Toxicology in Regulatory Process

Xin Zhang

Comprehensive Pneumology Center

11.03.19

Love Canal Disaster

Regulatory toxicology

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

Chemical Resource:

Cosmetics, consumer products
- Safety assessment

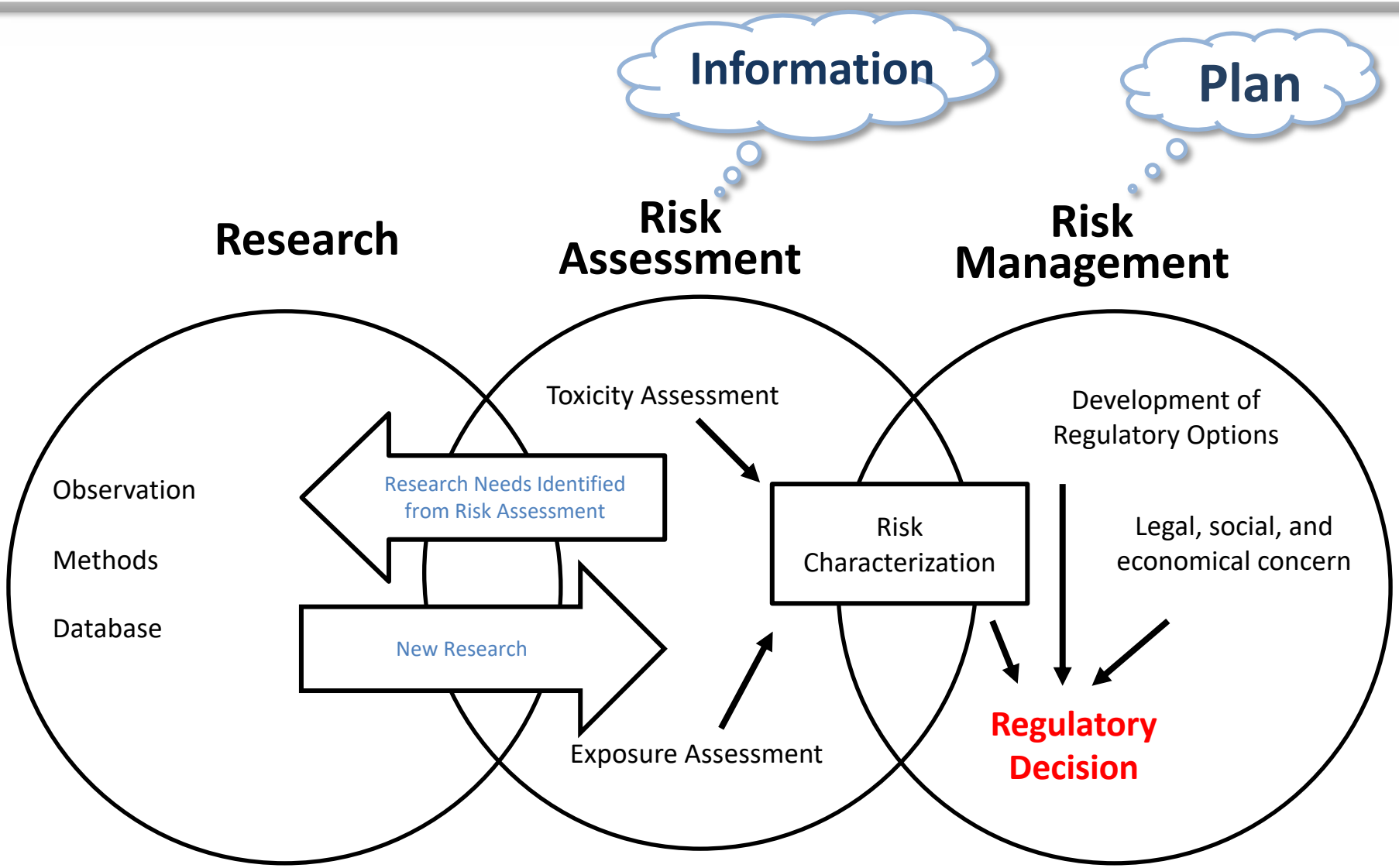
Environmental contaminants
- Drinking water
- outdoor/indoor air
- soil, waste sites

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

Food safety
- Addictive
- Contaminants

Occupational safety
- Hazardous substances at workplace

Regulatory Process



Scientific Frontiers in Developmental Toxicology and Risk Assessment, 2000

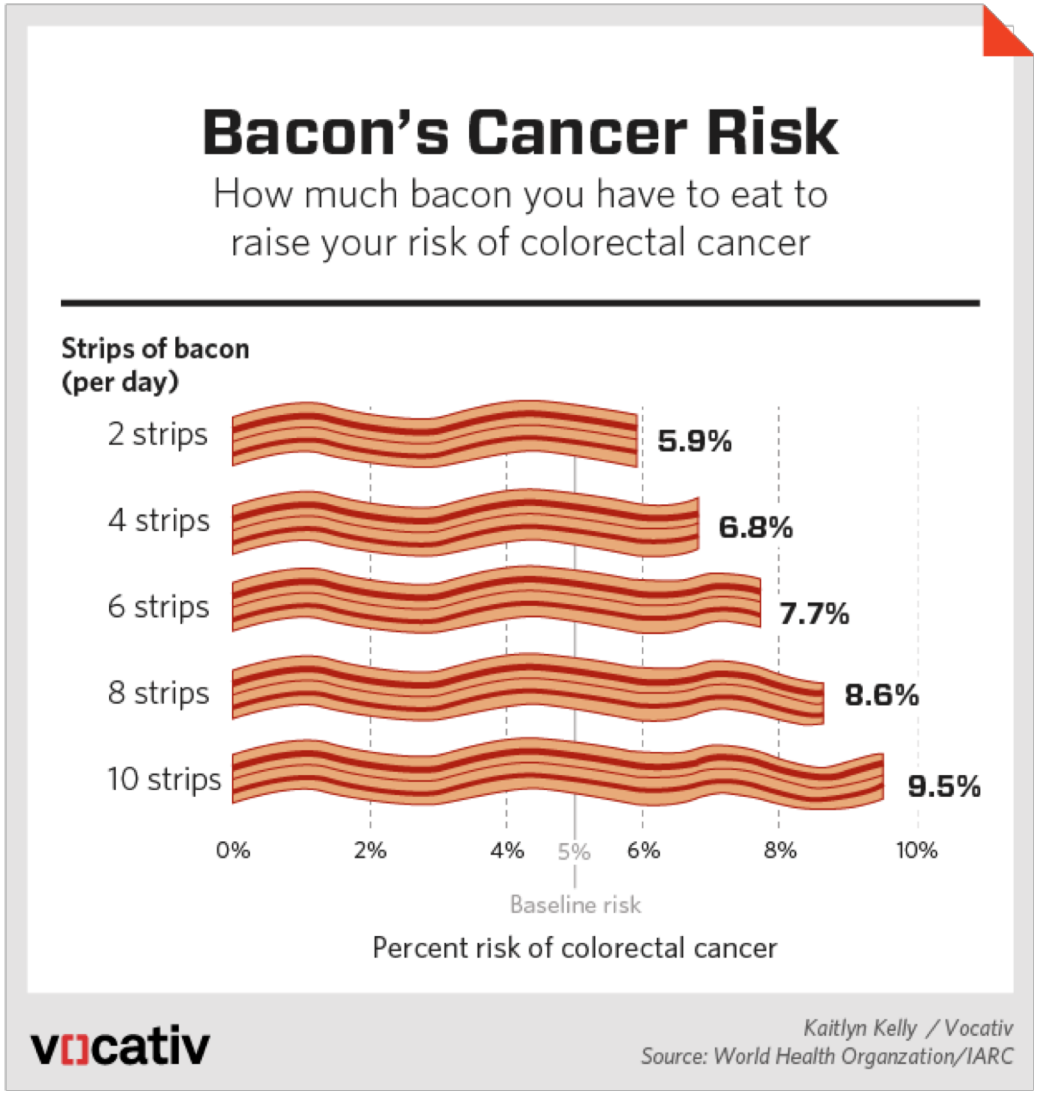
Step-1 Hazard Identification

- **What might be harming you?**

Red and processed meat ? ⟹ Cancer

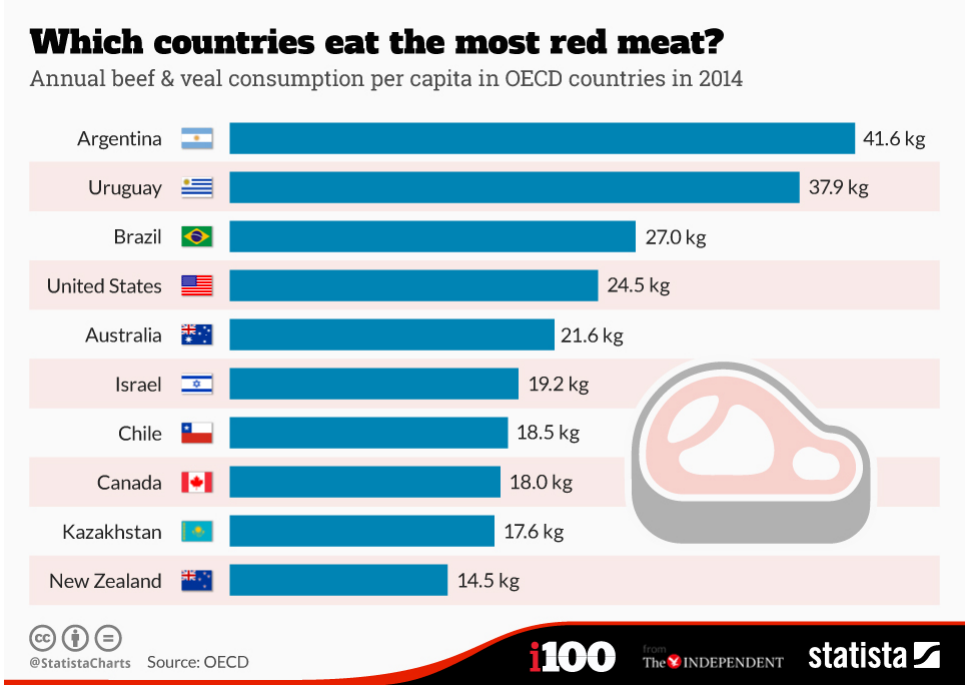
Step 2 Dose-Response Evaluation

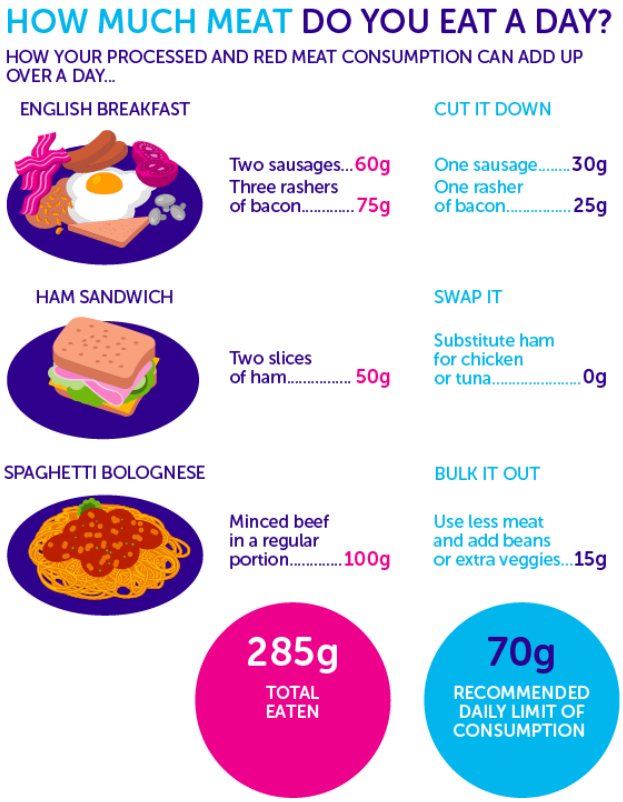
- Health problems at different exposures?



Step 3 Exposure Assessment

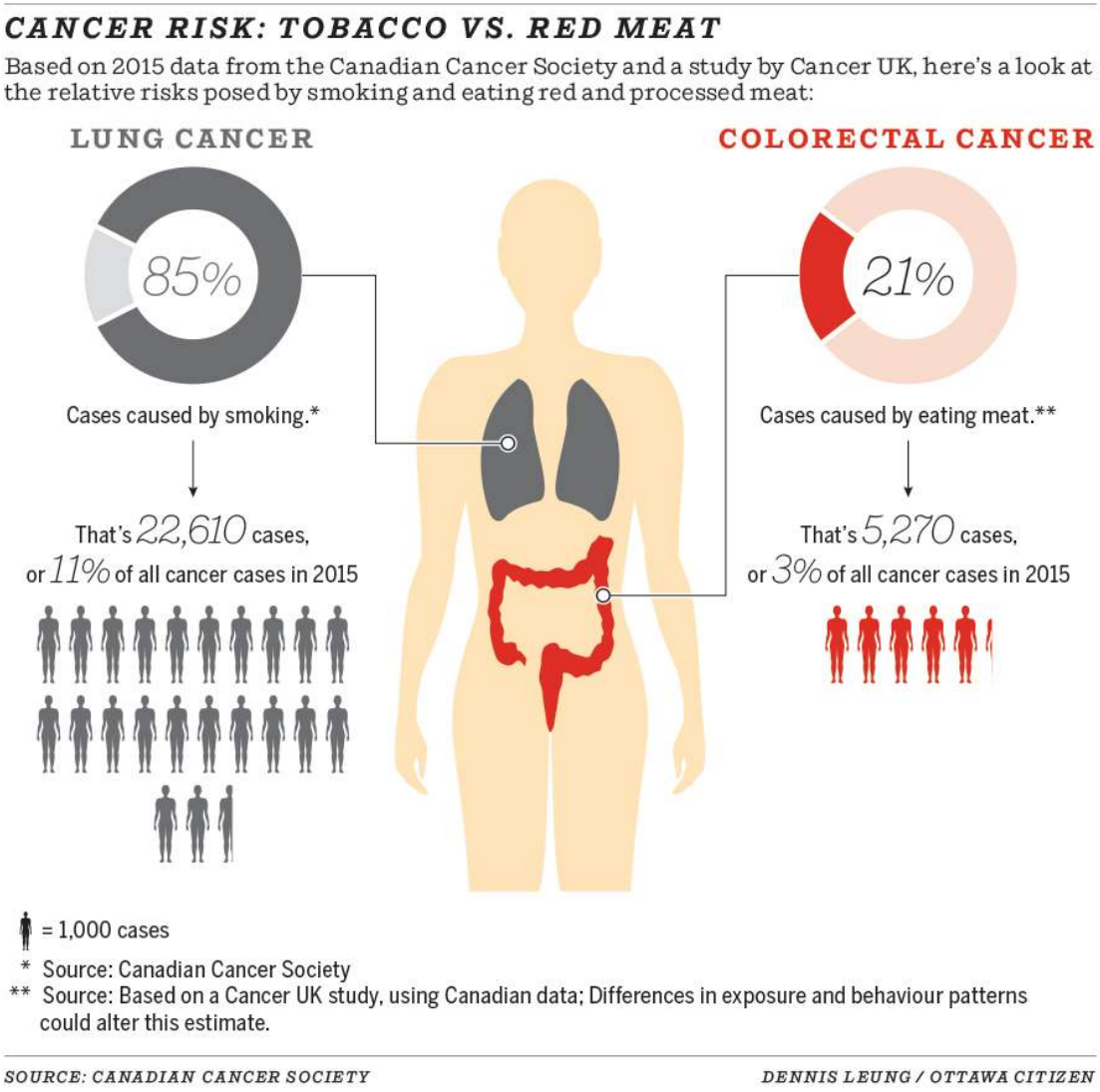
- Who eats the most meat?
- How much do they eat?





Step 4 Risk Characterization

- Is the hazard likely to harm you?



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

Information for assessment

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

LEUKÆMIA IN BENZENE WORKERS

PETER F. INFANTE
JOSEPH K. WAGONER
ROBERT A. RINSKY
RONALD J. YOUNG

Industrywide Studies Branch, Division of Surveillance, 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 ($P<0{\cdot}002$) 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)

Benzene: A Multipotential Carcinogen. Results of Long-Term Bioassays Performed at the Bologna Institute of Oncology

Cesare Maltoni, MD, Barbara Conti, MD, and Giuliano Cotti, PhD

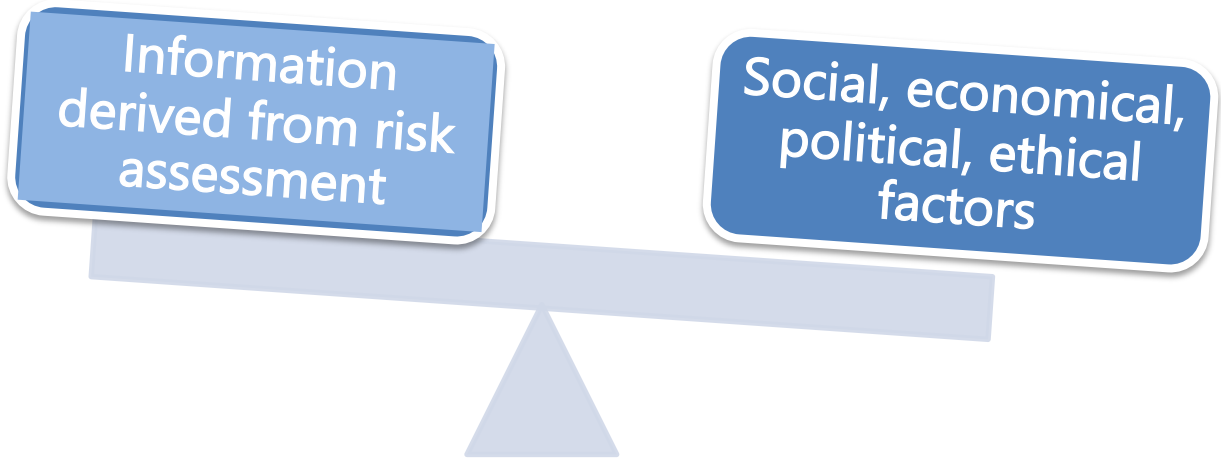
Until recently, the evidence of benzene carcinogenicity was based only on the association between benzene occupational exposure and human leukemia, with many limited case reports and scanty epidemiological data. Available experimental studies up to 1976 on animals were rare, fragmentary, and inadequate, and had failed to prove the carcinogenic effects of benzene. However, an integrated project of long-term carcinogenicity bioassays, begun in our laboratory in 1976 and still continuing, has shown that benzene produces a variety of tumors in rats including Zymbal gland carcinomas, carcinomas of the oral cavity, hepatocarcinomas, and possibly mammary carcinomas, lymphoreticular neoplasias, and other malignancies. Some of the tumors caused by benzene are uncommon or unusual in the breed of rats studied. Therefore benzene must be considered, under the studied experimental conditions, a strong multipotential carcinogen. The need for more experimental research is emphasized, particularly to assess the carcinogenic effects of low doses. Also recommended are more comprehensive epidemiological investigations, extended to all types of malignancies, and the application of adequate measures for primary prevention.

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

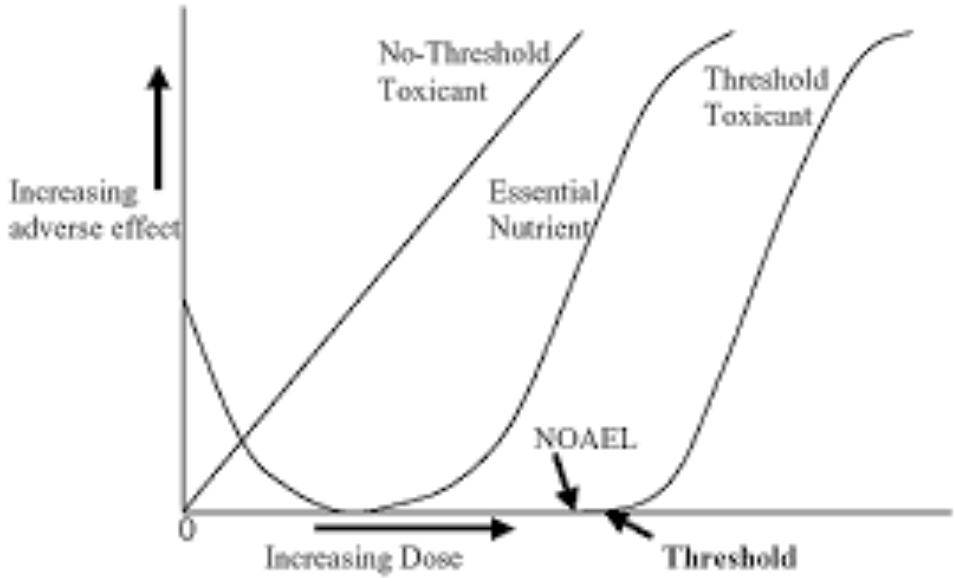
Process of identifying, evaluating, selecting, and implementing actions to reduce risk to human health and ecosystems.



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)

GEORGE C., Handbook on the Toxicology of Metals (Third Edition), 2007

Systemic Toxicant Evaluation

- Uncertainty factors

U.S. EPA Guidelines for Development of RfD*

Extrapolation	Uncertainty Factor
Animal to Human (H)	10
Average to Sensitive Human (S)	10
LOAEL to NOAEL (L)	10
Less than Chronic to Chronic (C)	10
Data Quality (MF)	1-10

Systemic Toxicant Evaluation

- RfD calculation

$$\mathrm{RfD} = \frac{\mathrm{LOAEL\ or\ NOAEL}}{\mathrm{UF}_1 \times \mathrm{UF}_2 \times \mathrm{UF}_n}$$

Uncertainty involved

LOAEL: lowest-observed-adverse-effect level
NOAEL: no-observed-adverse-effect level

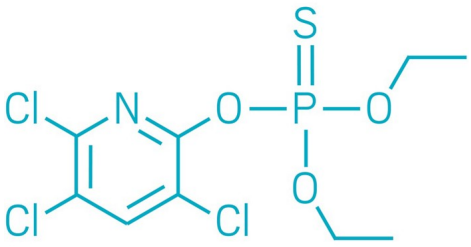
Exception: multiple factors can yield unrealistically conservative RfDs

- 4 factors: 3000-fold UF
- 5 factors: 10,000-fold UF

Systemic Toxicant Evaluation

- Example:

Insecticide: chlorpyrifos (CPS)
One-dose NOAEL in rat: 0.5 mg/kg



Chlorpyrifos

Chronic RfD in human?

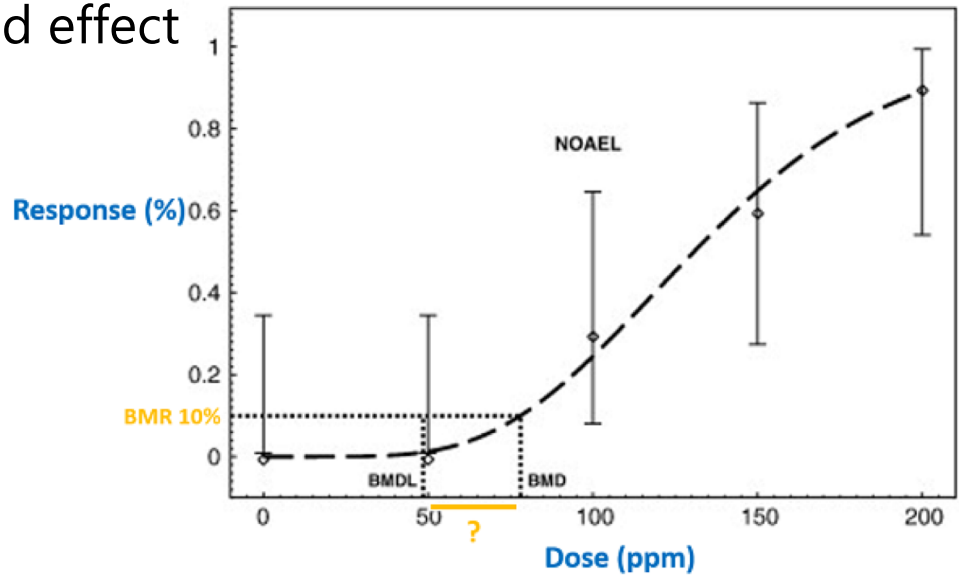
NOAEL (0.5)/UF_H/UF_S/UF_c =0.0005 mg/kg/day

$$\mathrm{RfD} = \frac{\mathrm{LOAEL\ or\ NOAEL}}{\mathrm{UF}_1 \times \mathrm{UF}_2 \times \mathrm{UF}_n}$$

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

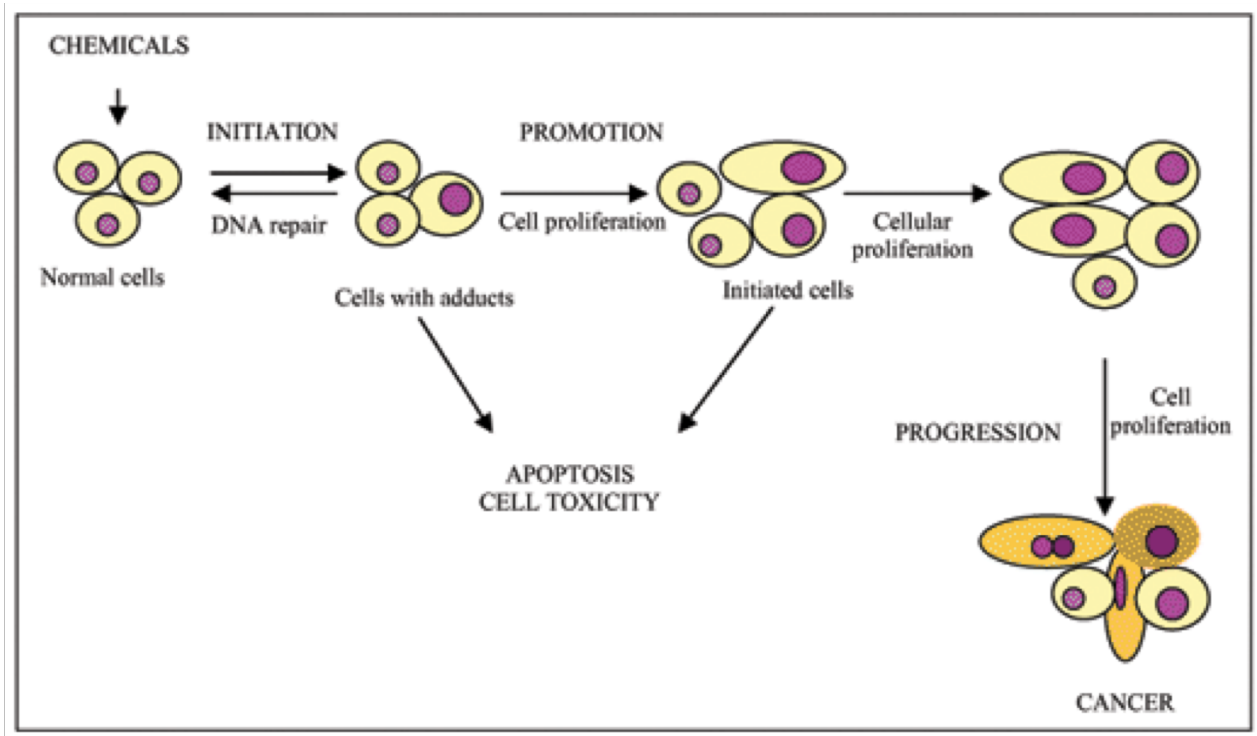


Fig. 2 – Chemical carcinogenesis stages and the occurrences involved in each one.

Paula A., Chemical carcinogenesis, 2007

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

Carcinoge

- Carcinc

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

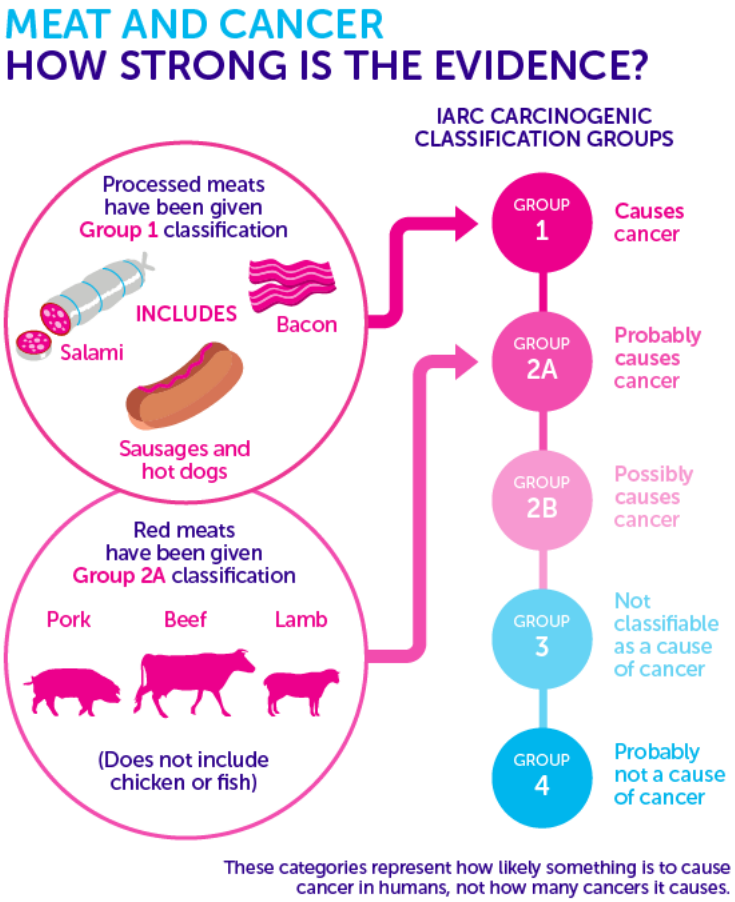
Altered gene expression

Decision Point 2: Evaluation of results from stages A through C.

Classification Schemes for Carcinogens

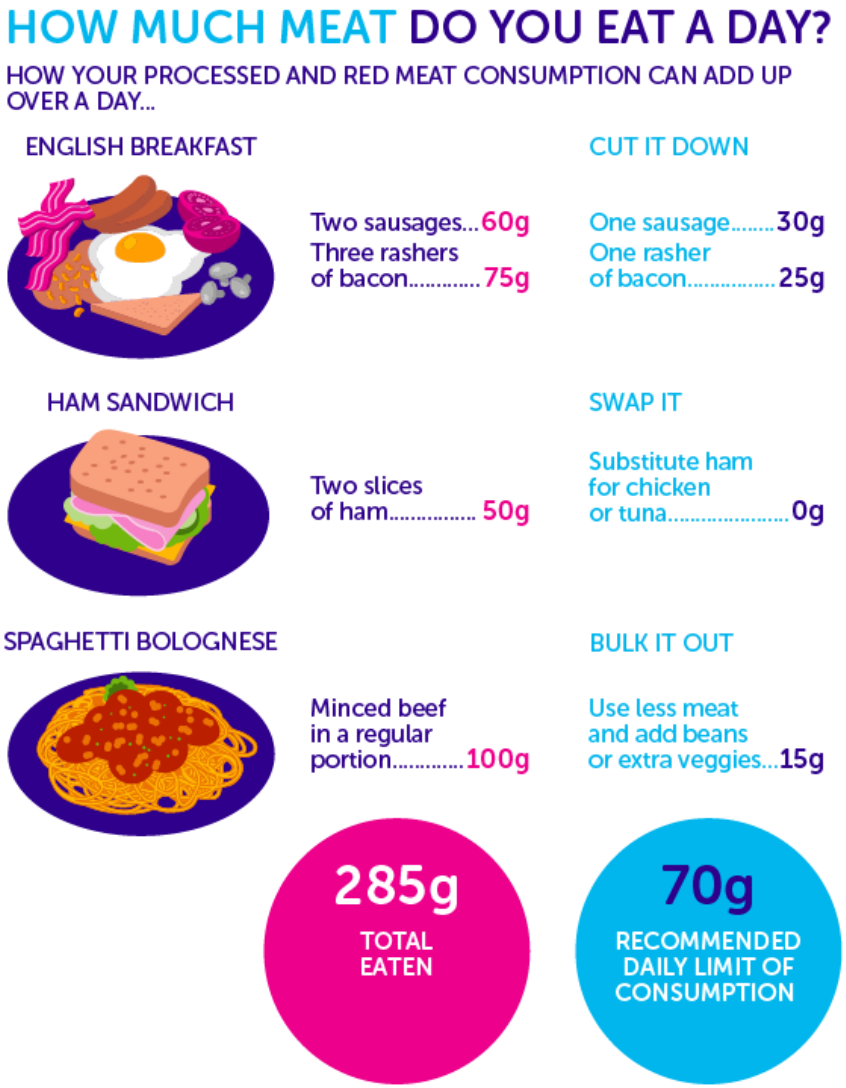
IARC Carcinogen Classification

GROUP	MEANING	AGENTS
1	Carcinogenic to humans	118 Includes tobacco, alcohol, and processed meat
2A	Probably carcinogenic to humans	75 Includes anabolic steroids, UV radiation, and red meat
2B	Possibly carcinogenic to humans	288 Includes coffee (urinary bladder) gasoline,and nickel
3	Not classifiable as to its carcinogenicity to humas	503 Includes caffeine, tea, and acrylic fibers,
4	Probably not carcinogenic to humans	1 Caprolactam: common synthetic polymer



When applying assessment result to regulation

- High Risk Groups



Life is a fatal process. Most of us will not die from chemical exposure.

Thank you for your listening

Questions ?