Use of Toxicity Data in Cancer Risk Assessment

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**Standard Components of Cancer Risk Assessment Used by Environmental Agencies**

<table>
<thead>
<tr>
<th>Risk Assessment Step</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hazard Identification</td>
<td>Level of Evidence for Carcinogenicity</td>
</tr>
<tr>
<td>2. Dose Response Assessment</td>
<td>Cancer risk versus exposure</td>
</tr>
<tr>
<td>3. Exposure Assessment</td>
<td>Human exposure estimates</td>
</tr>
<tr>
<td>4. Risk Characterization</td>
<td>Estimates of cancer risk for those exposed</td>
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</tbody>
</table>
Cancer Hazard Identification
Evidence Labels

- **Environmental Protection Agency:**
  - “suggestive of carcinogenic potential”
  - “likely human carcinogen”
  - “carcinogenic to humans”

- **National Toxicology Program:**
  - “known human carcinogen”
  - “reasonably anticipated to be carcinogenic to humans”

- **International Agency for Research on Cancer:**
  - “possibly carcinogenic to humans”
  - “probably carcinogenic to humans”
  - “carcinogenic to humans”

- **California’s Proposition 65:**
  - “known to the state to cause cancer”
Biological systems for hazard and dose response assessment

Animal (mammalian) “in vivo”

Human “in vivo”

“Other Relevant Data”
## Evidence Maps to Cancer Classifications

<table>
<thead>
<tr>
<th>Direct Human</th>
<th>Direct Animal</th>
<th>Mechanistic / Indirect</th>
<th>IARC</th>
<th>US EPA</th>
<th>NTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>--</td>
<td>--</td>
<td>Sufficient Strong human mechanistic data</td>
<td>Carcinogenic to humans (Group 1)</td>
<td>Carcinogenic to humans</td>
</tr>
<tr>
<td>Limited</td>
<td>Sufficient</td>
<td>--</td>
<td>--</td>
<td>Probably carcinogenic to humans (Group 2A)</td>
<td>Likely to be carcinogenic to humans</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Sufficient</td>
<td>Strong</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Sufficient</td>
<td>Strong</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>Limited</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Limited</td>
<td>--</td>
<td>Inadequate</td>
<td>Inadequate Information to Assess</td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>Inadequate</td>
<td>Strong &amp; same class as other carcinogens</td>
<td>Possibly carcinogenic to humans (Group 2B)</td>
<td>Strong/convincing</td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>Limited</td>
<td>--</td>
<td>Not classifiable</td>
<td>Suggestive</td>
<td>Not classified</td>
</tr>
</tbody>
</table>
Need to Address Background and Vulnerability Impact on Risk

- **Background**
  - Biological
  - Exposure

- **Vulnerability, e.g., from**
  - Life stage
  - Genetics
  - Health disease status

Source: Woodruff et al. 2008
Toxicity Testing Goal
- Dose Response Assessment

![Graph showing dose response relationship](image-url)
Deriving Dose Response Relationships

• Bioassay
  – Homogeneous animals
  – First exposed as adult animals
  – Controlled dose
  – Controlled environment
  – High Dose

• Worker populations
  – Exposed as adults
  – Relatively high dose
  – “Healthy workers”
  – Heterogeneous
  – Similar communities

Extrapolation

• General Population
  – All ages
  – Male and female
  – Heterogeneous Pharmacokinetics
  – Heterogeneous Pharmacodynamics
  – Varied environments
“When the host is unable to adapt because of underlying nutritional, genetic, disease or life-stage status, biologic function is compromised, and this leads to toxicity and disease.”
Toxicological Data

10’s/year

100’s/year

10,000’s/day

100,000’s/day

1-3/year

High Throughput Molecular mechanism