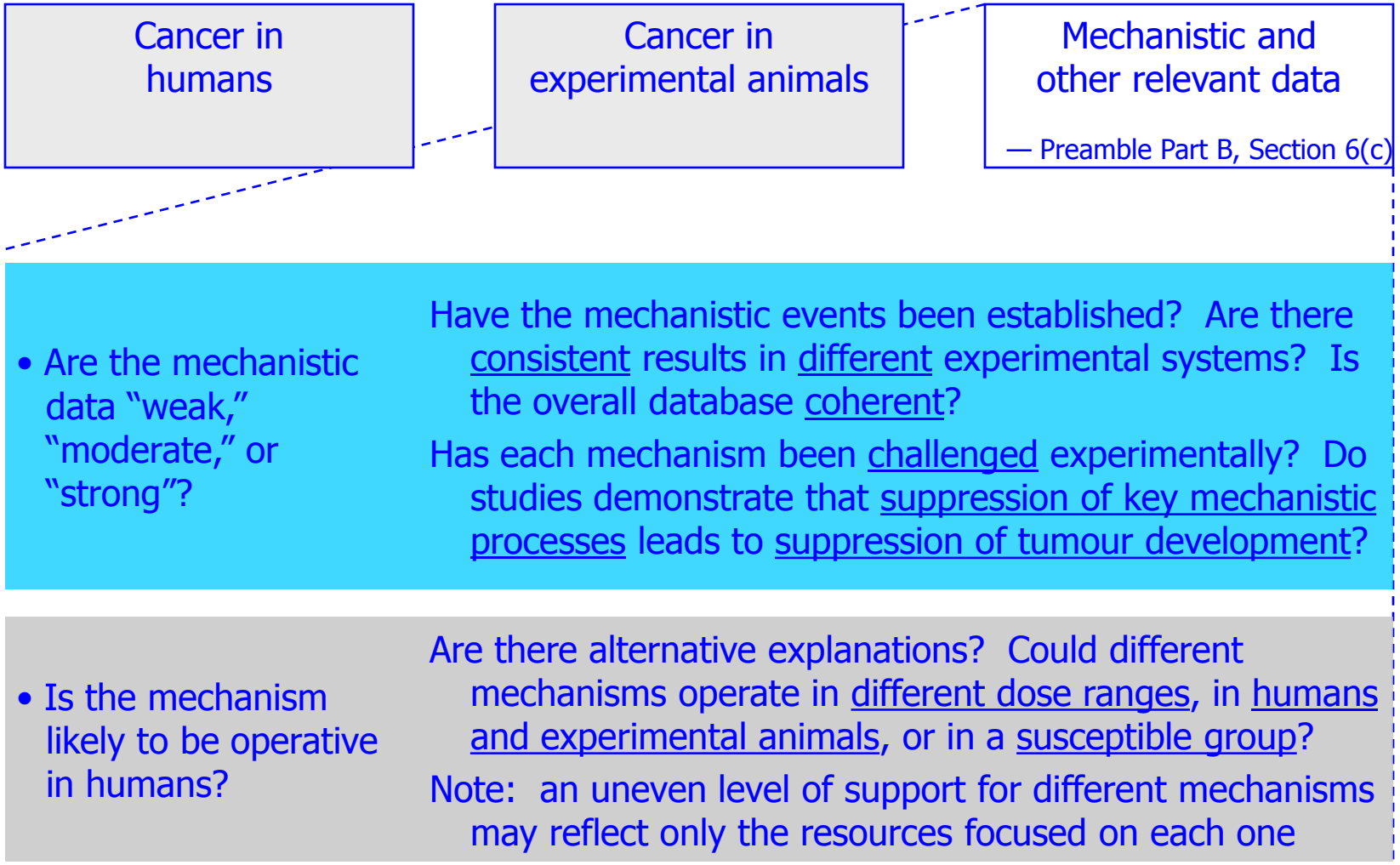
Evaluating human data

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	

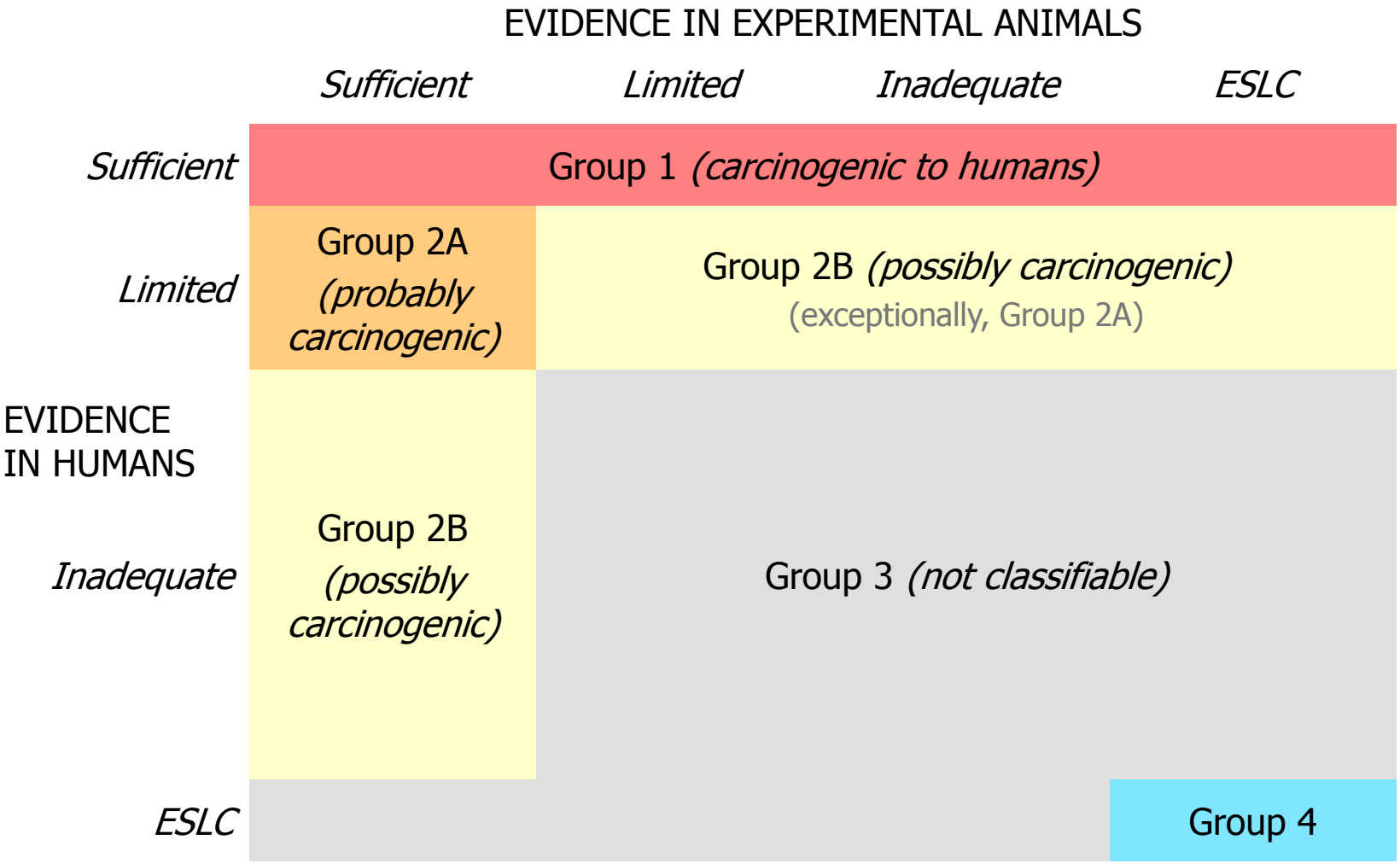
Hierarchy in epidemiological studies ?

- 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

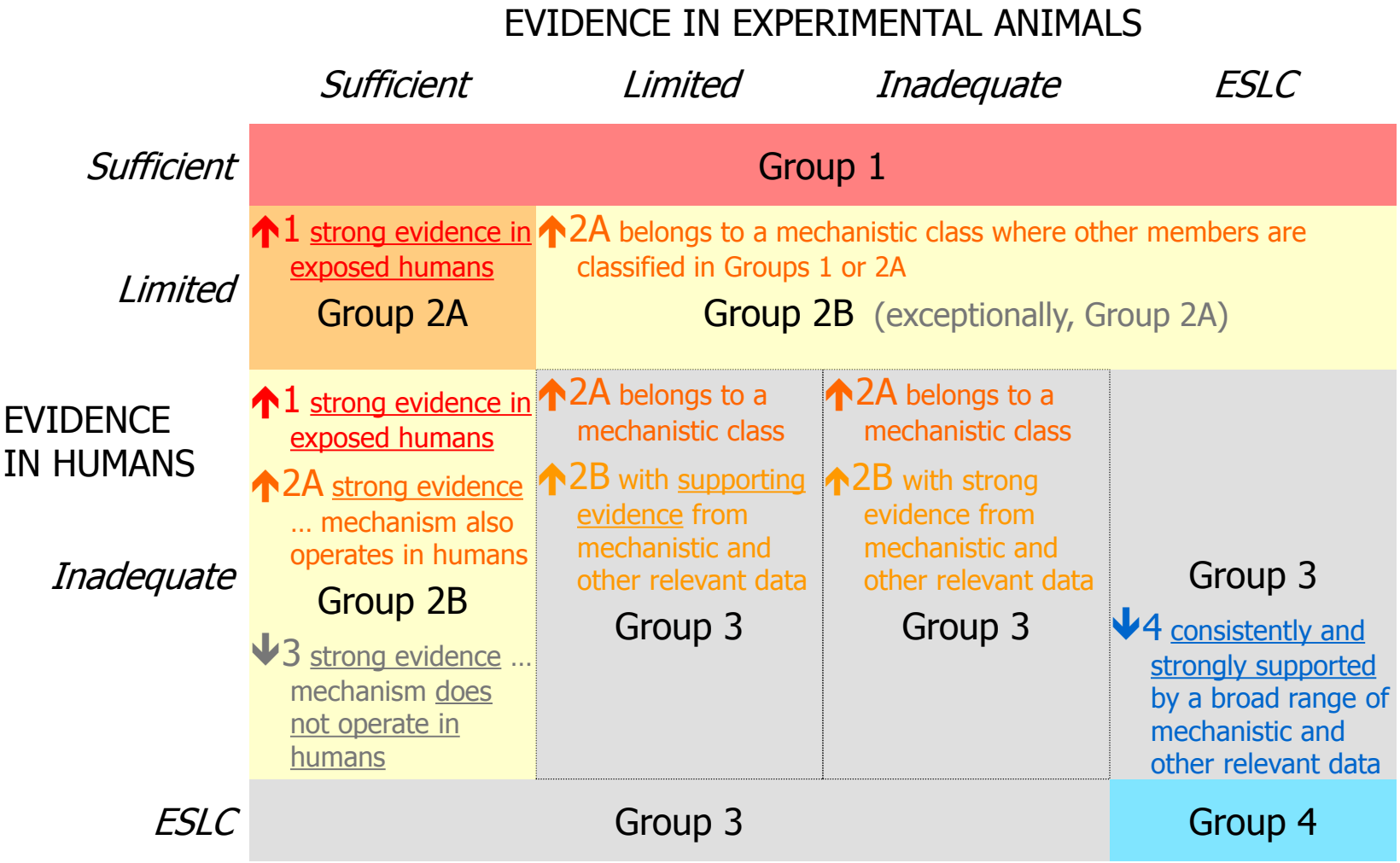
Evaluating mechanistic and other data



The plenary sessions combine the human and experimental evaluations



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



Volume 100 compiled information for subsequent scientific publications

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