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

Cancer in humans

- Sufficient evidence
- Limited evidence
- Inadequate evidence
- Evidence suggesting lack of carcinogenicity

Cancer in experimental animals

- Sufficient evidence
- Limited evidence
- Inadequate evidence
- Evidence suggesting lack of carcinogenicity

Mechanistic and other relevant data

- Mechanistic data “weak,” “moderate,” or “strong”?
- Mechanism likely to be operative in humans?

Overall evaluation

- Group 1: Carcinogenic to humans
- Group 2A: Probably carcinogenic to humans
- Group 2B: Possibly carcinogenic to humans
- Group 3: Not classifiable as to its carcinogenicity to humans
- Group 4: Probably not carcinogenic to humans
### Evaluating experimental animal data

#### Causal relationship in experimental animals

- **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

#### Cancer in humans

- Mechanistic and other relevant data

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# Evaluating human data

<table>
<thead>
<tr>
<th><strong>Cancer in humans</strong></th>
<th><strong>Cancer in experimental animals</strong></th>
<th><strong>Mechanistic and other relevant data</strong></th>
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<tbody>
<tr>
<td>— Preamble Part B, Section 6(a)</td>
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</table>

**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, e.g. Aristolochic acid and kidney cancer
Evaluating mechanistic and other data

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

Cancer in humans

Cancer in experimental animals

Mechanistic and other relevant data

— Preamble Part B, Section 6(c)
The plenary sessions combine the human and experimental evaluations

<table>
<thead>
<tr>
<th>EVIDENCE IN EXPERIMENTAL ANIMALS</th>
<th>Sufficient</th>
<th>Limited</th>
<th>Inadequate</th>
<th>ESLC</th>
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<tbody>
<tr>
<td>Sufficient</td>
<td></td>
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<td>Limited</td>
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<td>Inadequate</td>
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<tr>
<td>ESLC</td>
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- **Group 1** (*carcinogenic to humans*)
- **Group 2A** (*probably carcinogenic*)
- **Group 2B** (*possibly carcinogenic*)
  - (exceptionally, Group 2A)
- **Group 2B** (*possibly carcinogenic*)
- **Group 3** (*not classifiable*)
- **Group 4**
Mechanistic data can be pivotal when the human data are not conclusive

<table>
<thead>
<tr>
<th>EVIDENCE IN HUMANS</th>
<th>Sufficient</th>
<th>Limited</th>
<th>Inadequate</th>
<th>ESLC</th>
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<tbody>
<tr>
<td>Sufficient</td>
<td></td>
<td></td>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td>Limited</td>
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<tr>
<td></td>
<td>1 strong evidence in exposed humans</td>
<td>2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A</td>
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<tr>
<td></td>
<td>Group 2A</td>
<td>Group 2B</td>
<td>(exceptionally, Group 2A)</td>
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<tr>
<td>Inadequate</td>
<td></td>
<td></td>
<td></td>
<td>Group 3</td>
</tr>
<tr>
<td></td>
<td>1 strong evidence in exposed humans</td>
<td>2A belongs to a mechanistic class</td>
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<tr>
<td></td>
<td>Group 2A</td>
<td>2A with supporting evidence from mechanistic and other relevant data</td>
<td>Group 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2A with strong evidence from mechanistic and other relevant data</td>
<td>Group 3</td>
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<tr>
<td>ESLC</td>
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<td>Group 4</td>
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<td>4 consistently and strongly supported by a broad range of mechanistic and other relevant data</td>
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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