The IARC, Mechanistic Evidence and the Precautionary Principle

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Introduction

1. IARC: searching for causes of human cancer
   - epidemiological data in humans
   - experimental data in animals
   - mechanistic and other relevant data
2. Problem: use of mechanistic data too limited
   - extrapolation animals $\rightarrow$ humans: $\pm$ OK
   - the problem of confounders: NOK
   - assessment of temporal stability: NOK
3. Defense: precautionary principle

The IARC

The IARC

What International Agency for Research on Cancer (WHO, Lyon)

advisory groups (scientific experts, declaration of interests)

Goal To identify the causes of human cancer

- → cancer *hazard*, not cancer *risk*
- → evaluates the available evidence on the carcinogenicity of agents: chemicals, biological agents, lifestyle factors, . . . (1,000 agents studied so far)

1. epidemiological evidence on humans
2. experimental evidence on laboratory animals
3. also mechanistic and other data (since 1990s)

IARC procedures (without mechanistic data)

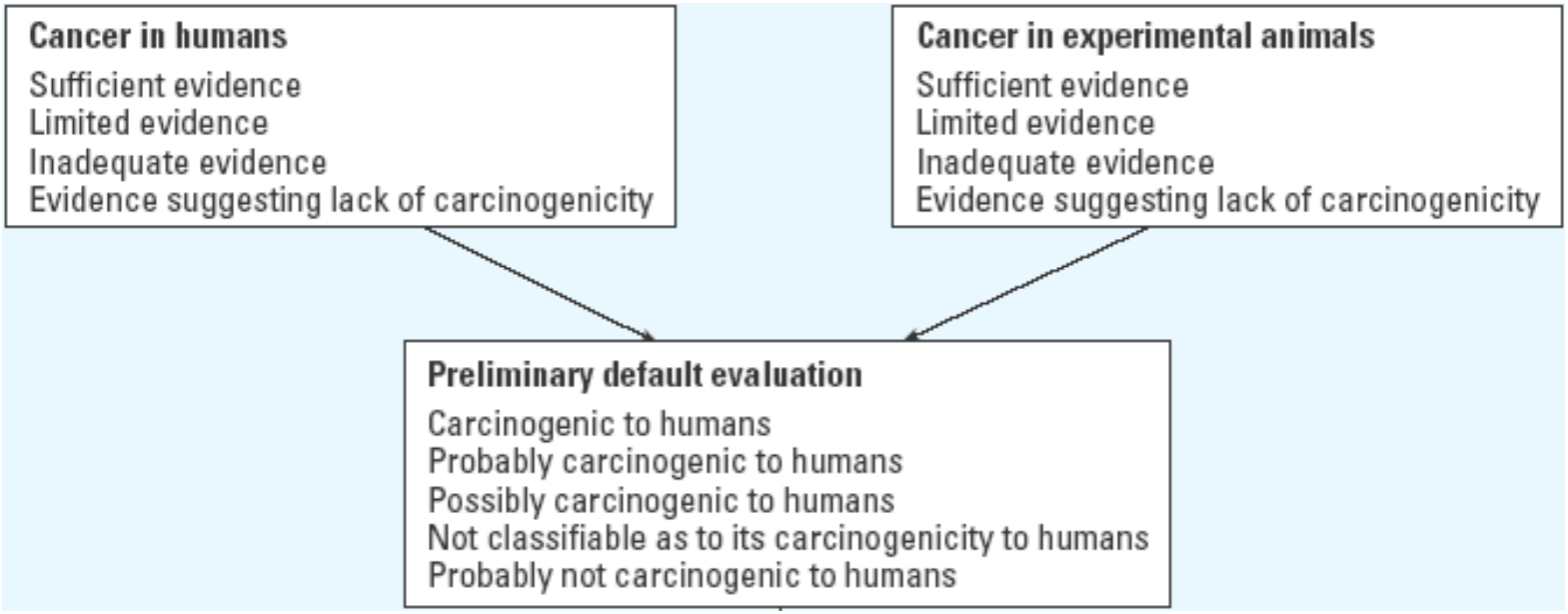

Figure: Cogliano et al. (2004, 1272)

IARC procedures (without mechanistic data)

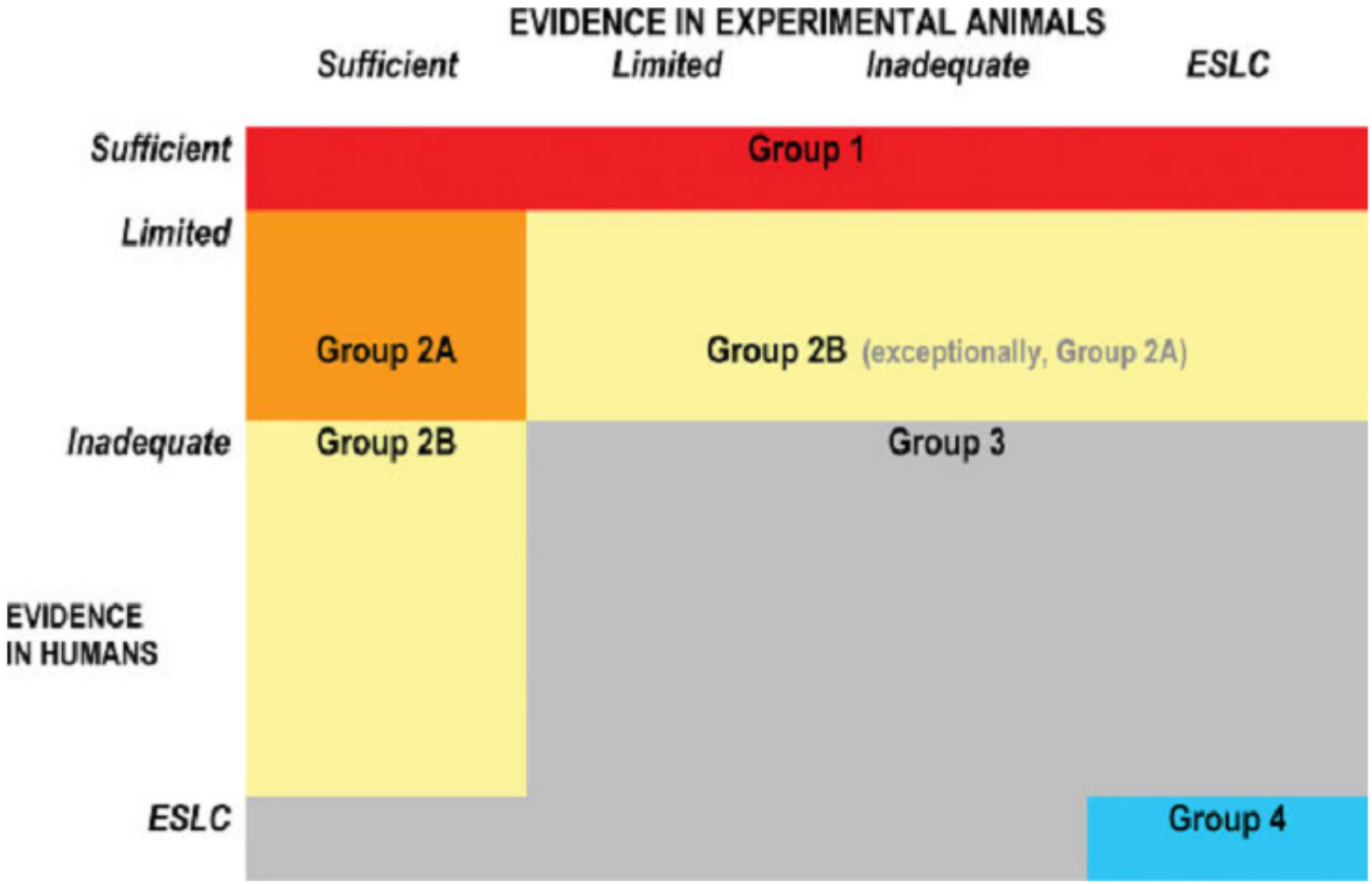

Figure: Cogliano et al. (2008, 102)

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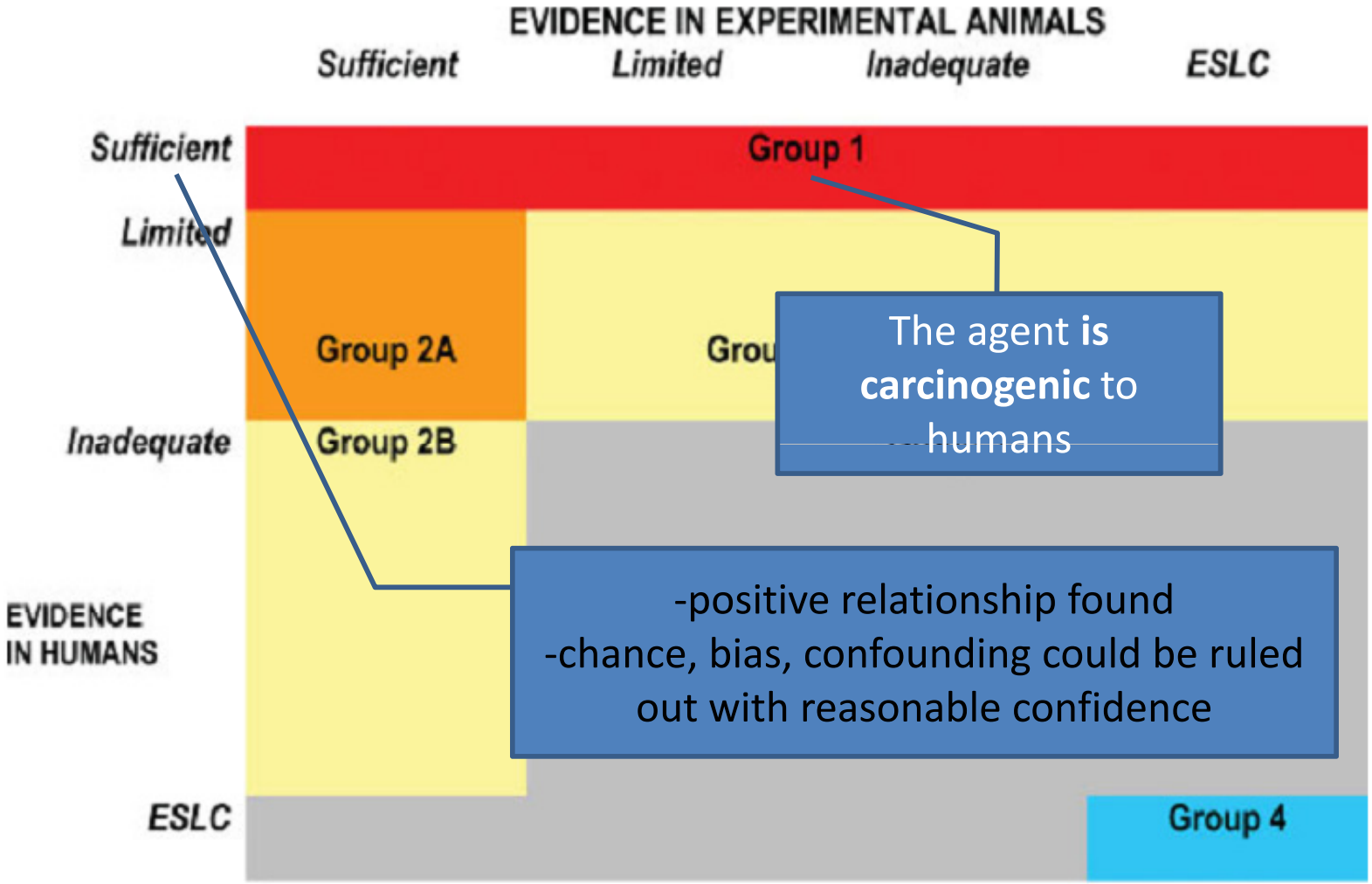

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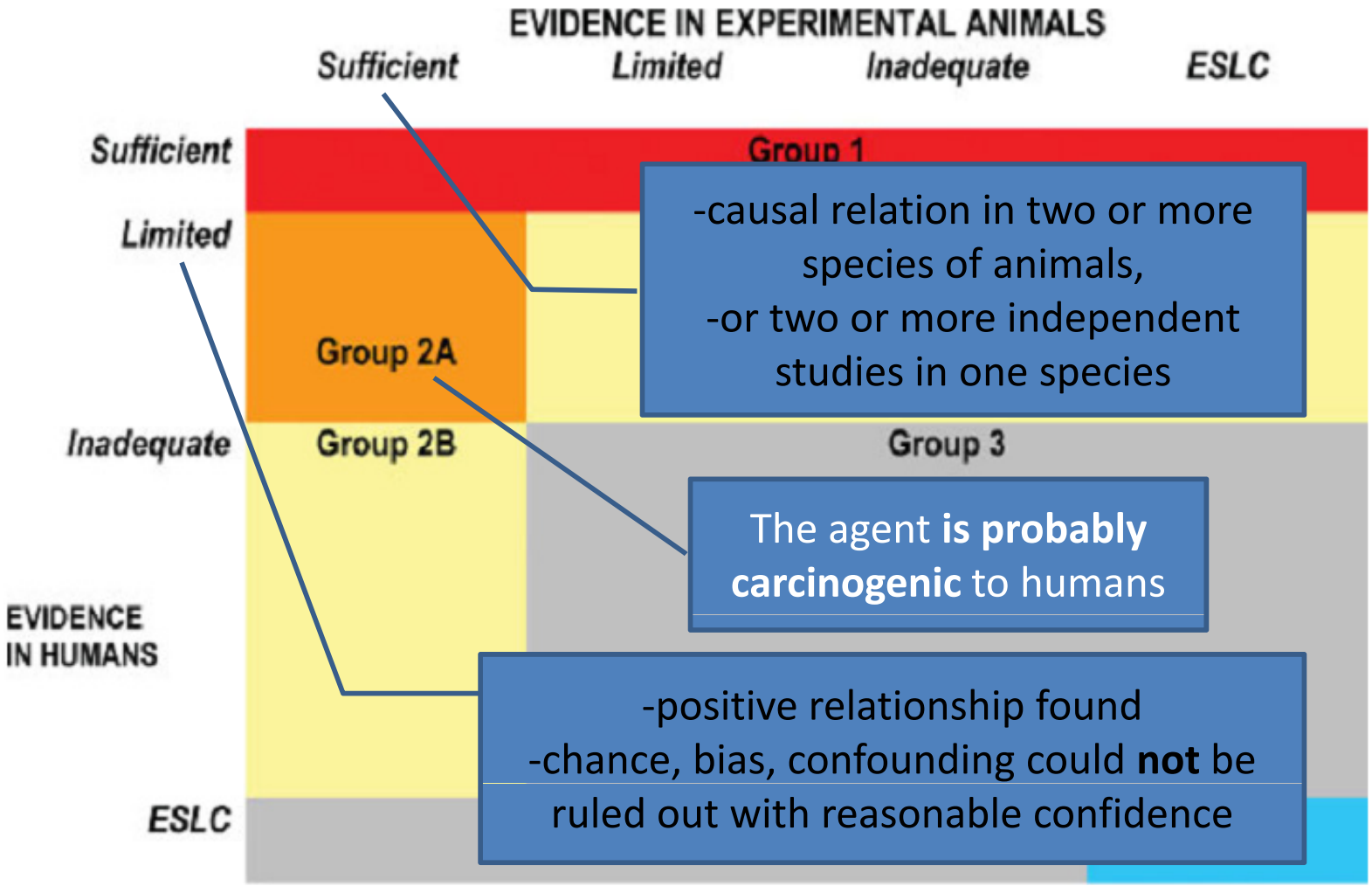

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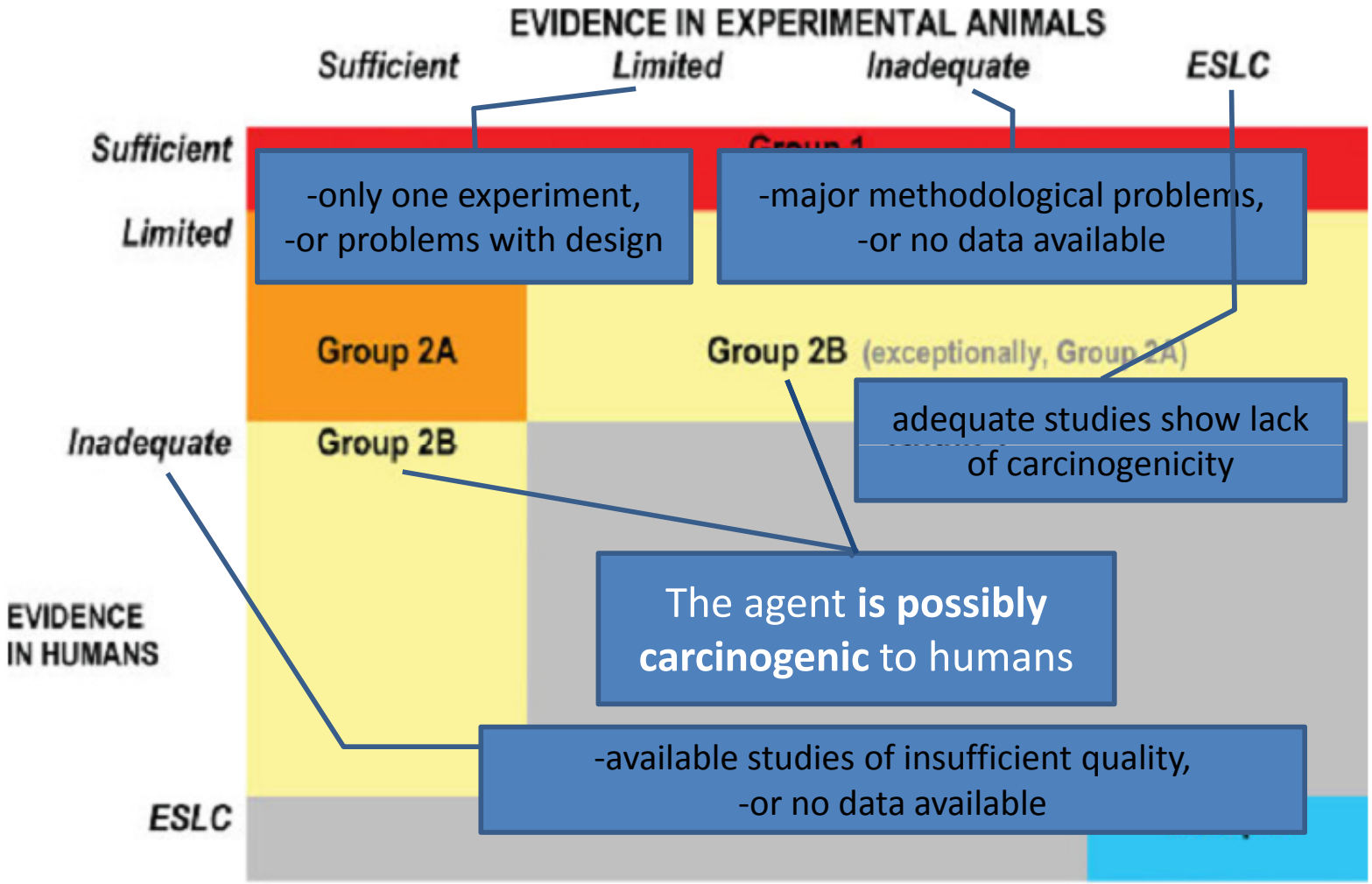


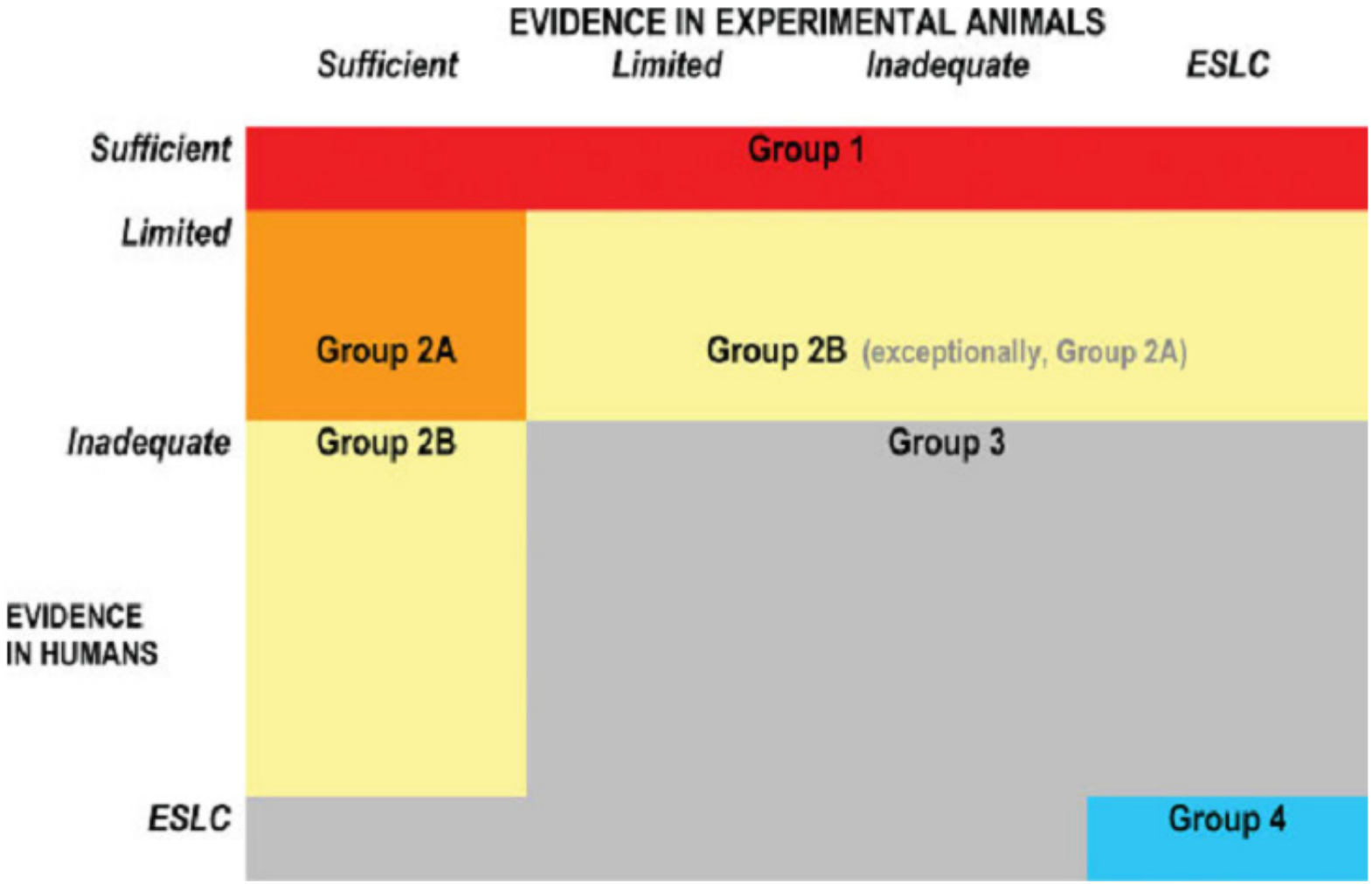
Figure: Cogliano et al. (2008, 102)

The Use of Mechanistic Evidence

Outline

- Before 1990s: only epidemiological and experimental data
- Since 1990s: also mechanistic and other data
  - toxicokinetic data
    - absorption, distribution, metabolism, . . . of agents
    - in humans, experimental animals, and cellular systems
  - data on mechanisms of carcinogenesis
    - changes in physiology, at cellular level, at molecular level (DNA), . . .
  - etc.
- Use of mechanistic evidence:
  - extrapolation: animals $\rightarrow$ humans: $\pm$ OK
  - the problem of confounders: NOK
  - assessment of temporal stability: NOK

Extrapolation from animals to humans: ± OK



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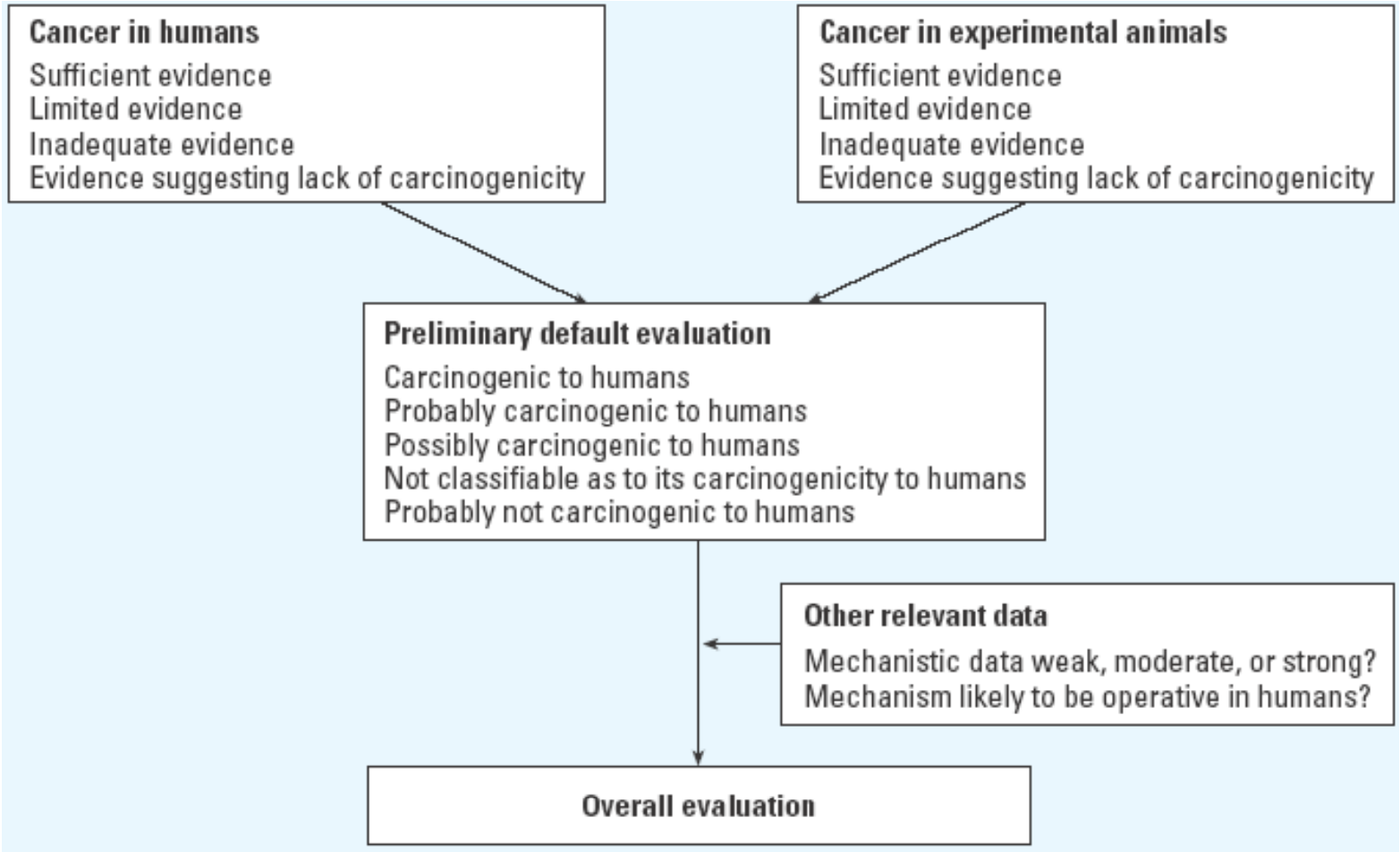

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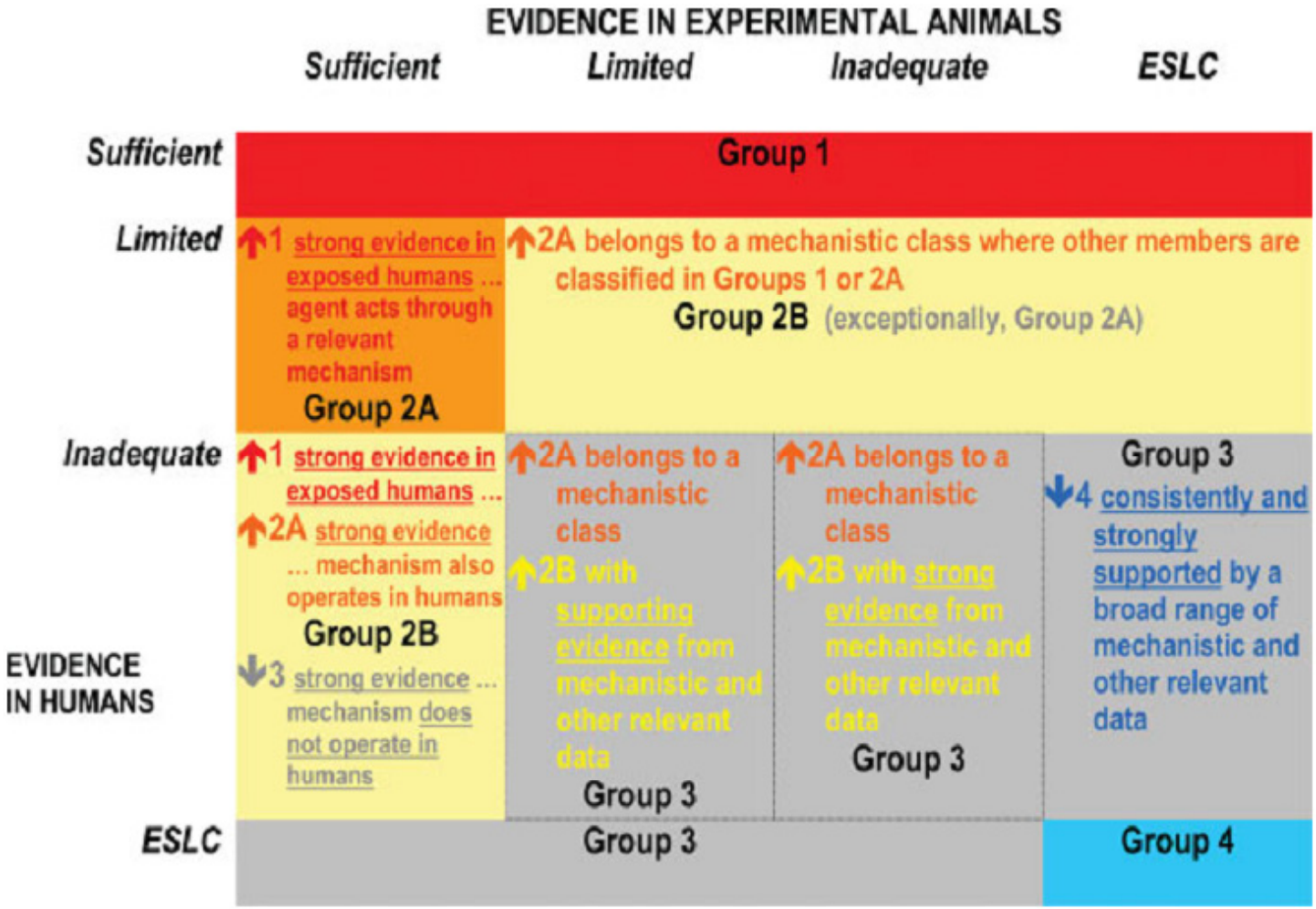

Figure: Cogliano et al. (2008, 103)

The problem of confounders: NOK

Epidemiological evidence is *sufficient*, only if *confounding* is excluded with reasonable confidence

Is it possible to exclude confounding in epidemiology?

- Dan Steel (2004): NO (social sciences)

  → "[. . .] social scientists are rarely able to measure all potential common causes. [. . .] [This] is a basic element of the problem of confounders, to which mechanisms are being considered as a partial solution." (Steel 2004, 63)

  → if we find a mechanism, we can conclude that there is a causal relation between the correlated variables

- no reason to think that exhaustive enumeration of all potential confounders is possible in epidemiology

Conclusion:

→ the IARC's assumption is problematic

→ strictly speaking, "sufficient epidemiological evidence" is an empty category

Assessing temporal stability: NOK

Causal relations may change over time

Example: breast cancer

- causes of breast cancer: hormone use, alcohol consumption, breast feeding, electromagnetic fields, etc.
- however: susceptibility to these factors determined by epigenetic factors
  - may be influenced by maternal diet (Hilakivi-Clarke & de Assis, 2006)
  - maternal diet during pregnancy/lactation $\rightarrow$ epigenetic changes in foetus/baby $\rightarrow$ higher susceptibility of post-puberal daughter
  - maternal diet may change quickly in population $\rightarrow$ NOT stable of time

Conclusion:

$\rightarrow$ The IARC should assess the temporal stability of the carcinogenicity relations discovered

$\rightarrow$ To that end it needs to rely on mechanistic evidence

The Precautionary Principle

Outline

Consequence: Too little use of mechanistic evidence $\rightarrow$ problem of *false positives* in current IARC conclusions:

- 'sufficient' epidemiological evidence even if not exhaustively controlled for confounders
- agents carcinogenic at t_1 becoming non-carcinogenic at t_2

  (note: reverse may also hold – agents later becoming carcinogenic, *false negatives*)

Question 1: Should the IARC procedures be improved? We claim YES.
Question 2: Should we dismiss the IARC conclusions obtained so far? NO

- False positives not worst possible problem
- Better false positives than *false negatives*

$\Rightarrow$ Precautionary Principle

Claim: The IARC procedures do implicitly (and somehow explicitly) incorporate precautionary principles

This claim is not trivial

"The IARC evaluations do not build in precaution, rather, they strive for a balanced evaluation of the overall weight of the evidence. [. . .] Precaution does not mean taking limited evidence and calling it sufficient. Precaution means that risk management officials are prepared to act on less than sufficient evidence when warranted. The scientific evaluation serves to indicate when precaution may be appropriate in risk management."
(Cogliano 2007, 572, our emphasis)

A semi-formal representation of the PP

A semi-formal representation (Hughes 2006, *cf.* Manson 2002):

- If there is evidence stronger than *E* that an activity will cause harm more serious than *S*, then take action of type *A*.

Standard versions of the PP

Standard versions of the PP:

- **Strong:** low standards for *E* (any 'lack of full scientific certainty')
- **Normative:** *A* is an 'action' in the strict sense (precautionary measures to prevent environmental degradation)
- Examples:
  - Where there are threats of serious or irreversible damage, **lack of full scientific certainty** shall not be used as a reason for postponing cost-effective **measures to prevent** environmental degradation. (United Nations Rio Declaration, 1992)
  - When an activity raises threats of harm to human health or the environment **precautionary measures** should be taken even if some cause and effect relationships are **not fully established scientifically** [. . .]. (Wingspread Conference, 1998)

Problems with the standard versions

Standard versions of the PP: strong + normative

Problems:

1. Problematic in themselves: Peterson (2006, 2007), Hughes (2006), Harris & Holm (2002)
   - too vague
   - too absolutistic
   - incoherent (paradox of precaution)
2. Not applicable to IARC:
   - IARC does not engage in legislation or regulation (no precautionary measures)
   - IARC assessments not proportional to regulatory decisions:
     - alcoholic beverages: Group 1, but loosely regulated
     - tobacco: Group 1, somewhat more regulated
     - asbestos: Group 1, strictly prohibited

But IARC implicitly applies Weak Epistemic Precautionary Principles (which are not problematic)

Weak Epistemic Precautionary Principles

- If there is evidence stronger than *E* that an activity will cause harm more serious than *S*, then take action of type *A*.
- Weak versions of the PP: Hughes (2006)
  - high standards for *E*
  - high standards for *S*
  - *A* not too invasive
- Epistemic versions of the PP: Peterson (2007)
  - recommended action *A* is not about what to *do*, but about what to *believe*

Some Examples

Example 1:

If there are "studies in which bias/confounding/chance could be ruled out with reasonable confidence" (E^1) indicating that an agent will cause cancer (S), then "believe that there is *sufficient* epidemiological evidence of carcinogenicity" (A^1)

- E^1 and S set high standards
- A^1 is epistemic and not too invasive

Example 2:

If there are "studies in which bias/confounding/chance could *not* be ruled out with reasonable confidence" (E^2) indicating that an agent will cause cancer (S), then "believe that there is *limited* epidemiological evidence of carcinogenicity" (A^2)

- E^2 sets somewhat lower standards than E^1
- but A^2 is also weaker than A^1 (and also epistemic)

Some Examples

Example 3:
If there is "*limited epidemiological* and *sufficient experimental* evidence" (E^3) indicating that an agent will cause cancer (S), then "believe that the agent is *probably carcinogenic* (Group 2A)" (A^3)

- E^3 and S set high standards
- A^3 is epistemic and not too invasive

Example 4:
If there is "*inadequate epidemiological* and *sufficient experimental*, but *no negative mechanistic* evidence" (E^4) indicating that an agent will cause cancer (S), then "believe that the agent is *possibly carcinogenic* (Group 2B)" (A^4)

- E^4 sets somewhat lower standards than E^3
- but A^4 is also weaker than A^3 (and also epistemic)

Introduction

Argument

The IARC

Mechanistic evidence

Precautionary principle

Conclusion

Conclusion

Conclusion

- IARC:
  - cancer hazard identification
  - epidemiological + experimental + mechanistic evidence
- Problems with use of mechanistic evidence:
  - extrapolation: $\pm$ OK
  - confounders: NOK
  - temporal stability: NOK

  $\Rightarrow$ problem of *false positives*
- Precautionary principle as a solution:
  - preference of false positives over false negatives
  - we should not dismiss the IARC's current evaluations
  - supported by presence of Weak Epistemological Precautionary Principles in procedures
- Afterthought 1: precautionary reasoning provides no reason not to improve the IARC's procedures!!!
- Afterthought 2: IARC should make its precautionary reasoning explicit

The risk assessment paradigm

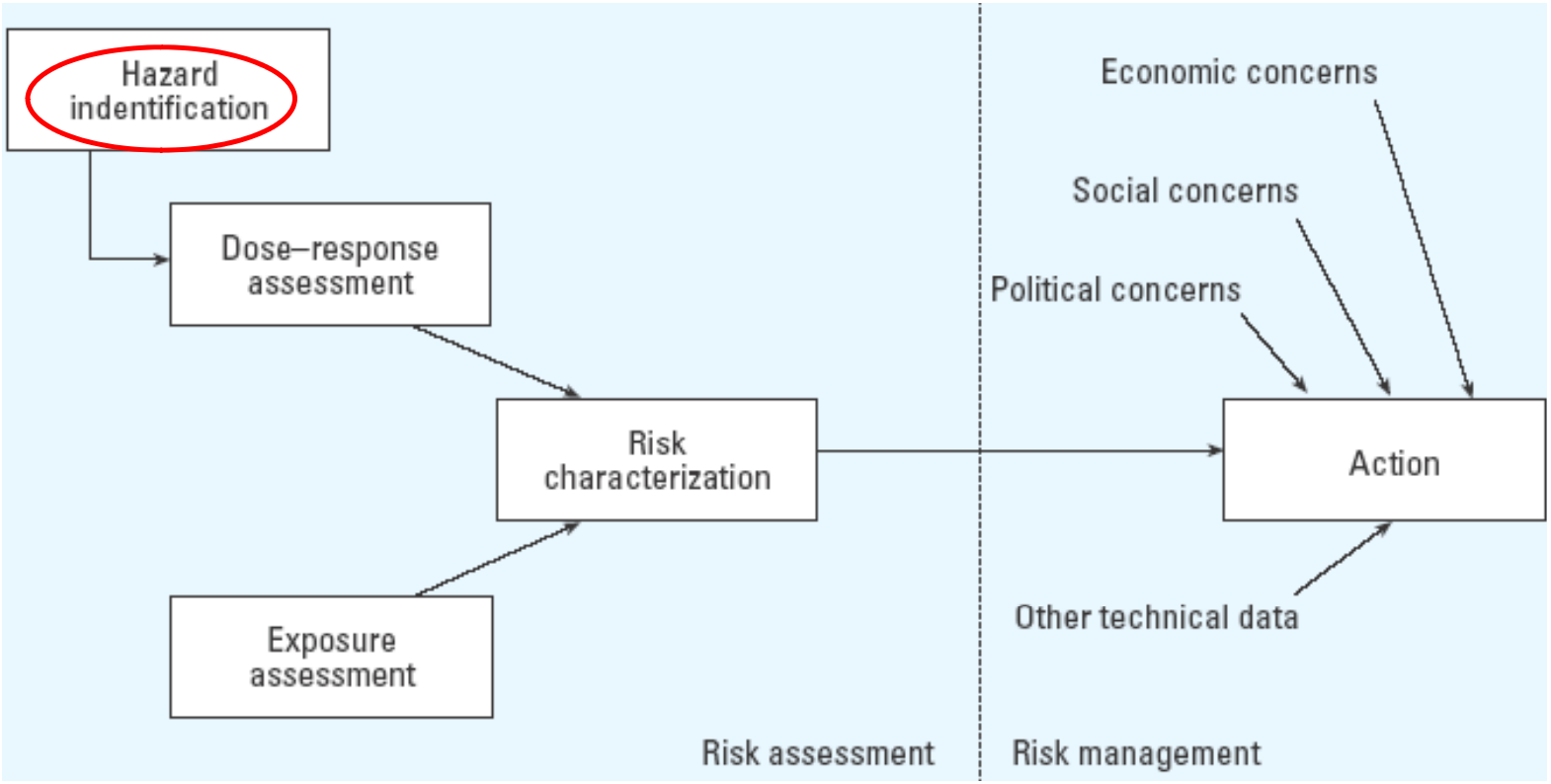

Figure: Cogliano et al. (2004, 1270)

The first phase

Goal individual assessment of available studies for agent *X*

- epidemiological studies of *X*
  - are bias, confounding, chance excluded?
  - cf. Hill-criteria
- experimental studies of *X*
  - animals randomly allocated?
  - more than one species?
  - both sexes of same species?
  - ...
- mechanistic studies: cf. *infra*

The second phase

Goal assessment per group of studies of agent *X*

- epidemiological studies
  - there is *sufficient* epidemiological evidence
  - there is *limited* epidemiological evidence
  - the epidemiological evidence is *inadequate*
  - there is epidemiological evidence suggesting *lack* of carcinogenicity
- experimental studies
  - there is *sufficient* experimental evidence
  - there is *limited* experimental evidence
  - the experimental evidence is *inadequate*
  - there is experimental evidence suggesting *lack* of carcinogenicity
- mechanistic studies: cf. *infra*

The third phase

Goal overall assessment of studies of $X \rightarrow$ The agent is ...

- Group 1: ... ***carcinogenic*** *to humans* (105)
  - e.g. tobacco, solar radiation, wood dust
- Group 2A: ... ***probably carcinogenic*** *to humans* (66)
  - e.g. diesel engine exhaust, sunlamps and sunbeds (use of)
- Group 2B: ... ***possibly carcinogenic*** *to humans* (248)
  - e.g. chloroform, printing processes (occupational exposures in)
- Group 3: ... ***not classifiable*** *as to its carcinogenicity to humans* (515)
  - e.g. chromium[III] compounds, polypropylene, tea
- Group 4: ... ***probably not carcinogenic*** *to humans* (1!)
  - only caprolactam

The IARC's goal is not regulation/legislation

"Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations."
(IARC 2006, 3)

The IARC's precautionary reasoning

"Although this association cannot establish that all agents and mixtures that cause cancer in experimental animals also cause cancer in humans, nevertheless, in the absence of adequate data on humans, it is biologically plausible and *prudent* to regard agents and mixtures for which there is sufficient evidence [. . .] of carcinogenicity in experimental animals *as if* they presented a carcinogenic risk to humans."
(IARC, volume 89, 2007, 17-18, emphasis adjusted)