I. The Difficulties of Regulating Toxic Substances

A. The Problem of Uncertainty
   - The paucity of information
     - NAS (1984): toxicity info on most chemicals is scanty
     - Extensive testing only where warranted by category/form or intended use
       - may ignore some significant risks if not carcinogenic
       - does not consider synergistic effects
   - The difficulty of determining cancer risk
     - Epidemiology studies
       - can only be done after a significant unintended exposure
     - Animal bioassays
       - variability of animal species to various cancers and susceptibility
       - translating animal exposure to human exposure (weight or area?)
       - extrapolating from high levels of exposure to low levels
       - in vitro cell and tissue cultures (better?)

B. Risk-Benefit Statutes
   - Federal Insecticide, Fungicide and Rodenticide Act
   - Toxic Substances Control Act
   - Paralysis by Analysis
   - Criticisms

C. Informational Approaches
   - The Toxic release Inventory
   - CAS’s Proposition 65

Summary

- The Difficulties of Regulating Toxic Substances
  - Is “Tolerable Risk” an Oxymoron?
  - The Problem of Uncertainty
    - The paucity of information
    - The difficulty of determining cancer risk
    - Regulating under uncertainty
  - Major Regulatory Options
    - Pure Health-based Statutes
    - Feasibility Statutes

- What is the fundamental disagreement between these two authors?
  - How to best direct research efforts and funding
  - The potential human risks and exposures of natural vs. synthetic chemicals
  - The proper procedure and data upon which to base health risk estimates
  - The best public health policy
II. Major Regulatory Options
A. Pure Health-based Statutes - FDA
- Delaney Clauses – unsafe additives in foods, drugs, cosmetics
- Only apply to additives, not naturally occurring carcinogens
- No harm? few additives are of sig. economic or societal benefit
- Better? risk-risk comparisons
- 1996 – extended to raw foods
- Acceptable threshold: 1 in a million

B. Feasibility Statutes - OSHA, SDWA
- exposure stds must be both tech. and economically feasible
- MCL’s – no known or anticipated adverse effects w safety margin
- MCL’s (1996) – maximize health risk reduction benefits at a cost justified by benefits

C. Risk-Benefit Statutes – IFRA
- when used correctly, will not pose an unreasonable risk to man or the environment, taking into account all benefits

Rodent Carcinogens – setting priorities
Gold, Slone, Stern, Manley, Ames (UCB, 1992)
- Humans exposed to 99.95% more natural than synthetic chemicals
- Evolved defenses against natural chemicals should lower our susceptibility to synthetic chemicals
- Carcinogenic potential of synthetic & natural chem. similar
- Many common foods would not pass the regulatory criteria applied to synthetic chemicals
- Widespread exposure to naturally occurring rodent carcinogens may cast doubt on the relevance of far lower exposures to synthetic rodent carcinogens
- Need better studies of: species differences, defense/repair systems, effects on human cell division

HERP Index
human exposure / rodent potency
where
human lifetime exposure [mg/kg/d]
Flaws: based on “typical” adult @ 70 kg
rodent potency = TD50 [mg/kg/d]
(required half the number of tumor-free animals by end of study)
Flaws: TD50 or TD01 better
Does not consider multisite, multispecies affects

Risks from this study

<table>
<thead>
<tr>
<th>HERP (%)</th>
<th>Daily human exposure</th>
<th>Rodent carcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Sleeping pill</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>4.7-2.8</td>
<td>Wine (250 mL), Beer (12 oz)</td>
<td>Ethyl alcohol</td>
</tr>
<tr>
<td>1.4-0.4</td>
<td>Mobile home air (14 h)</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td>.12</td>
<td>Diet Cola (24 oz)</td>
<td>Saccharin</td>
</tr>
<tr>
<td>.10</td>
<td>Coffee (3 c)</td>
<td>Caffeic acid</td>
</tr>
<tr>
<td>.03</td>
<td>OJ (138 mL)</td>
<td>d-limonene</td>
</tr>
<tr>
<td>.02</td>
<td>DDT</td>
<td>DDT (pre-ban)</td>
</tr>
<tr>
<td>.01</td>
<td>Chlorinated H2O (1 L)</td>
<td>Chloroform</td>
</tr>
<tr>
<td>.006-.0003</td>
<td>Silicon Valley’s/Woburn Well</td>
<td>TCE (2.8 mg,21 ug)</td>
</tr>
<tr>
<td>.006</td>
<td>Bacon (100 g)</td>
<td>Diethylnitrosamine</td>
</tr>
<tr>
<td>.0005</td>
<td>Hamburger/Salmon (85 g)</td>
<td>PhIP</td>
</tr>
<tr>
<td>.00005</td>
<td>Parsnip/Parsley</td>
<td>8-methoxypsoralen</td>
</tr>
<tr>
<td>.00003</td>
<td>1:1 Million threshold</td>
<td></td>
</tr>
</tbody>
</table>

What to believe?
- “Strong epidemiological evidence indicates that a low intake of fruits and veggies doubles the risk of most types of cancer compared to high intake.”
  - anti-carcinogenic antioxidants and vitamins
- Major preventable cancer risk factors include:
  - tobacco, dietary imbalances, hormones, chronic infections
- “High caloric intake may be the most striking rodent carcinogen b/c restriction markedly lowers cancer rates and increases longevity.”
- Is it cost effective to prevent 1:1 Million risks?

Alleged “misconceptions” distort perceptions of environmental cancer risks
Tomatis, Melnick, Haseeman, Barrett, Huff (NIEHS, 2001)
- “In the absence of human data, animal studies are the most definitive way to assess human cancer risks.”
- Cancer is the 2nd leading cause of death;
- 1.7 M new cases/yr; 580 k annual deaths (2013)
- Most effective prevention strategies:
  - avoiding hazardous occupational exposures, reducing: smoking, exposure to sunlight, exposure to carcinogens
Flaws in Ames’ Approach

- Evaluation of carcinogenicity based on panel vs. single positive trial
- CPDP overestimates by 3-4 the number of potential human carcinogens
- Natural carcinogens seem to be balanced by natural anti-carcinogens that accompany the same food.

Alleged Misconceptions

1. Cancer rates are soaring – 2nd leading cause of death
2. Environmental synthetic chemicals are an important cause of human cancer - can’t affect voluntary risk but can affect involuntary risk
3. Reducing pesticide residues is an effective way to prevent diet-related cancer – go organic
4. Human exposures to carcinogens and other potential hazards are primarily to synthetic chemicals – need to focus on human potency
5. Cancer risks to humans can be assessed by standard high-dose animal cancer tests – all known human carcinogens have been shown to be carcinogenic in animal studies

Alleged Misconceptions

6. Synthetic chemicals pose greater carcinogenic hazards than natural chemicals – for workers, controlling synthetics is critical; risk of natural pesticides is unproven
7. The toxicity of synthetic chemicals is different from that of natural chemicals – depends on chemical
8. Pesticides and other synthetic chemicals are disrupting human hormones – plausible; age groups
9. Regulating low hypothetical risks advances public health – must act on best knowledge

Why Prevention is a Hard Sell

- “There is no drama in prevention; non-events are not counted; statistical lives don’t have immediacy; prevention is not profitable; prevention often runs against commercial interests; it may conflict with personal preferences or religious beliefs; and there is declining trust in leaders and institutions, challenging people’s willingness to follow guidelines.”

EPA Hazard Identification for Carcinogens

Weight-of-Evidence (WOE) of human response, not risk
- Carcinogenic to Humans – typ. epidemiological data
- Likely to be Carcinogenic to Humans – animal bioassay
- Suggestive Evidence of Carcinogenic Potential
- Inadequate Information to Assess Carcinogenic Potential
- Not Likely to be Carcinogenic to Humans – in at least 2 animal species and/or human data
- Inhalation (URE): continuous lifetime exposure of 1 ug/msup
- Ingestion (CPS): 95% C.I. of pop. affected per mg/kg/day

EPA Risk Assessment Cancer Guidelines

- Hazard Assessment
  - Weight-of-Evidence evaluation
- Dose-Response Assessment
  - Linear or non-linear
- Exposure Assessment
- Risk Characterization

www.epa.gov/cancerguidelines
Specific Guidelines – Animal Studies

2.2.2.1 Current standardized carcinogenicity studies in rodents test at least 50 animals per sex per dose group in each of three treatment groups and in a concurrent control group, usually for 18 to 24 months, depending on the rodent species tested (OECD, 1981; U.S. EPA, 1998c). The high dose in long-term studies is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects while not compromising the outcome of the study through excessive toxicity or inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms). The purpose of two or more lower doses is to provide some information on the shape of the dose-response curve.

EPA 2005 Cancer Guidelines

Dose-Response Relationship:

As the dose of a toxicant increases, so does the response

Limitations
- Often derived from acute exposure data.
- Species variation

Ranges:
- 4 Maximum Response
- 2-3 Linear Range
- 0-1 NOAEL

Dose determines the biological response

Two-step approach to dose-response will encourage the use of more data.

Cancer on Tap, Fleckenstein, 2001

- The risks of drinking chlorinated water ...
- ...regulations reflect an accommodating view toward organochlorines.
- ...industry officials and regulators operate with an innocent until proven guilty prejudice.
- ...the Morris study found disinfection by-products in chlorinated water to be responsible for 9% of all bladder cancers and 15% of rectal cancers in the U.S. This translates into 10,000 deaths.
- ...pregnant women with high exposure to chlorinated drinking water nearly doubled their risk of miscarriage, from a rate of 9.5% to 16%
- The effect of all the factors (genetic, diet, exposure to other pollutants) in addition to the one under study, such as chlorinated drinking water, tends to obscure causal relationships.
- ...it is important to recognize that the EPA did not set the standard for disinfection by-products in drinking water based only on their health effects.
Is 10,000 deaths accurate?

- Bladder cancer kills 14,880 people annually
- Colon/rectal cancer kills 51,690 people/yr

National Cancer Inst. (seer.cancer.gov/statistics)

\[ 14,880 \times 0.09 = 1,339 \]
\[ 51,690 \times 0.15 = 7,753 \]
\[ \text{sum} = 9,092 \]

Other factors
- Smoking: OR = 4.2
- Coffee (>4 cups): OR = 3.3

EPA has taken a series of steps ...
Differences between the Rules

Stage 1
- Establishes limits:
  - Chemical disinfectants: maximum residual disinfectant level goals (MRDLG) and maximum residual disinfectant levels (MRDLs) for Cl₂, ClO₂
- Disinfection byproducts:
  - maximum contaminant level goals (MCLGs) and maximum contaminant levels (MCLs) for total trihalomethanes, haloacetic acids, chlorite and bromate

Stage 2
- Tightens compliance monitoring
- Evaluate distribution systems for high risk areas
- Site specific – locational running annual average (LRRA)
- Who:
  - Nontransient CWS, >25, > 6 mo

EPA Stage 2 DBP Rule Compliance Deadlines

<table>
<thead>
<tr>
<th>PUBLIC WATER SYSTEMS</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Submit IDSE, monitoring plan, system specific study plan, or 40-30 certification</td>
</tr>
<tr>
<td>CWs and NTICWs serving at least 100,000</td>
<td>October 1, 2006</td>
</tr>
<tr>
<td>CWs and NTICWs serving 50,000–99,999</td>
<td>April 1, 2007</td>
</tr>
<tr>
<td>CWs and NTICWs serving 10,000–49,999</td>
<td>October 1, 2007</td>
</tr>
<tr>
<td>CWs serving fewer than 10,000</td>
<td>April 1, 2008</td>
</tr>
<tr>
<td>NTICWs serving fewer than 10,000</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Stones may grant up to an additional two years for systems making capital improvements.

Cost-Benefit Process

- Based on Willingness-to-pay (WTP) for given risk reduction
- Value of Statistical Life (VSL) $\approx 7.4$ M/SL/yr
- Value of Mortality Risk (VMR) $\$/\mu\text{risk}/\text{pp}/\text{yr}