Toxicology in Regulatory Process

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Comprehensive Pneumology Center

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Love Canal Disaster
Regulatory toxicology

• Uses scientific knowledge to develop regulations and other strategies for reducing and controlling exposure to dangerous chemicals.

Chemical Resource:

Chemicals, biocides, drugs
• Regulation of admission, production, and use

Cosmetics, consumer products
• Safety assessment

Environmental contaminants
• Drinking water
• outdoor/indoor air
• soil, waste sites

Food safety
• Addictive
• Contaminants

Occupational safety
• Hazardous substances at workplace
Regulatory Process

Research
- Observation
- Methods
- Database

Risk Assessment
- Toxicity Assessment
- Exposure Assessment
- Research Needs Identified from Risk Assessment
- New Research

Risk Management
- Development of Regulatory Options
- Risk Characterization
- Legal, social, and economical concern

Information

Plan

Regulatory Decision

Scientific Frontiers in Developmental Toxicology and Risk Assessment, 2000
Step-1 Hazard Identification

• What might be harming you?
  Red and processed meat
  ➔ Cancer
Step 2 Dose-Response Evaluation

• Health problems at different exposures?

**Bacon’s Cancer Risk**
How much bacon you have to eat to raise your risk of colorectal cancer

<table>
<thead>
<tr>
<th>Strips of bacon (per day)</th>
<th>Percent risk of colorectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 strips</td>
<td>5.9%</td>
</tr>
<tr>
<td>4 strips</td>
<td>6.8%</td>
</tr>
<tr>
<td>6 strips</td>
<td>7.7%</td>
</tr>
<tr>
<td>8 strips</td>
<td>8.6%</td>
</tr>
<tr>
<td>10 strips</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Baseline risk

Source: World Health Organization/IARC
Step 3 Exposure Assessment

- Who eats the most meat?
- How much do they eat?

**Which countries eat the most red meat?**
Annual beef & veal consumption per capita in OECD countries in 2014

<table>
<thead>
<tr>
<th>Country</th>
<th>Consumption (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>41.6 kg</td>
</tr>
<tr>
<td>Uruguay</td>
<td>37.9 kg</td>
</tr>
<tr>
<td>Brazil</td>
<td>27.0 kg</td>
</tr>
<tr>
<td>United States</td>
<td>24.5 kg</td>
</tr>
<tr>
<td>Australia</td>
<td>21.6 kg</td>
</tr>
<tr>
<td>Israel</td>
<td>19.2 kg</td>
</tr>
<tr>
<td>Chile</td>
<td>18.5 kg</td>
</tr>
<tr>
<td>Canada</td>
<td>18.0 kg</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>17.6 kg</td>
</tr>
<tr>
<td>New Zealand</td>
<td>14.5 kg</td>
</tr>
</tbody>
</table>

**How much meat do you eat a day?**

**ENGLISH BREAKFAST**
- Two sausages: 60g
- Three rashers of bacon: 75g

**CUT IT DOWN**
- One sausage: 30g
- One rasher of bacon: 25g

**HAM SANDWICH**
- Two slices of ham: 50g

**SWAP IT**
- Substitute ham for chicken or tuna: 0g

**SPAGHETTI BOLOGNESE**
- Mince in a regular portion: 100g

**BULK IT OUT**
- Use less meat and add beans or extra veggies: 15g

**285g TOTAL EATEN**
**70g RECOMMENDED DAILY LIMIT OF CONSUMPTION**
Step 4 Risk Characterization

• Is the hazard likely to harm you?

**CANCER RISK: TOBACCO VS. RED MEAT**
Based on 2015 data from the Canadian Cancer Society and a study by Cancer UK, here’s a look at the relative risks posed by smoking and eating red and processed meat:

**LUNG CANCER**
85%
- Cases caused by smoking.*
- That’s 22,610 cases, or 11% of all cancer cases in 2015

**COLORECTAL CANCER**
21%
- Cases caused by eating meat.**
- That’s 5,270 cases, or 3% of all cancer cases in 2015

* Source: Canadian Cancer Society
** Source: Based on a Cancer UK study, using Canadian data; Differences in exposure and behaviour patterns could alter this estimate.

SOURCE: CANADIAN CANCER SOCIETY  DENNIS LEUNG / OTTAWA CITIZEN
4 Steps in Risk Assessment

**Hazard Identification**
Whether a particular chemical can cause an adverse health effect in humans
- qualitative
- weight-of-evidence

**Dose-Response Assessment**
Relationship between the dose of a chemical and the incidence or severity of adverse effect in exposed population

**Exposure Assessment**
Determination of the amount of a chemical to which humans are exposed

**Risk Characterization**
Prediction of the frequency and severity of effects in the exposed population
Epidemiology

- **Advantage:** realistic exposure, in human
- **Disadvantage:**
  - difficult in defining exposure
  - lack of causal element (confounding exposure)
  - limited by statistical significance

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**LEUKÆMIA IN BENZENE WORKERS**

**Peter F. Infante**
**Joseph K. Wagoner**

**Robert A. Rinsky**
**Ronald J. Young**

Institute for Studies in Health and Disease Prevention, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Center for Disease Control, Cincinnati, Ohio 45202, U.S.A.

**Summary.** Workers occupationally exposed to benzene in 1940-49 were followed for vital status up to 1975. In comparison with two control populations, a significant (p<0.002) excess of leukæmia was observed. A five-fold excessive risk of all leukæmias and a ten-fold excess of deaths from myeloid and monocytic leukæmias combined are demonstrated in the study population compared with controls. These figures underestimate the true leukæmia risk to benzene-exposed workers, because follow-up is only 75% complete and the untraced 25% of the study population were all regarded, in the statistical analysis, as being alive at the end of the study period.

The environment of the workers in the study population was not contaminated with solvents other than benzene, and existing records indicate that the benzene levels themselves were generally below the limits recommended at the time of their measurement.
Information for assessment

• Animal experiment
  – Advantage:
    • greatest control over exposure condition, exposed target characteristics, effect measured
  – Disadvantage:
    • uncertainty in extrapolation (species, dose, time frame)
Information for assessment

• Controlled clinical exposures
  – Advantage:
    • defined exposure and population, in human
  – Disadvantage:
    • Exposure at low concentration and short-term
    • Limit to small group and minor effect
    • Most susceptible group not appropriate for study
Risk management

Process of identifying, evaluating, selecting, and implementing actions to reduce risk to human health and ecosystems.

- Information derived from risk assessment
- Social, economical, political, ethical factors
Application in systemic toxicant
Systemic Toxicant Evaluation

- Chemicals that are postulated to induce effect through a threshold mechanism
Systemic Toxicant Evaluation

• Calculate exposure limit
  – Acceptable Daily Intake, ADI (mg/kg/day)
    • estimated (maximum) amount of an agent exposed over lifetime without appreciable health risk (also TDI, tolerable daily intake)

  – Risk reference dose, RfD
    • estimate of the daily exposure that is likely to be without deleterious effects even if continued exposure occurs over a lifetime.

  – ADI/RfD are derived from uncertainty factors (UF)
Systemic Toxicant Evaluation

- Uncertainty factors

<table>
<thead>
<tr>
<th>Extrapolation</th>
<th>Uncertainty Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal to Human (H)</td>
<td>10</td>
</tr>
<tr>
<td>Average to Sensitive Human (S)</td>
<td>10</td>
</tr>
<tr>
<td>LOAEL to NOAEL (L)</td>
<td>10</td>
</tr>
<tr>
<td>Less than Chronic to Chronic (C)</td>
<td>10</td>
</tr>
<tr>
<td>Data Quality (MF)</td>
<td>1-10</td>
</tr>
</tbody>
</table>
Systemic Toxicant Evaluation

- RfD calculation

\[ \text{RfD} = \frac{\text{LOAEL or NOAEL}}{\text{UF}_1 \times \text{UF}_2 \times \text{UF}_n} \]

**Exception**: multiple factors can yield unrealistically conservative RfDs
- 4 factors: 3000-fold UF
- 5 factors: 10,000-fold UF

**LOAEL**: lowest-observed-adverse-effect level
**NOAEL**: no-observed-adverse-effect level
Systemic Toxicant Evaluation

- Example:

  Insecticide: chlorpyrifos (CPS)

  One-dose NOAEL in rat: 0.5 mg/kg

  Chronic RfD in human?

  \[
  \text{NOAEL (0.5)} / \text{UF}_H / \text{UF}_S / \text{UF}_c = 0.0005 \text{ mg/kg/day}
  \]

  \[
  \text{RfD} = \frac{\text{LOAEL or NOAEL}}{\text{UF}_1 \times \text{UF}_2 \times \text{UF}_n}
  \]

  - Animal to Human (H)
  - Average to Sensitive Human (S)
  - LOAEL to NOAEL (L)
  - Less than Chronic to Chronic (C)
  - Data Quality (MF)
Systemic Toxicant Evaluation

• BMD
  – a dose or concentration that produces a predetermined change in the response rate of an adverse effect.
  • Alternative to RfD
  • Address experimental quality, shape of dose-response curve
  • Less dependant on study design
  • Threshold and non-threshold effect
Application in carcinogen
Carcinogen Evaluation

- Carcinogenesis:
  - initiation, promotion, progression

Fig. 2 – Chemical carcinogenesis stages and the occurrences involved in each one.
Carcinogen Evaluation

• Carcinogen
  – Classified according to their mode of action into genotoxic and non genotoxic.
  – Genotoxic: damage to DNA
  – Non-genotoxic: enhance growth of tumor

• Dose-response relationship
  – Threshold or non-threshold
Carcinogen Identification

Carcinogen Evaluation

Decision Point Approach in Carcinogen Testing

Stage A. Structure of chemical
   1. Possible electrophiles
   2. Relation to known carcinogens

Stage B. Short-term genotoxicity assays
   1. Bacterial mutagenesis; hepatocyte DNA repair
   2. Other

   Decision Point 1: Evaluation of findings in stages A and B.

Stage D. In vivo assays
   1. DNA reactivity
      DNA damage assays
   2. Limited bioassays
      Preneoplastic lesions (rat liver, mouse skin, mouse lung, rat breast)
      Transgenic mice

   Decision Point 3: Evaluation of results from stages A to C and selected tests in stage D

Stage E. Carcinogenicity bioassays
   1. Accelerated bioassays
   2. Long-term bioassays

   Decision Point 4: Final evaluation of all results and cancer hazard assessment

   Induction of cytochrome P450
   Peroxisome proliferation
   Hormone perturbation
   Gap junction protein downregulation
   Enhancement of preneoplastic lesions
   Immunosuppression
   Altered gene expression

   Decision Point 2: Evaluation of results from stages A through C.
### Classification Schemes for Carcinogens

#### IARC Carcinogen Classification

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEANING</th>
<th>AGENTS</th>
<th>HOW STRONG IS THE EVIDENCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carcinogenic to humans</td>
<td>118</td>
<td>GROUP 1: Causes cancer</td>
</tr>
<tr>
<td></td>
<td>Includes tobacco, alcohol,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and processed meat</td>
<td></td>
<td>GROUP 2A: Probably causes</td>
</tr>
<tr>
<td></td>
<td>Include anabolic steroids, UV</td>
<td></td>
<td>cancer</td>
</tr>
<tr>
<td></td>
<td>radiation, and red meat</td>
<td></td>
<td>GROUP 2B: Possibly causes</td>
</tr>
<tr>
<td></td>
<td>Include coffee (urinary bladder)</td>
<td></td>
<td>cancer</td>
</tr>
<tr>
<td>2B</td>
<td>Possibly carcinogenic to humans</td>
<td>288</td>
<td>GROUP 3: Not classifiable</td>
</tr>
<tr>
<td></td>
<td>Includes gasoline and nickel</td>
<td></td>
<td>as a cause of cancer</td>
</tr>
<tr>
<td>3</td>
<td>Not classifiable as to its</td>
<td>503</td>
<td>GROUP 4: Probably not a</td>
</tr>
<tr>
<td></td>
<td>carcinogenicity to humans</td>
<td></td>
<td>cause of cancer</td>
</tr>
<tr>
<td>4</td>
<td>Probably not carcinogenic to humans</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caprolactam: common synthetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>polymer</td>
<td></td>
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</tbody>
</table>

These categories represent how likely something is to cause cancer in humans, not how many cancers it causes.
When applying assessment result to regulation

• High Risk Groups

**HOW MUCH MEAT DO YOU EAT A DAY?**
HOW YOUR PROCESSED AND RED MEAT CONSUMPTION CAN ADD UP OVER A DAY...

**ENGLISH BREAKFAST**
- Two sausages... **60g**
- Three rashers of bacon... **75g**

**CUT IT DOWN**
- One sausage... **30g**
- One rasher of bacon... **25g**

**HAM SANDWICH**
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**SWAP IT**
- Substitute ham for chicken or tuna... **0g**

**SPAGHETTI BOLOGNESE**
- Minced beef in a regular portion... **100g**

**BULK IT OUT**
- Use less meat and add beans or extra veggies... **15g**

**TOTAL EATEN** **285g**

**RECOMMENDED DAILY LIMIT OF CONSUMPTION** **70g**
Life is a fatal process. Most of us will not die from chemical exposure.
Thank you for your listening

Questions ?