GOOD JOBS

Protect Workers Now

SAFE JOBS

Workers Memorial Day
April 28
AFL-CIO
Station Identification:

- National Toxicology Program Board of Scientific Counselors
- National Academic of Sciences Committee on Risk Assessment Methodology
- International Agency for Research on Cancer Monograph Working Group
Risk Assessment Paradigm (NAS, 1983):

- Hazard Identification
- Dose-Response Assessment
- Exposure Assessment
- Risk Characterization:
  
  Dose-Response $\times$ Exposure
OSHA Health Standards [6(b)]:

• Hazard Identification:
  “material impairment to health or functional capacity”

• Dose response assessment:
  “significant risk”
Competing Schemes:

• OSHA Cancer Policy
• IARC
• National Toxicology Program Report on Carcinogens
• ACGIH
Quantitative Limits of Direct Observation
Dose Response Relationship

Range of direct observation through animal bioassay is limited;

High background tumors can be observed only at higher absolute risks and therefore higher doses;

Low background tumors can be observed only in larger studies.
Dose Response Relationship

Epidemiology can detect somewhat smaller relative risks, but studies have many additional limitations.
Dose Response Relationship

Extrapolation to population exposure levels is beyond the range of direct observation.
No Observed Effect Level is still a “Significant Risk”

- “No Observed Effect Level” in laboratory study (below an established effect level) corresponds to a risk of about 5 - 10% (above a zero background)
- Benchmark dose = Statistical NOEL = 5 – 10% risk
- “No Observed Effect Level” in epidemiology study depends on the background risk of the cancer site and size of the study
- Significant risk < 1/1000 or 0.1%
OSHA Cancer Policy (1980):

1990, Identification, Classification, and Regulation of Carcinogens.

• 1990.111, General Statement of Regulatory Policy. This part establishes the criteria and procedures under which substances will be regulated by OSHA as potential occupational carcinogens.

• 1990.112, Classification of Potential Carcinogens.

• 1990.121, Candidate List of Potential Carcinogens (Stayed, 1983)

• 1990.143, General Provisions for the Use of Human and Animal Data.
OSHA Categories:

• **Category I Potential Human Carcinogen:**
  (1) humans, or
  (2) **single** long-term bioassay where the results are in concordance, or
  (3) **single** long-term bioassay, where the Secretary determines the requirement for concordance is not necessary.

• **Category II Potential Human Carcinogen:**
  human evidence “suggestive,” bioassay with no concordance
Monographs:

• First monograph: 1972
• Working group – 4 committees:
  Exposure
  Laboratory studies
  Epidemiology
  Other toxicology
• Evidence in experimental animals
• Evidence in humans
• Overall Evaluation
Terminology for evidence in experimental animals or humans:

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

http://193.51.164.11/monoeval/preamble.html
IARC Overall Evaluations:

- Carcinogenic (Group 1)
- Probably carcinogenic (Group 2A)
- Possibly carcinogenic (Group 2B)
- Not classifiable (Group 3)
- Probably not (Group 4)
Group 1:
The agent (mixture) is carcinogenic to humans.

The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.
Limited evidence of carcinogenicity (people):

“A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.”
Group 2

This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals.

Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.
Group 2A: The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans.
Sufficient evidence of carcinogenicity (laboratory):

• The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.
NTP
NTP Report on Carcinogens:

- Mandated by law 1978
- Law defines two categories:
  
  Known to be carcinogenic

  Reasonably anticipated to be carcinogenic
Process for NTP ROC:

- Nominations for listing, de-listing
- Contractor prepares literature reviews
- RG 1: NIEHS/NTP staff
- RG 2: Interagency staff
- Board of Scientific Counselors
- NTP Executive Committee
- NIEHS-NTP Director
- Sec’y of HHS
Contrasting OSHA, NTP and IARC:

- **OSHA:** “Category I” = one study and concordance (supporting data)
- **IARC:**
  “possibly carcinogenic” = two studies, may be in the same species
  “probably carcinogenic” = some type of evidence in people
- **NTP:**
  “reasonably anticipated” = two species
## NTP v IARC Carcinogen Classification

<table>
<thead>
<tr>
<th>NTP</th>
<th>IARC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known to be carcinogenic to humans</td>
<td>Carcinogenic to humans (Group 1)</td>
</tr>
<tr>
<td>Multiple positive epidemiology studies</td>
<td>“Sufficient” evidence in people - Multiple epidemiology studies</td>
</tr>
<tr>
<td>Reasonably anticipated to be carcinogenic to humans</td>
<td>Possibly carcinogenic to humans (Group 2A)</td>
</tr>
<tr>
<td>Laboratory studies showing tumors in two species or multiple sites in a single species</td>
<td>Possibly carcinogenic to humans (Group 2B)</td>
</tr>
<tr>
<td>Not Classifiable (Group 3)</td>
<td>“Inadequate” evidence in animals - one positive laboratory study</td>
</tr>
</tbody>
</table>
ACGIH
ACGIH Classification:

- A1 Confirmed human carcinogen
- A2 Suspected human carcinogen

- A3 Confirmed animal carcinogen with unknown relevance to humans: carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that may not be relevant to worker exposure.

- A4 Not classifiable as a human carcinogen
- A5 Not suspected as a human carcinogen
Diethanolamine
Bioassay Results for *skin exposure* to diethanolamine and condensates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Diethanolamine content</th>
<th>Male Mice Liver</th>
<th>Female Mice Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethanolamine</td>
<td>100%</td>
<td>Clear evidence</td>
<td>Clear evidence</td>
</tr>
<tr>
<td>Coconut oil acid diethanolamine condensate</td>
<td>18.2%</td>
<td>Clear evidence</td>
<td>Clear evidence</td>
</tr>
<tr>
<td>Lauric acid diethanolamine condensate</td>
<td>0.83%</td>
<td>no evidence</td>
<td>Some evidence</td>
</tr>
<tr>
<td>Oleic acid diethanolamine condensate</td>
<td>0.19%</td>
<td>no evidence</td>
<td>no evidence</td>
</tr>
</tbody>
</table>
### Bioassay Results for *skin exposure to diethanolamine*

#### Male Mice: Kidney renal tubule adenoma or carcinoma combined

<table>
<thead>
<tr>
<th>Dose</th>
<th>0 mg/kg</th>
<th>40 mg/kg</th>
<th>80 mg/kg</th>
<th>160 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>3/50 (6%)</td>
<td>5/50 (10%)</td>
<td>6/50 (12%)</td>
<td>8/50 (16%)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td>6.6%</td>
<td>10.4%</td>
<td>13.1%</td>
<td>17.8%</td>
</tr>
<tr>
<td><strong>Statistical Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life Table</td>
<td>P=0.030 *</td>
<td>P=0.400</td>
<td>P=0.193</td>
<td>P=0.056</td>
</tr>
</tbody>
</table>
Liver cancer in two studies of MWF-exposed workers:


Levels of Evidence for Mortality studies for cancer
Levels of Evidence for Epidemiology Studies:

• **Clear** Evidence for Carcinogenicity:
  Significant excess +
  Exposure response

• **Some** Evidence:
  Excess but not significant +
  Exposure response
  OR
  Significant excess but
  No exposure response
Levels of Evidence for Epidemiology Studies (2):

- **Equivocal Evidence:**
  - Excess not significant
  - No exposure response or Inverse OR
  - No excess + Exposure response

- **Inadequate Study:**
  - Cohort too small, too young, not observed long enough, exposure too low for effect or too uniform for exposure response

- **No evidence**
Levels of Evidence for Epidemiology Studies (3):

- Distinguish between evidence for exposure circumstance vs. specific substance
- Evidence applies to level of exposure in study -- may be no evidence because exposure too low
- Exposure response includes: quantitative, increase in higher exposure group, increase in longer exposure or longer latency
- How many “clear” studies = “Sufficient?”
- How many “some” = “clear”? 
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