Risk Assessment for Regulatory Decision Making

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Terminology

Risk: chance of an adverse outcome

Today's Focus

Risks that entail adverse impacts on human health, safety or the environment

Agenda

- Why do a risk assessment?
- How are risks identified?
- Key technical issues in quantification of risk

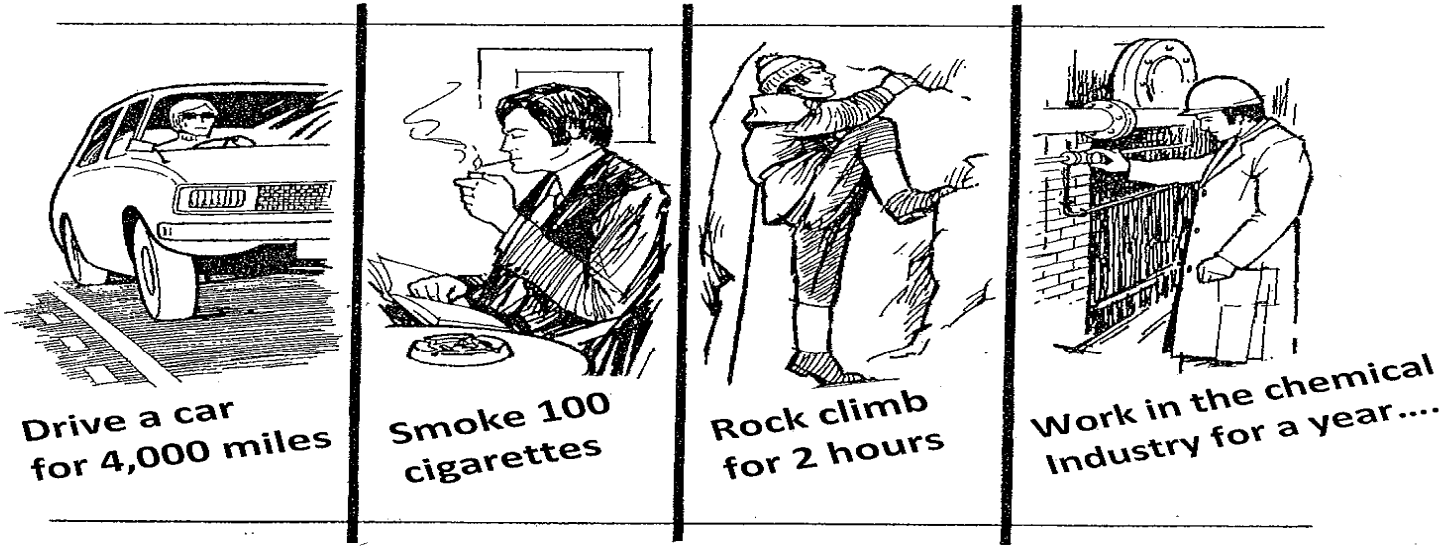
Why Do a Risk Assessment?

Provide Perspective on Magnitude of Risk

Question: Suppose a woman takes long term hormone replacement therapy after age 50. What are the largest changes in health risks?

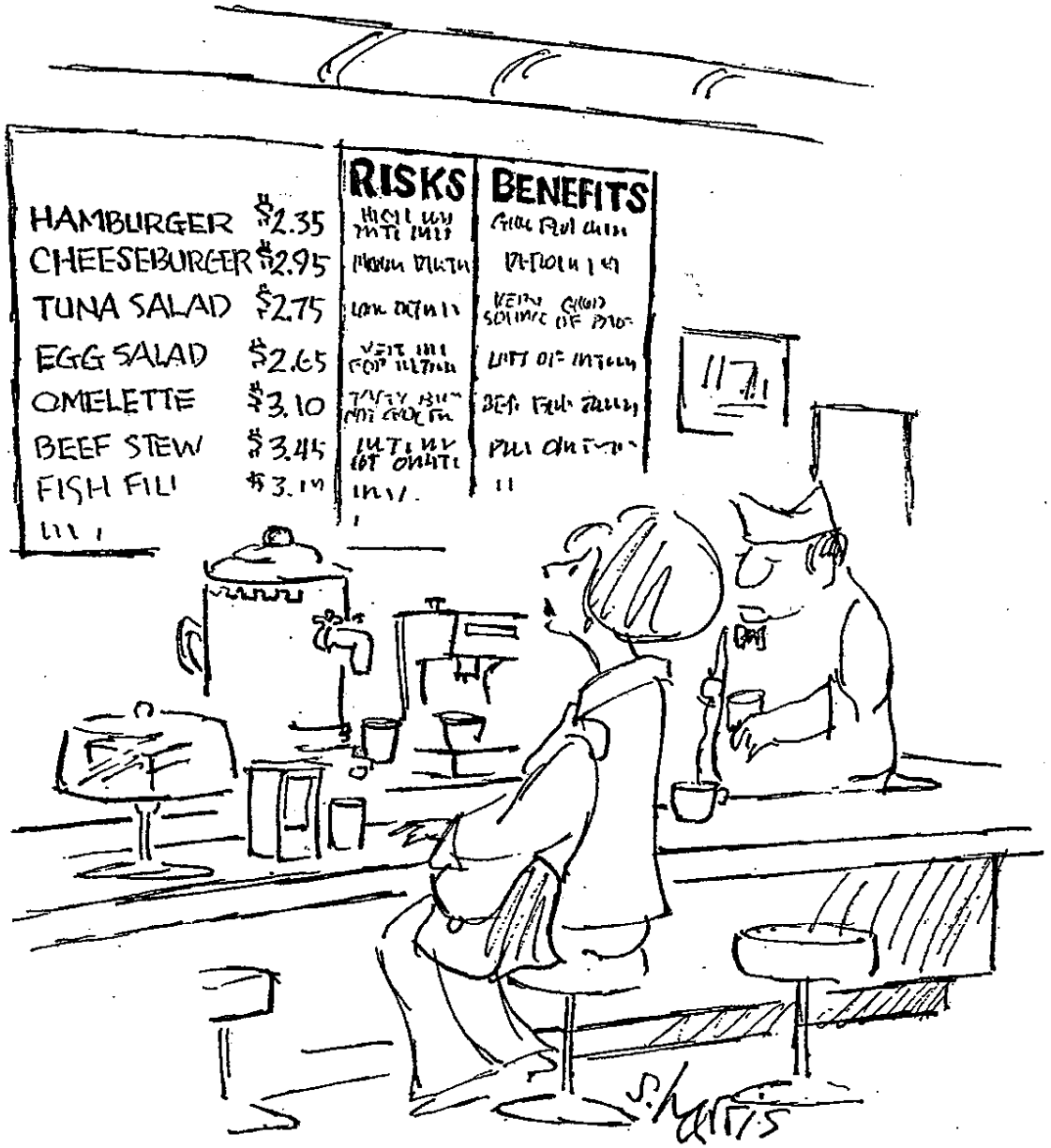
Change in lifetime probability of heart disease	-25% (0.461 to 0.342)
Change in lifetime probability of hip fracture	-17% (0.153 to 0.127)
Change in lifetime probability of breast cancer	+30% (0.102 to 0.130)

IF you...



...the risk to life is the same.

Compare Cost-Effectiveness of Regulatory Options



“League Tables” of Lifesaving Options

	Net Cost Per Life-Year Saved ($1995)
Restrict Cigarette Sales to Minors	$840
Education to Encourage Cholesterol Reduction	$3,400
Radon Mitigation in Homes	$47,000
Frontal-Crash Airbags	$96,000
Reduce Methylene Chloride Levels at Work	$160,000
General Population Screening for HIV	$1,500,000

Compare “Target” Risks to “Countervailing” Risks

(“Risk-Risk” or “Risk-Tradeoff” Analysis)

Nuclear vs. Coal Plants

Prediction (1978) of Law Professor Stephen Breyer (now U.S. Supreme Court Justice):

> If we build coal plants, instead of new nuclear plants, the number of lives lost will be (at least) ten times greater than the number of lives saved.

Small Cars: Greener but Risker?

	Mortality Impact of Replacing Large Cars with Small Cars (USA)
Single-Vehicle crashes	Increase
Multi-Vehicle Crashes	
–Car – Car Crashes	Ambiguous
–Car– SUV Crashes	Increase
–Car – Heavy Truck Crashes	Increase
Crashes with Pedestrians & Cyclists	Reduce
OVERALL IMPACT	Increase

The Biggest Myth about Risk Assessment

"It is an anti-regulatory tool that undermines protection of the public."

Pro-Regulation Uses of Risk Assessment (USA 2001-2006)

Agency	Rule(s)
FDA	Label foods for trans-fat content
DOT	Fuel-saving mileage rules for SUVs
EPA	Reduce air pollution from diesel engines and coal plants
OSHA	Reduce worker exposures to hexavalent chromium

How Risks Are Identified

1) Clinical Case Reports

- Turkish hematologist Aksoy reported treating shoe makers with fatal diseases of the bone marrow (benzene was used as an adhesive).

- Clinicians reported autoimmune disorders among women with silicone breast implants (suspected leaking implants).

Clinical Reports (cont.)

•Aksoy hypothesis was confirmed in study of U.S. rubber manufacturing (two Ohio factories)

Observed Deaths from Acute M. Leukemia	Expected Deaths	Relative Risk
7	1.5	4.7

•Hypothesis of auto immune disorders from silicone breast implants was not confirmed in large sample of U.S. patients

2)Epidemiology: Patterns of Disease in Human Populations

- many physicians doubted that smoking causes lung cancer (1950's).
  - some patients who smoked heavily did not develop lung cancer
  - some nonsmoking patients were treated for lung cancer
  - required large-scale statistical studies (U.K. physicians!) to see the association.

- Both clinical case reports and epidemiology, while valuable, are too reactive to inform prevention.

3) Controlled Experiments

- Human Volunteers (informed consent)

  Example: Safe level of carbon monoxide (USA) in outdoor air (9 parts per million) was set by controlled study of adult angina patients who exercised vigorously at different CO levels. Outcome: time to patient reports of chest pain.

  Note: There are growing ethical constraints but such studies of human volunteers remain critical to understanding metabolism and pharmacokinetics of drugs, pesticides, pollutants, food additives and industrial chemicals.

- Animal Experiments (short term or lifetime exposures)

  –surprise finding (1979): formaldehyde causes nasal cancer in Fischer 344 rats
  –typically 2-year experiments with rodents to detect chronic diseases from repeated exposures.

Formaldehyde Concentration (ppm in air)	Malignant Tumor Counts (%)
	Rats
0	0/208 (0)
2.0	0/210 (0)
5.6	2/210 (2)
14.3	103/206 (50)

Note: exposures for six hours/day, five days/week; F-344 rats.

4)Theory and Mechanistic Studies

- chemicals that cause mutations or other genetic changes in cells may pose particular risk.

- chemicals that are not mutagens and cause cancer only at high doses via cell proliferation may be of less concern.

  Example: the artificial sweetener saccharin.

5) Fault-Tree Analysis

- Designed for low-probability, high-consequence events
- Applications to nuclear power plants, chemical factories, terrorist attacks
- Frequency of calamities is too small to rely on empiricism yet frequency of precursor events can be modeled

6) Large-Scale, Integrated Computer Models

- model inputs derived from hard data, theory, analogy and assumptions

- played critical role in identifying risks of stratospheric ozone depletion and global climate change

Issues in Quantification of Risk

1)Extrapolation from one species to another

Formaldehyde Concentration (ppm in air)	Tumor Counts (%)	Malignant Tumor Counts (%)
	Rats	Mice
0	0/208 (0)	0/72 (0)
2.0	0/210 (0)	0/64 (0)
5.6	2/210 (2)	0/73 (0)
14.3	103/206 (50)	2/60 (3.3)

Note: exposures for six hours/day, five days/week; F-344 rats and B6CF1 mice.

2) Extrapolation from high to low doses

Worker Exposure Level	Excess Lifetime Cancers Per 100,000 Persons			
	Multistage Model		Probit Model	
	MLE	UCL	MLE	UCL
1.0 ppm	7.4	411	3.8	73
0.1 ppm	0	102	0.1	3

3) Weighing Multiple Studies

Example: Lung Cancer and Environmental Tobacco Smoke (conflicting results)

Study Type	Relative Risk of Lung Cancer Among Non-Smoking Women
Case-Control Design (N=35)	1.19 (95% C.I.: 1.10-1.29)
Cohort Design (N=5)	1.29 (95% C.I.: 1.04-1.62)

Beware: Subjective decisions in “meta=analysis”: which studies to include, how to adjust for study quality, and investigator reputation.

Note: 95% C.I. = 95 percent confidence interval.

4) Conveying Uncertainty

- Subjective probabilties: The United Nations IPCC recently upgraded the probability of human-induced climate change from 0.6 to 0.9 on a 0-1.0 probability scale.

- Question: How should disputing experts be handled?

- Combining Hard Data and Subjective Probabilities through Simulation

Annual U.S. Cancer Incidence
Due to Inhaling 2.8 ppb Formaldehyde

Percentile	Excess Cancer Cases
5th	0
25th	0
50th	~0
75th	0.05
95th	220
99th	>800

Note: Exposed population is assumed to be 240 million Americans for a lifetime.

5) Accounting for Variability

- Genetic susceptibility to disease may vary widely in the population

Example

One simulation study of cancer risk suggested that the 80% of the U.S. population who are least susceptible to cancer risk incur only 10% of the overall risk.

- Exposure to risk also varies widely (e.g., intake of dietary cholesterol: 2 eggs/day versus 2 eggs/month).

Issues of equity: Proximity of Coke Plants and the Poor

	Percent Poor	Percent Nonwhite	Percent Hispanic
U.S. Average	13.1	19.7	8.8
Census Tracts w/Coke Plants	25.1	29.5	8.7
Census Tracts Adjacent to Coke Plants	18.3	22.1	6.9

Note: Coke plants are both a source of local employment and a source of localized air pollution.

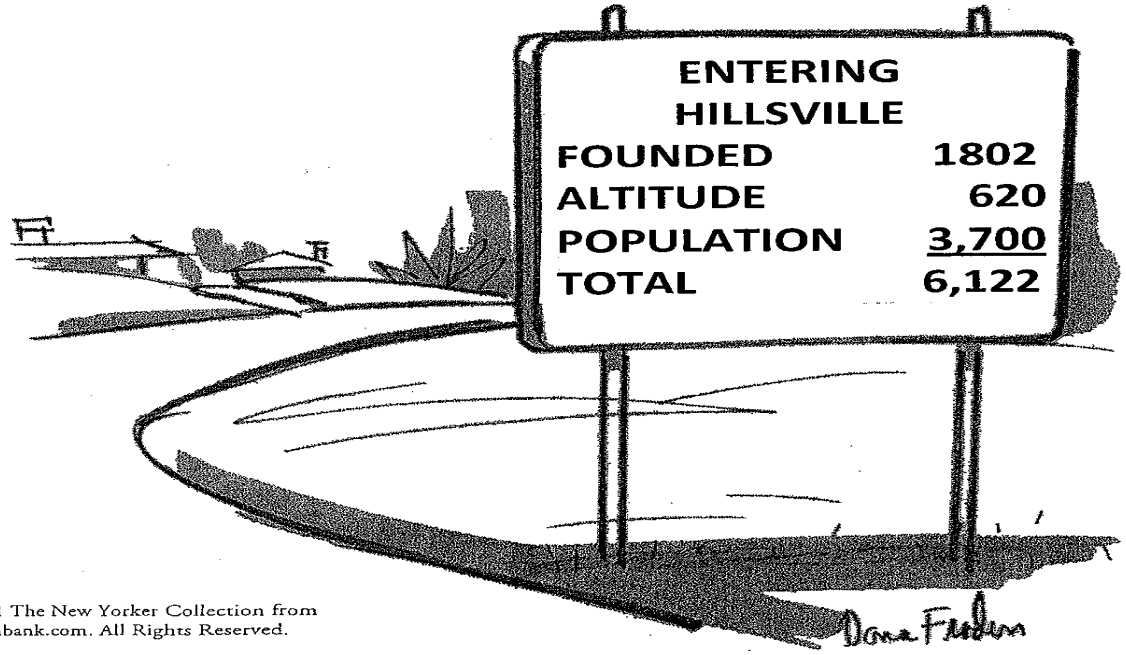
6) When is a biological event “adverse”?

Example

Should presence of a toxic material in blood be considered “adverse”? How about cellular changes due to a chemical exposure? How about metaplasia or a benign tumor?

Keys to Quality in Risk Assessment

- Transparency in data and models (ability to replicate)
- Rigorous expert peer reviews
- Opportunity for stakeholder comment and explicit response to those comments
- Responsiveness to informational needs of regulator



Useful Text

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Thank You!