Quantitative Risk Assessment: An Overview and Discussion of Emerging Issues

Anne-Marie Nicol, PhD

National Collaborating Centre for Environmental Health

Centre de collaboration nationale en santé environnementale

Today's talk

- Broader overview of Risk Assessment process (at the US EPA)
  - Explanation of the 4 step formal process
- Some of the current issues/problems with this approach
- New directions
- Broad discussion, not specific details
  - Have provided many links for those wanting more information

What is Risk Assessment?

- Process evolved in the US in the 1970s
- First ever risk assessment done for community exposures to Vinyl Chloride
  - (Kuzmack and McGaughy, 1975)

Setting the stage for environmental change

- Growing concern re: pollution during the 1960s
  - 1962 Rachael Carson's Silent Spring
- Nuclear power releases
  - 1966 coolant accident near Detriot, explosions in Idaho
- 1965 lead pollution from gasoline
- Environmental advocacy groups established
  - WWF, Environmental Defense Fund, Friends of the Earth
  - Sierra Club undertakes lawsuits on mines

Photos from
http://www.makingthemodernworld.org.uk

From the Ohio Historical Society http://www.ohiohistorycentral.org

Establishment of the US EPA

- EPA established Dec 2nd 1970
  - Richard Nixon in office
- Set national, environmental laws regulations to protect human health and safeguard air, water and land
- Governing body for Clean air act, followed by water and pesticide acts

Current EPA Seal, as of November 19, 2002

Original EPA Seal, from October 18, 1971

Intro: What is a hazard?

- Hazard- an agent, chemical or characteristic that can cause harm to humans
- Examples:
  - Pesticides in drinking water
  - Radon exposure in basements
  - Working Shift work
  - Sitting for prolonged periods
  - Fetal toxins

What is a risk?

- Risk: the ***probability*** that a hazard will cause harm in the future
- Often used inadvertently to mean hazard

Google's first definition:

risk
/risk/

Noun
A situation involving exposure to danger: "flouting the law was too much of a risk".

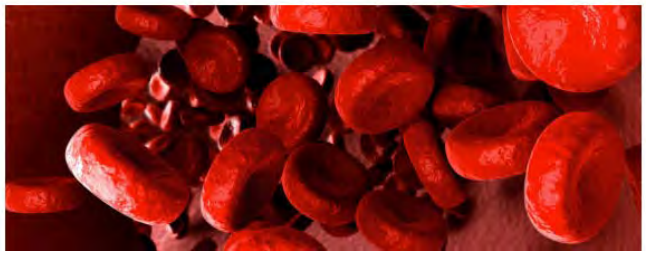
Verb
Expose (someone or something valued) to danger, harm, or loss: "he risked his life to save his dog".

Synonyms
noun. hazard - peril - jeopardy - danger - venture - chance
verb. hazard - venture - jeopardize - adventure - chance

Heart Risks From Sleep Apnea Similar To Those From Diabetes: Study

Posted: 12/17/2012 8:51 am EST

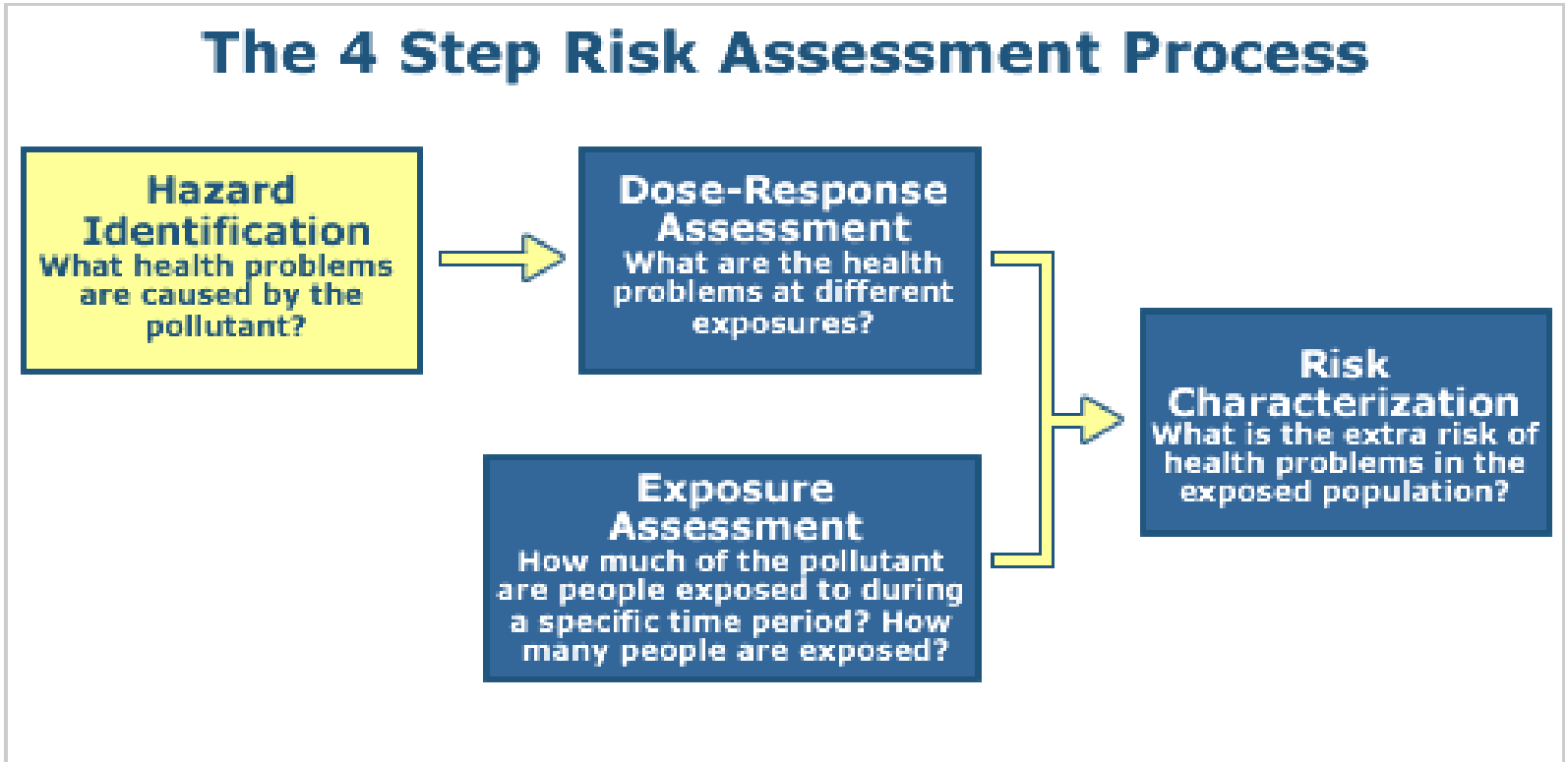
Like 134 people like this.



Risk Assessment- shifting definitions

- 1983 : characterization of the **potential adverse effects of human exposures** to environmental hazards
- 2004 EPA: **process** in which information is analyzed to determine if an environmental hazard might cause harm to exposed persons and **ecosystems.**

The formal, 4 step process



Step 1: Hazard Assessment

- What is the hazard?
- Does exposure to an agent cause an increase in the incidence of a health condition (EPA 1983)?
- Showcase of the evidence of causality
  - Animals studies, in vitro studies
  - Human studies where possible
    - Occupational exposures
    - Series of unfortunate events (environmental disasters)
      - Minimata in Japan

Step 1: Guidelines

- Human data trumps animal data
  - No uncertainty in extrapolating between species
  - Sadly(?) the database is often incomplete
- Which health outcome to choose?
  - "biologically relevant effect"
    - Cellular changes? Sweating?
  - Reversible versus irreversible?
  - Organism adapts to exposure?

Challenges

Who is the hazard for?

- Risk assessment bases assumptions of exposure effects, averaged over time, BUT EPA supplement notes:

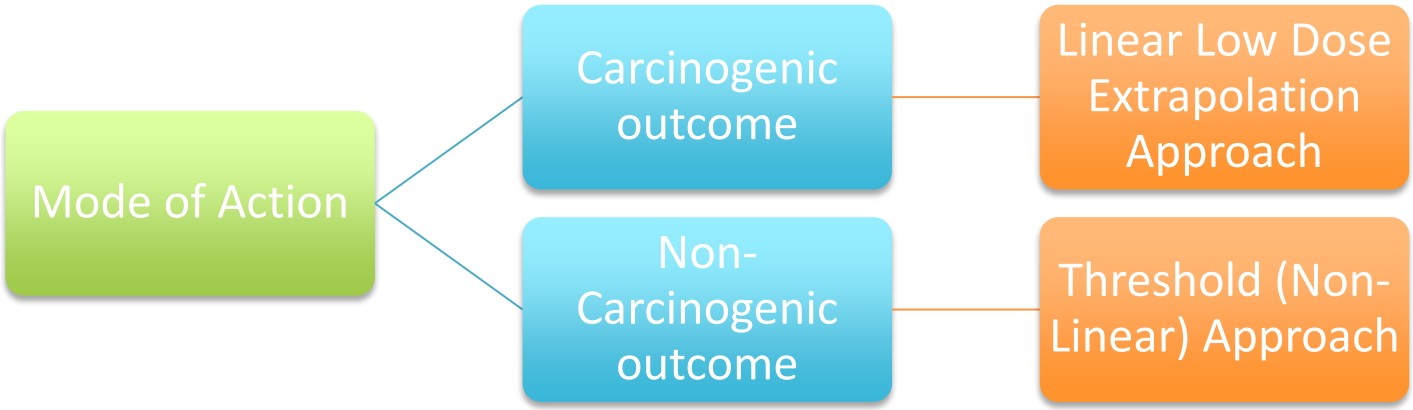
  "Analysis by Halmes et al. (2000) showed that, for six of the eleven chemicals and half the tumor sites, the assumption that the cancer risk would be equal when the product of concentration and time (i.e., C x T) was **constant was incorrect, and usually underestimated risk, as more of the risk came from the beginning of the exposure rather than the end."**

  -can be up to 10x higher risk for early life exposures than late

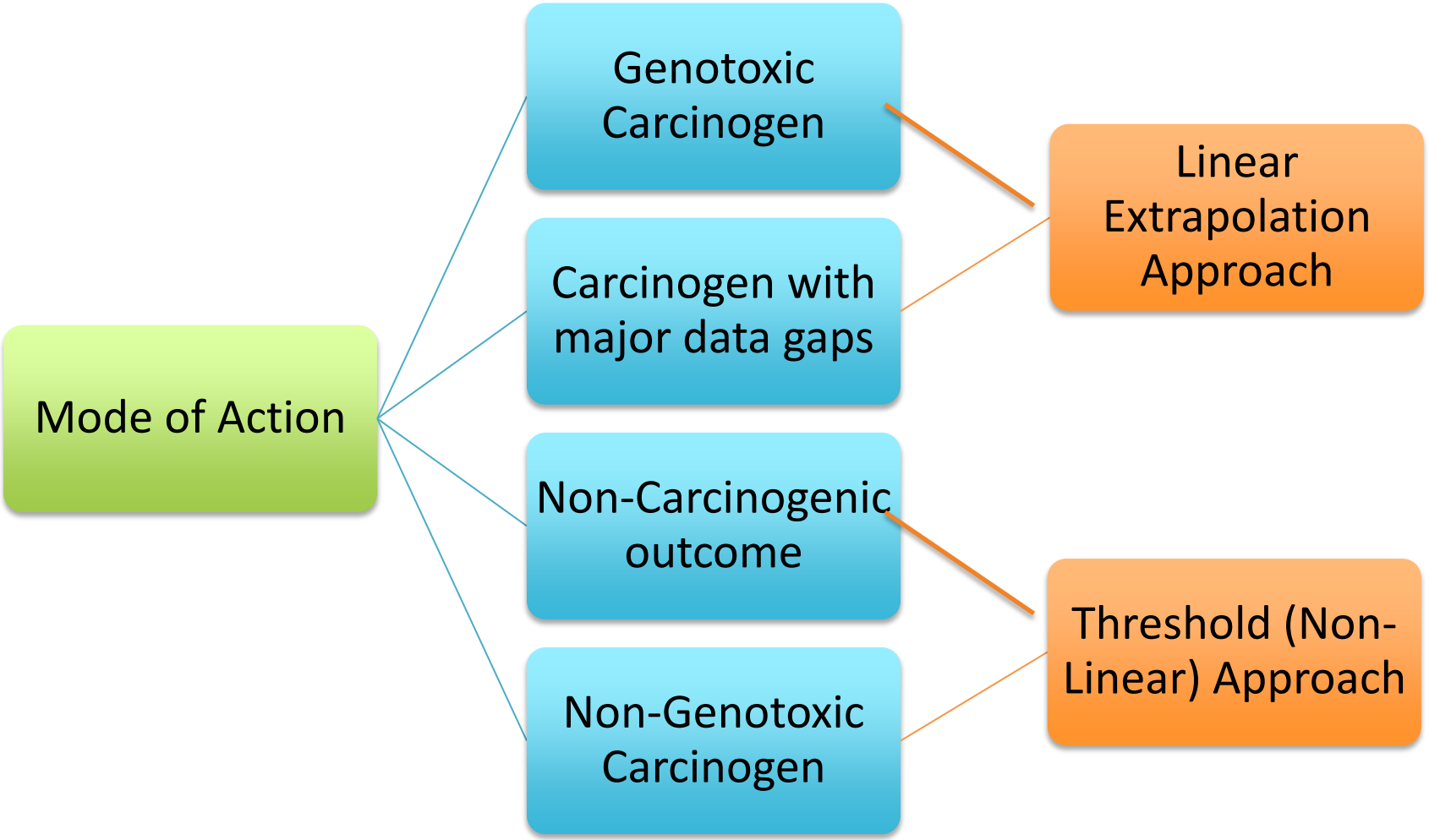
- **"Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens" EPA/630/R-03/003F- 2005**
- Encourages consideration of developing
  - separate risk assessments for children
  - using child specific diet and behavior patterns as these tend to increase exposure

Mode of Action: The Crux of the Matter

1983-2005

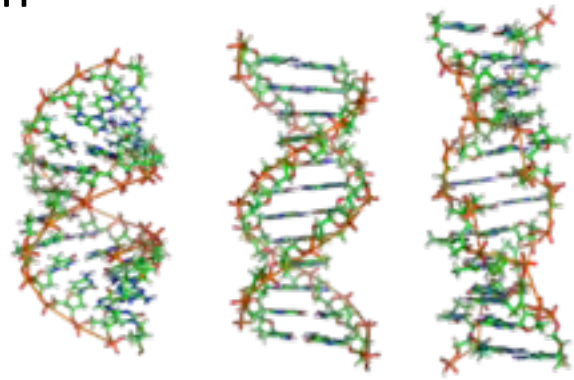


Changes in 2005



Why the Change?

- Initial models assumed that cancer causing agents lead to genetic alterations at any level
  - Research has shown however that some compounds may indicate a threshold effect
- So: Genotoxic
  - Compounds that directly break/ damage DNA
    - Ionizing radiation, vinyl chloride, aflatoxin
- Non-Genotoxic/Epigenetic
  - Contributes to tumour development
    - Encourages tumour growth
- Overall: Less ALARA Compounds…



Problems with this division

- Some *weak* genotoxic compounds indicate a threshold (formaldehyde)
- Some compounds have both modes of action
- Some are multi-organ toxicants (acrylonitrile)
    - Database not complete for all organs
- Some animal carcinogens don't seem to work the same way in humans (BHA, Phenobarbital)
  – Vice versa?

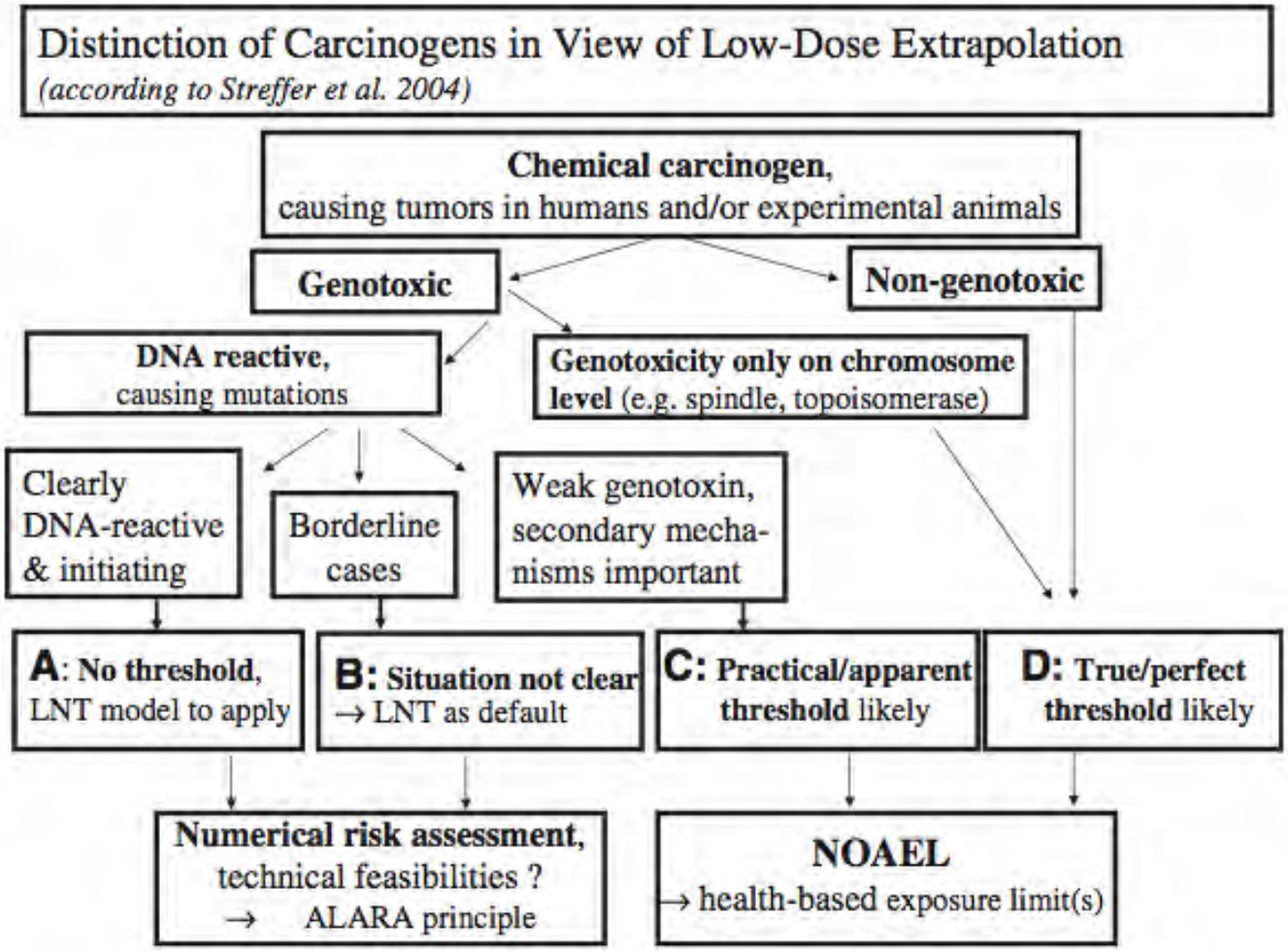
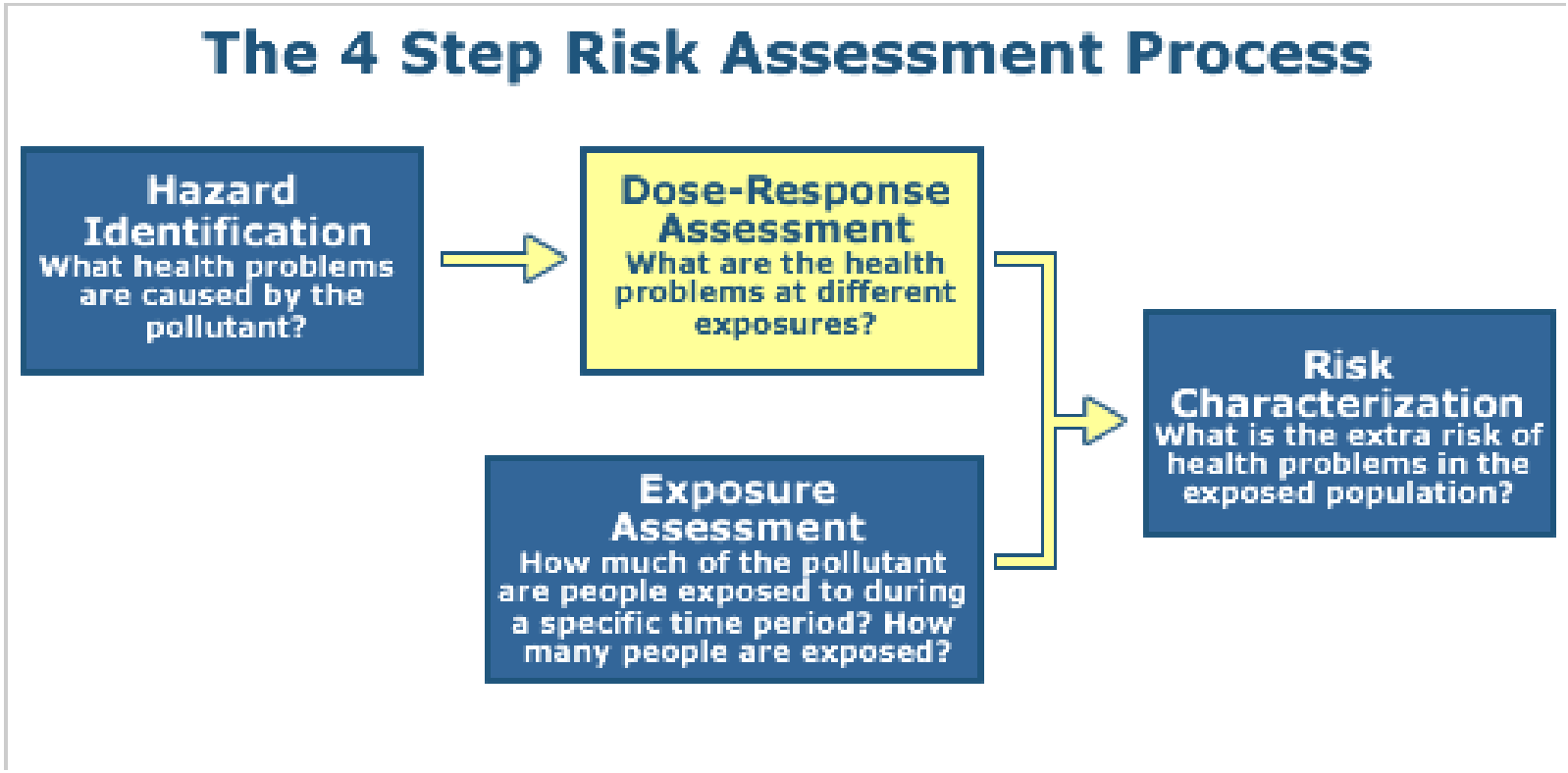


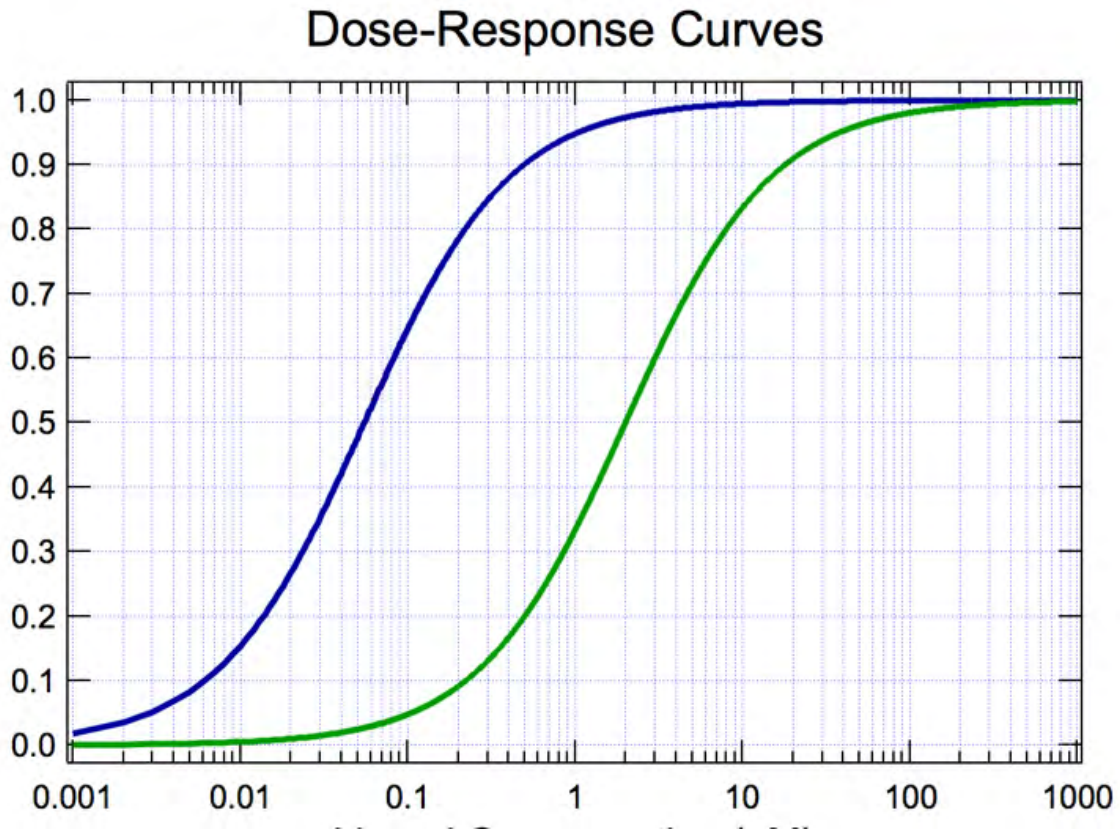
FIG. 1. Proposal to distinguish among groups of carcinogens (A–D) for the purposes of risk assessment and standard setting (Bolt *et al.*, 2004 modified).

Step 1 final result

- Chosen an adverse health outcome
  - Generally sensitive outcome for most sensitive population
  - Not always the worst condition (developmental versus cancer)
- Evaluated the weight of evidence
  - Discuss limitations, gaps
- Determined Mode of Action
  - Important for next step
- SOMETIMES STOP HERE: may be possible that there just isn't enough data

Step 2: Dose Response





Step 2: Dose- Response

"the dose makes the poison"- *Paracelcus*

What is the shape of the relationship between the dose and the response?

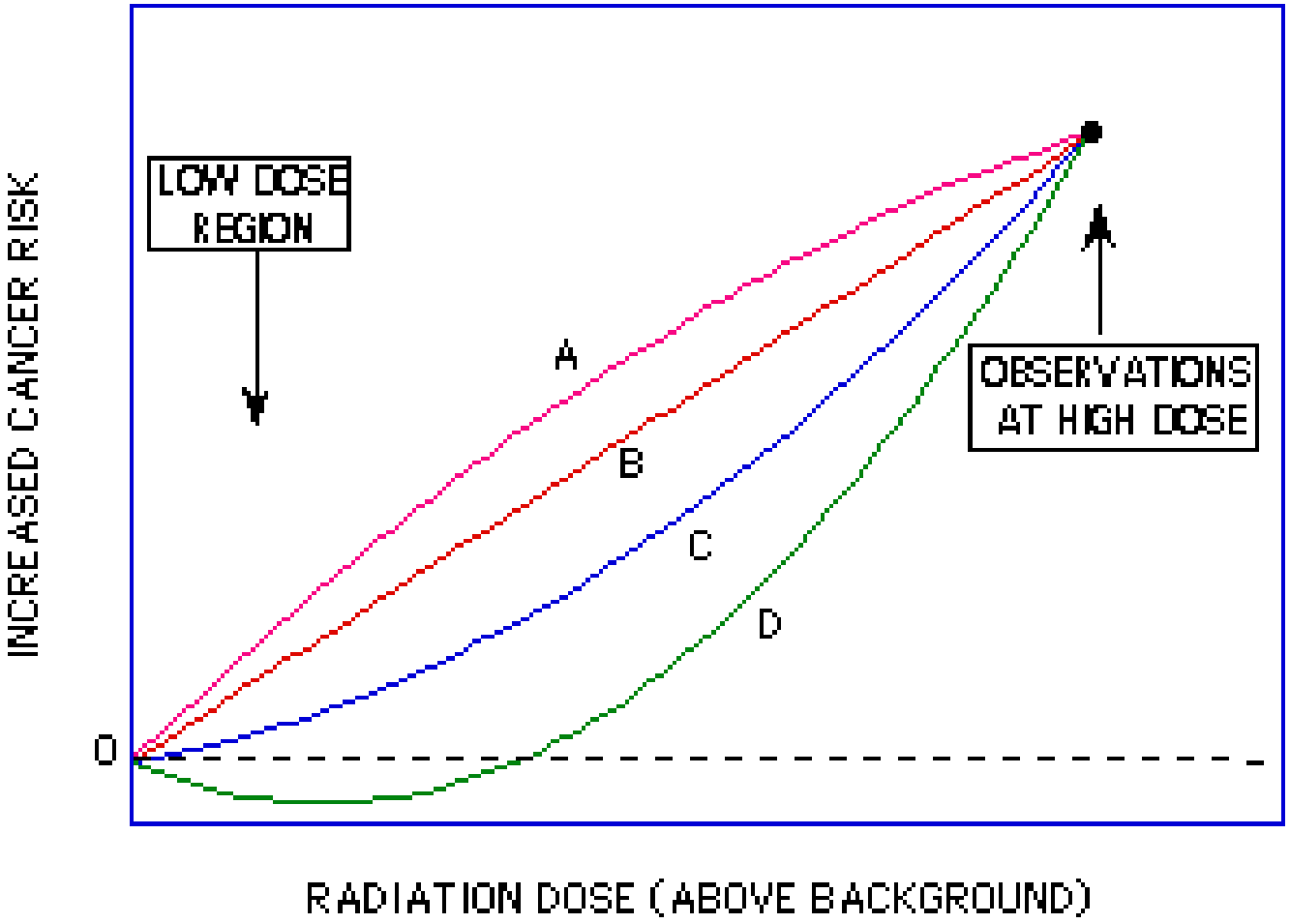
From toxicological data collected in Step 1

- Extrapolation:
  - Animals to Humans
  - Low Doses from high doses

http://www.atsdr.cdc.gov/hac/phamanual/ch8.html

Problems with extrapolation of animal and human data: Homogeneity in lab rats versus heterogeneity in human populations

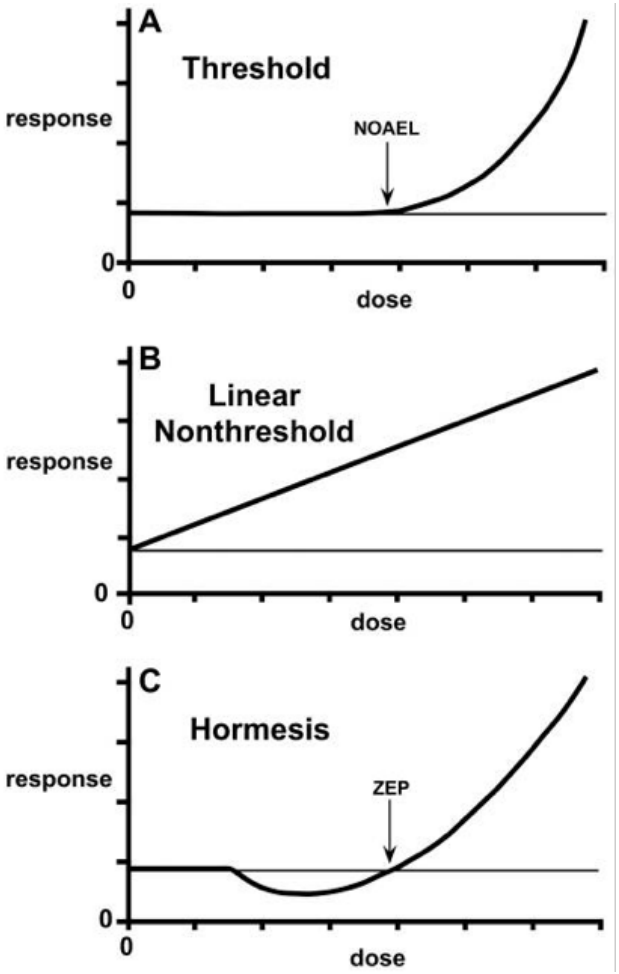
http://en.wikipedia.org/wiki/File:Radiations_at_low_doses.gif



What shape is the relationship below the lowest observable point?
Different toxicological systems can be engaged or overwhelmed
Really just a “best guess”

Hormesis: A revolution? A religion?

- Low dose beneficial, high dose harmful
  - Many compounds appear to act this way
    - Sunshine
    - Alcohol
    - Vitamins and supplements
- Still hotly debated



Dose Response. 2009; 7(1): 1–51.

Threshold Dose Response data

- Thresholds are points at which harm start
- From animal experiments, use NOAEL
  - "highest exposure without adverse effect"
- Benchmark dose alternative
  - Uses a dose the corresponds to actual change
  - Can reflect the nature of the dose response curve
- Develop a Reference Dose (RfD)

$$RfD(mg/kg/day) = \frac{NOEL(mg/kg/day)}{Uf_{inter} * Uf_{intra} * Uf_{other}}$$

TABLE 1
Description of Typical Uncertainty and Modifying Factors in the Development of Subthreshold Doses for Several Groups[a]

Uncertainty factor (UF)[b]	Guidelines[c]	Agency: Health Canada	IPCS	RIVM	U.S. ATSDR	U.S. EPA
				UF value		
Interhuman (or intraspecies)	Generally use when extrapolating from valid results from studies of prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among humans and is thought to be composed of toxicokinetic and toxicodynamic uncertainties.	1–10	10 (3.16 × 3.16)	10	10	10
Experimental animal to human	Generally use when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to humans and is also thought to be composed of toxicokinetic and toxicodynamic uncertainties.	1–10	10 (2.5 × 4.0)	10	10	10
Subchronic to chronic	Generally use when extrapolating from less than chronic results on experimental animals or humans. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs or LOAELs to chronic NOAELs or LOAELs.			10	NA[d]	<10
LOAEL to NOAEL	Generally use when extrapolating an LOAEL to a NOAEL. This factor is intended to account for the experimental uncertainty in developing a subthreshold dose from an LOAEL, rather than a NOAEL.			10	10	<10
Incomplete data base to complete	Generally use when extrapolating from valid results in experimental animals when the data are "incomplete." This factor is intended to account for the inability of any single study to adequately address all possible adverse outcomes.	1–100	1–100	NA	NA	<10

Taken from Dourson et al. REGULATORY TOXICOLOGY AND PHARMACOLOGY 24.108-120 (1996)

Linear Dose Response (Cancer Slope Factor)

- Apply model to a data to determine slope
  - Or use a published one
  - Slope Factor (SF) is the upper bound, generally 95% confidence interval of the line

_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Benzene
CASRN — 71-43-2
Last Revised — 01/19/2000

_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

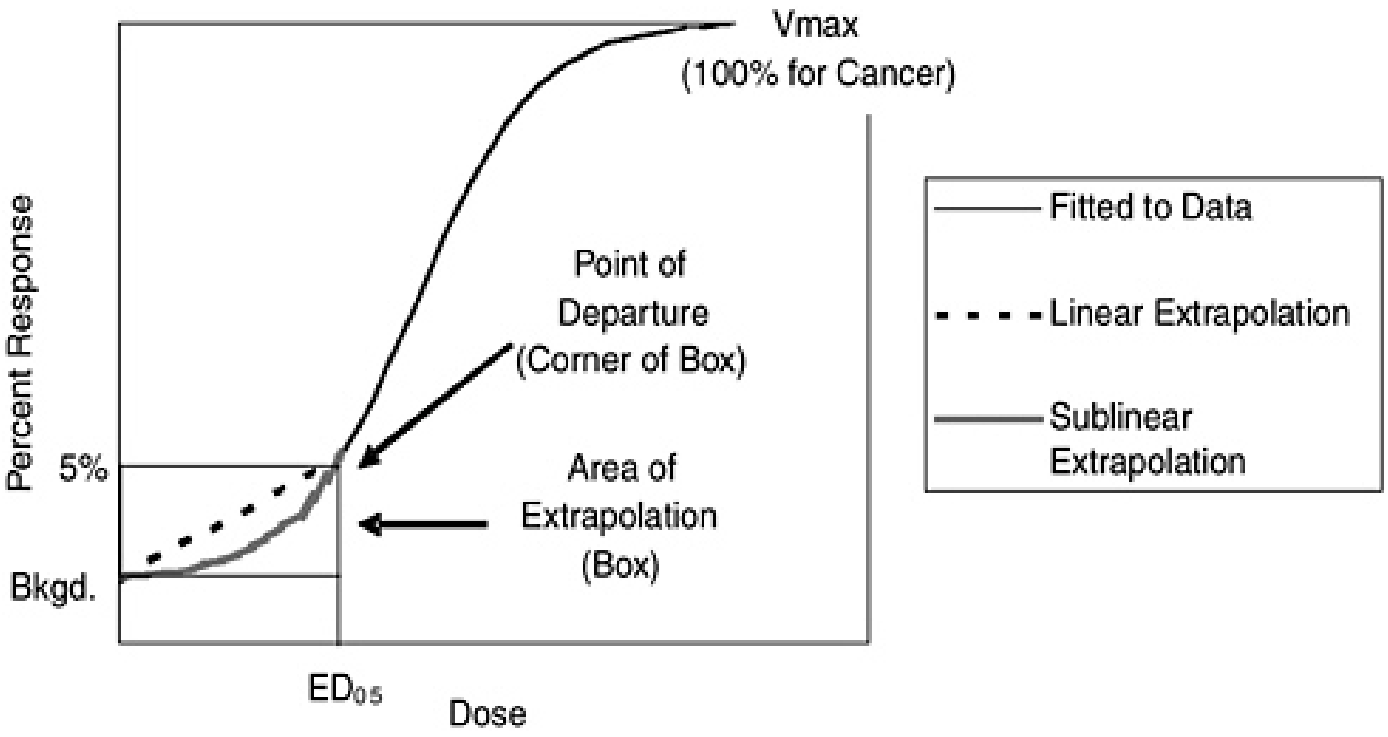
__II.B.1. Summary of Risk Estimates

___II.B.1.1. Oral Slope Factor — 1.5×10^{-2} to 5.5×10^{-2} per (mg/kg)/day

___II.B.1.2. Drinking Water Unit Risk — 4.4×10^{-7} to 1.6×10^{-6} per (ug/L)

___II.B.1.3. Extrapolation Method — Linear extrapolation of human occupational data

National Academies of Science: [Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment (2006) Board on Environmental Studies and Toxicology (BEST)]



Integrated Risk Information System (IRIS)

IRIS Public Stakeholder Engagement

- IRIS Stakeholder Meeting Web site
- Science Matters Blog: Key to building within the IRIS Program
- Science Matters Blog: Your Voice Matters

IRIS Most Viewed Chemicals

Full List of IRIS Chemicals

Acrylamide	Cadmium	Mercury, elemental
Arsenic, Inorganic	Chromium (VI)	Methylmercury (MeHg)
Benzene	1,4-Dioxane	Polychlorinated biphenyls (PCBs)
Bisphenol A	Formaldehyde	Silver

EPA's Integrated Risk Information System (IRIS) is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. Through the IRIS Program, EPA provides the highest quality science-based human health assessments to support the Agency's regulatory activities. The IRIS database is web accessible and contains information on more than 550 chemical

Federal Contaminated Site Risk Assessment In Canada: Part II: Health Canada Toxicological Reference Values (TRVs)

Previous | Table of Contents | Next

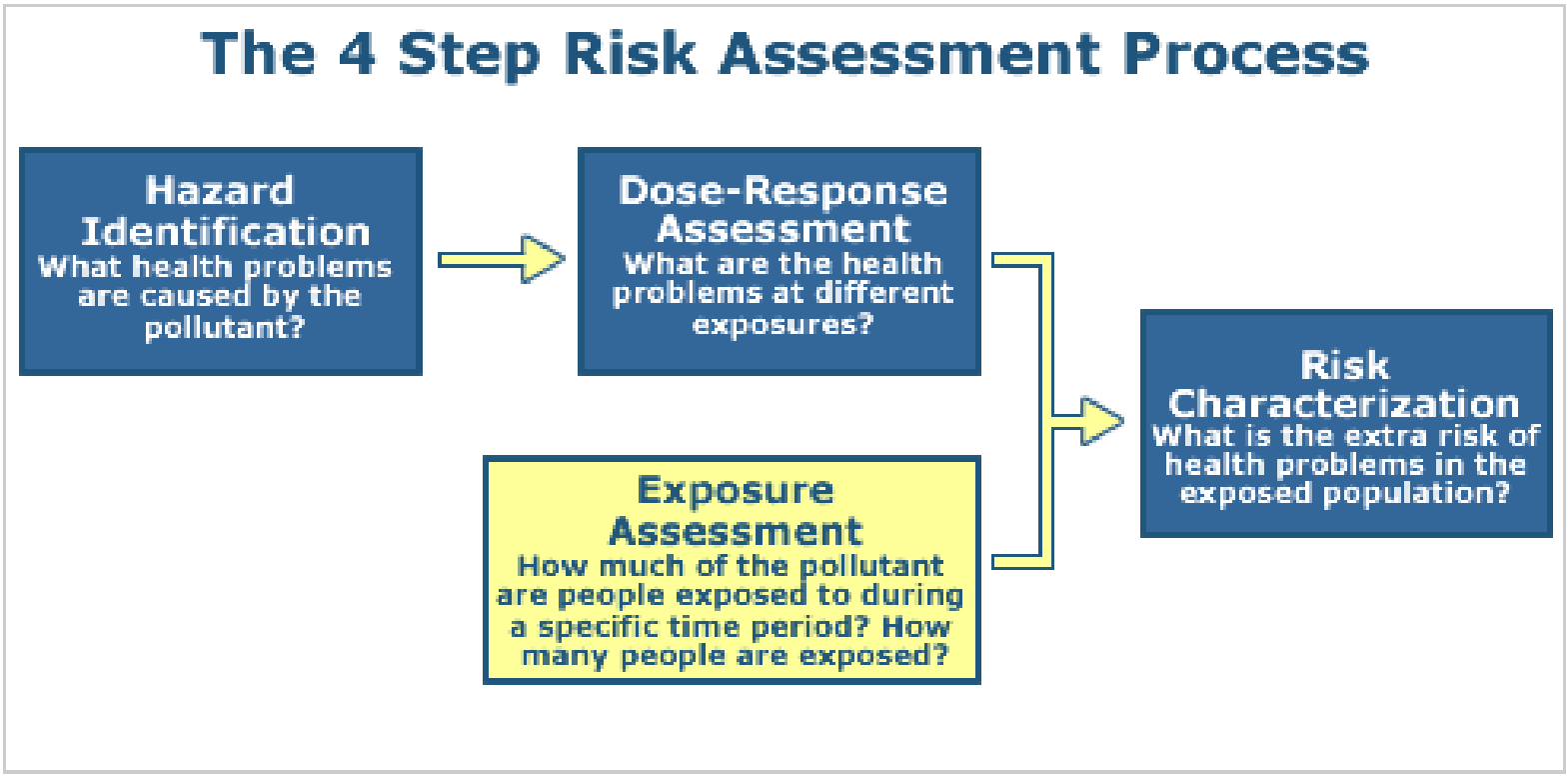
Health Canada Toxicological Reference Values (TRVS)

Name	Non-Carcinogenic Toxicological Reference Values		Carcinogenic Toxicological Reference Values			
	Health Canada TDI *a* (mg/kg-d)	Health Canada TC (mg/m3)	Oral slope factor from TD_{05} *b* (mg/kg-d)-1	Inhalation slope factorfrom TC_{05} *c* (mg/kg-d)-1	Inhalation unit risk from TC_{05} c(mg/m3)-1	Oral slope factor from DWQG *a* (mg/kg-d)-1
Aldicarb	0.001					
Aldrin + dieldrin	0.0001					
Aniline	0.007 *b*					
Arsenic			2.8	2.80E+01	6.40E+00	1.7 *h*
Atrazine + metabolites	0.0005					
Azinphos-methyl	0.0025					
Barium	0.016					
Bendiocarb	0.004					
Benzene				1.46E-02	3.30E-03	3.10E-01
Benzo(a)pyrene				1.37E-01	3.10E-02	2.30
Benzo(b)fluoranthene				8.20E-03	1.90E-03	
Benzo(j)fluoranthene				6.80E-03	1.60E-03	
Benzo(k)fluoranthene				5.50E-03	1.30E-03	
Bis(2-ethyl-hexyl)phthalate	0.044 *b*					

Step 2 Final Product

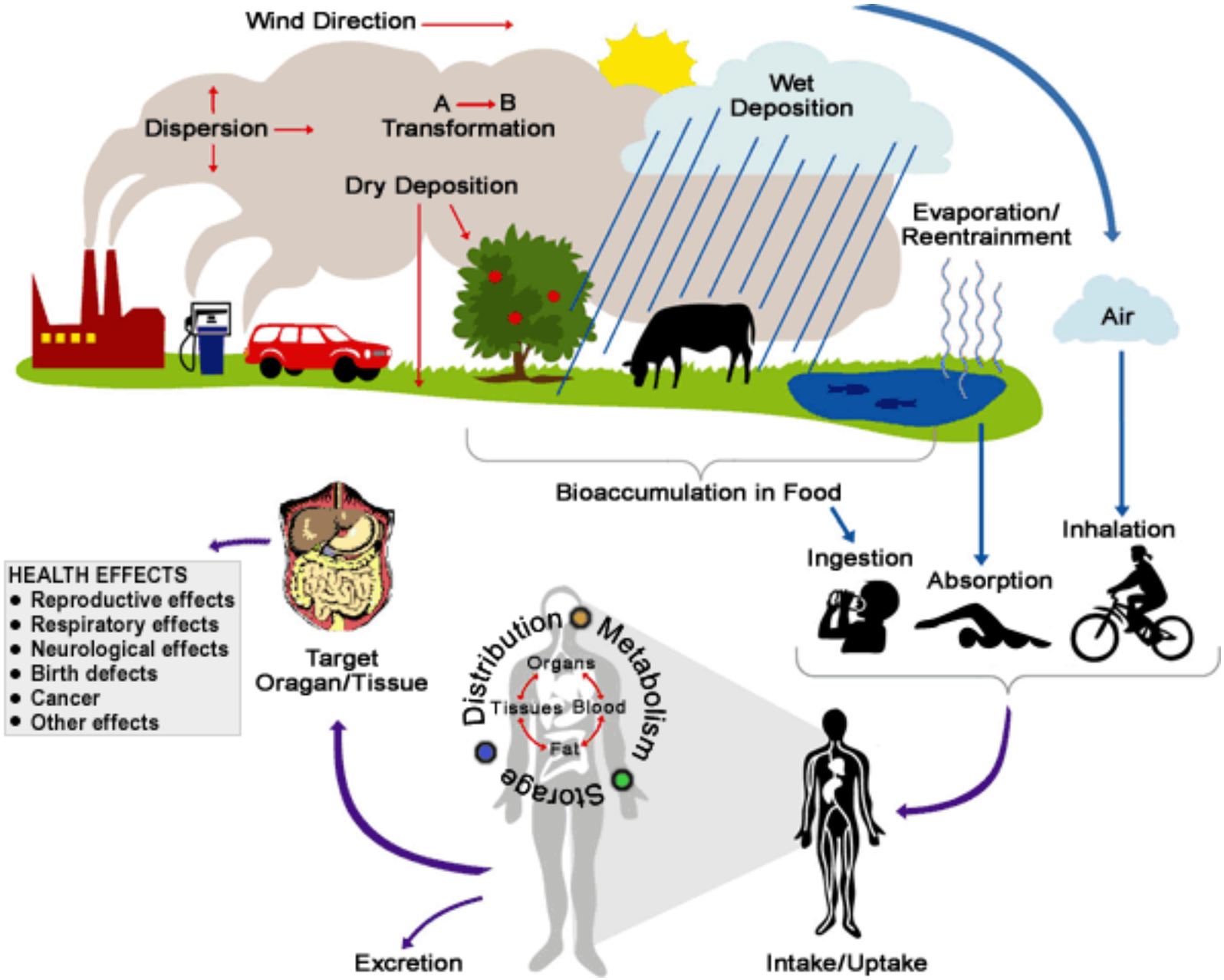
- Have either:
  - Reference Dose (RfD)
  - Slope Factor
- Discussion of uncertainty, limitations, data gaps

Step 3: Exposure Assessment



Step 3: Exposure Assessment

- How are people exposed to the hazard and how much do they get?
- Some issues to consider
  - Measures in the environment
    - Air, water, soil, food, other
  - Exposure Factors
    - How do people interact with these media?
  - Time



http://www.in.gov/idem/images/risk_slide-01.gif

Where to find Exposure Measures?

- Published Data
  - Research studies
- Air quality Indices
- Food residue tracking
- Water quality monitoring
- Pesticide sales data
  - modeling

CAREX CANADA

www.carexcanada.ca


EPA
Exposure Factors Handbook: 2011 Edition


EPA
Child-Specific
Exposure Factors
Handbook

Table 17-9. Percentile Rankings for Total Exposure Time in Performing Household Tasks

Tasks	Percentile Rankings for Total Exposure Time Performing Task (hours/year)							
	Min	10th	25th	50th	75th	90th	95th	Max
Clean Bathroom Sinks and Tubs	0.4	5.2	13	26	52	91.3	121.7	365
Clean Kitchen Sinks	0.3	3.5	8.7	18.3	60.8	97.6	121.7	547.5
Clean Inside of Kitchen Cabinets	0.2	1	2	4.8	12	32.5	48	208
Clean Outside of Cabinets	0.1	1	2	6	17.3	36	78.7	780
Wipe Off Kitchen Counters	1.2	12	24.3	54.8	91.5	231.2	456.3	912.5
Thoroughly Clean Counters	0.2	1.8	6	13	26	52	94.4	547.5
Clean Bathroom Floors	0.1	2	4.3	8.7	26	36.8	71.5	365
Clean Kitchen Floors	0.5	4.3	8.7	14	26	52	97	730
Clean Bathroom or Other Tilted or Ceramic Walls	0.2	1	3	8.7	26	36	52	208
Clean Outside of Windows	0.1	1.5	2	6	11.5	24	32.6	468
Clean Inside of Windows	0.2	1.2	3	6	19.5	36	72	273
Clean Glass Surfaces Such as Mirrors and Tables	0.2	1.7	6	13	26	60.8	104	1460
Clean Outside Refrigerator and Other Appliances	0.1	1.8	4.3	13	30.4	91.3	95.3	365
Clean Spots or Dirt on Walls or Doors	0.1	0.6	2	8	24	52	78	312

Min = Minimum.
Max = Maximum.

Source: Westat (1987c).

Table 17-22. Number of Minutes Spent Using Any Microwave Oven (minutes/day)

Age Group	Percentiles												
	N	1	2	5	10	25	50	75	90	95	98	99	Max
5 to 11 years	62	0	0	0	1	1	2	5	10	15	20	30	30
12 to 17 years	141	0	0	0	1	2	3	5	10	15	30	30	60
18 to 64 years	1,686	0	0	1	2	3	5	10	15	25	45	60	121
> 64 years	375	0	0	1	2	3	5	10	20	30	60	60	70

Note: A value of "121" for number of minutes signifies that more than 120 minutes were spent; *N* = doer sample size; *percentiles* are the percentage of doers below or equal to a given number of minutes.

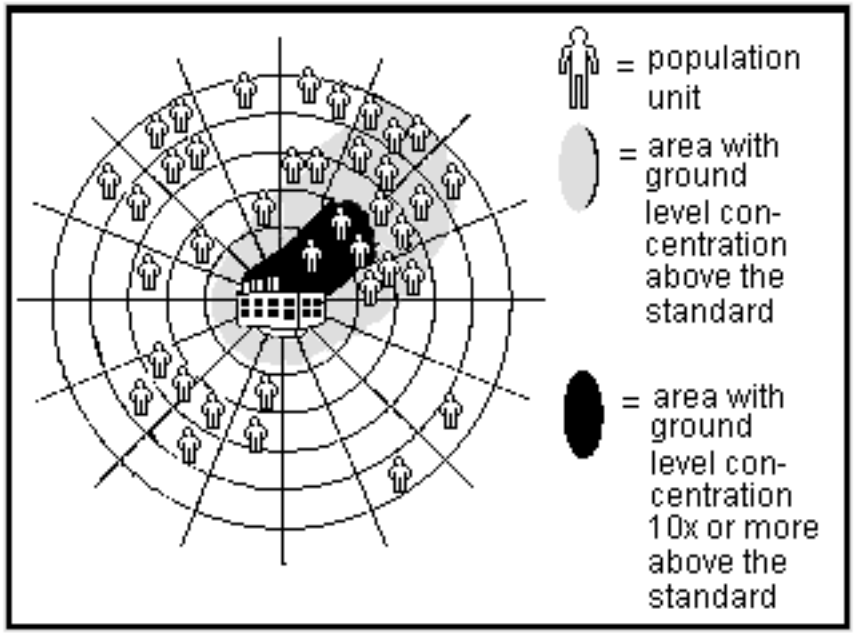
Source: U.S. EPA (1996).

Table 17-21. Paint Stripper Usage by Sex

	Sex	
	Males *N* = 156	Females *N* = 162
Mean number of months since last time paint stripper was used – includes all respondents (unweighted *N* = 1724).	32.07	47.63
Mean number of uses of product in the past year.	3.88	3.01
Mean number of minutes spent with the product during last use.	136.70	156.85
Mean number of minutes spent in the room after last use of product. (Includes all recent users.)	15.07	9.80
Mean number of minutes spent in the room after last use of product. (Includes only those who did not leave immediately.)	101.42	80.15
Mean ounces of product used in the past year.	160.27	114.05
Mean ounces of product used per use in the past year.	74.32	50.29

Exposure Modeling

- Using measured and/or modeled data
  - Transport models
- Can choose to do average exposure
  - Central Tendency
- Also: high exposure sub population
  - Community versus worker/community



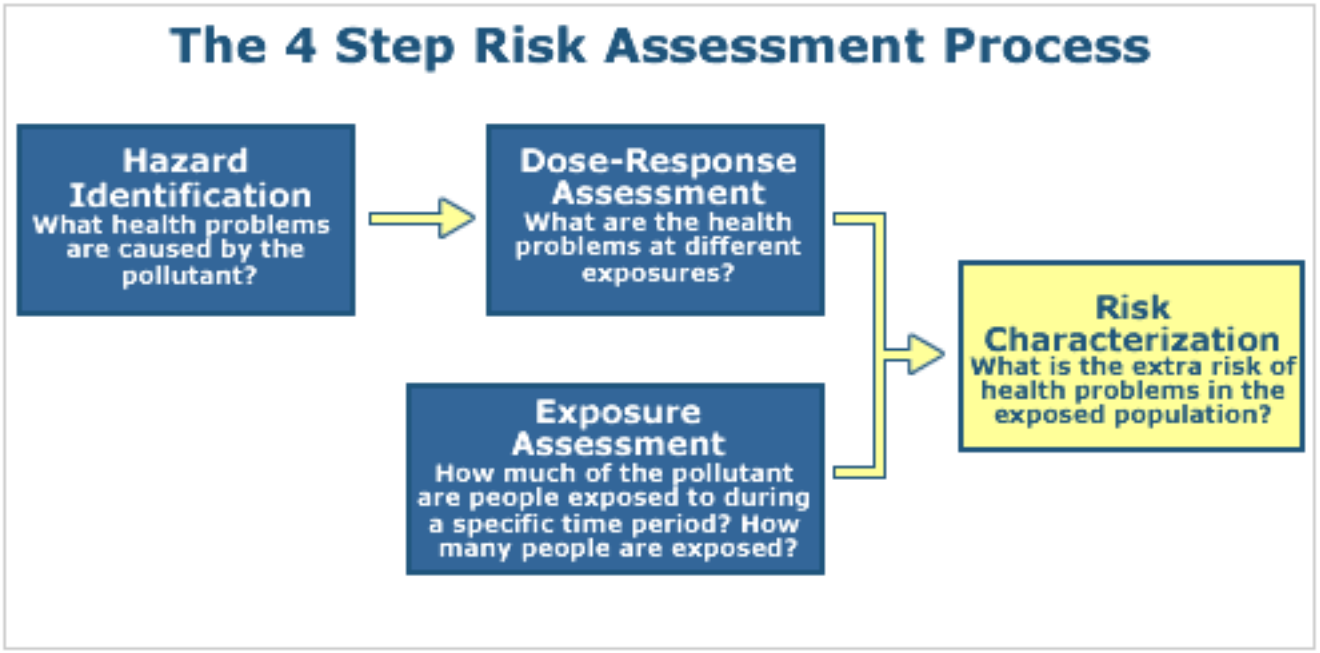
From Exposure to Dose

- Exposure measures external concentrations
- Dose is the amount taken in
  - Absorption, Distribution, Metabolism, Excretion
- Some compounds have better data than others
  - Internal Dose Model development initiated (ERDEM)
  - MTBE, TCE, some pesticides
  - See http://www.epa.gov/heasd/risk/projects/c1a_dose_models_development.html

Step 3 Final Results

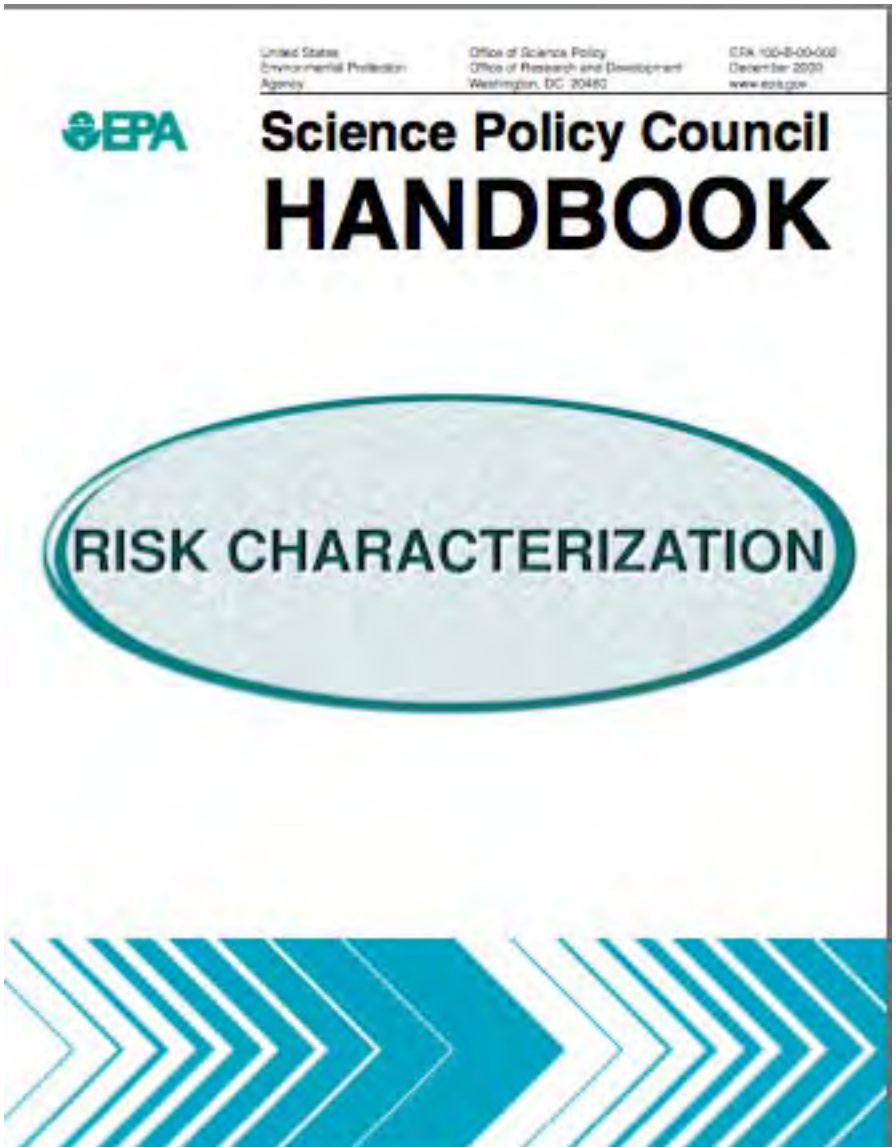
- Who is at risk? Need to determine the population
  - How many are there
  - Who are they? Workers, children, immunocompromized
- What are their exposure level(s)
  - Average with ranges and/or high exposure estimates

Step 4


The 4 Step Risk Assessment Process
Hazard Identification
What health problems are caused by the pollutant?
Dose-Response Assessment
What are the health problems at different exposures?
Exposure Assessment
How much of the pollutant are people exposed to during a specific time period? How many people are exposed?
Risk Characterization
What is the extra risk of health problems in the exposed population?

Step 4: Risk Characterization

- Final, integrative step
- Describes risk as well as uncertainty
- Clearly outlines assumptions and default values
  - Emphasis on Transparency



For Threshold Risks

- Produces a RATIO (Hazard Quotient)
- If less than or equal to 1, no appreciable risk
- If >1, some probability of risk

NONCANCER HAZARD QUOTIENT

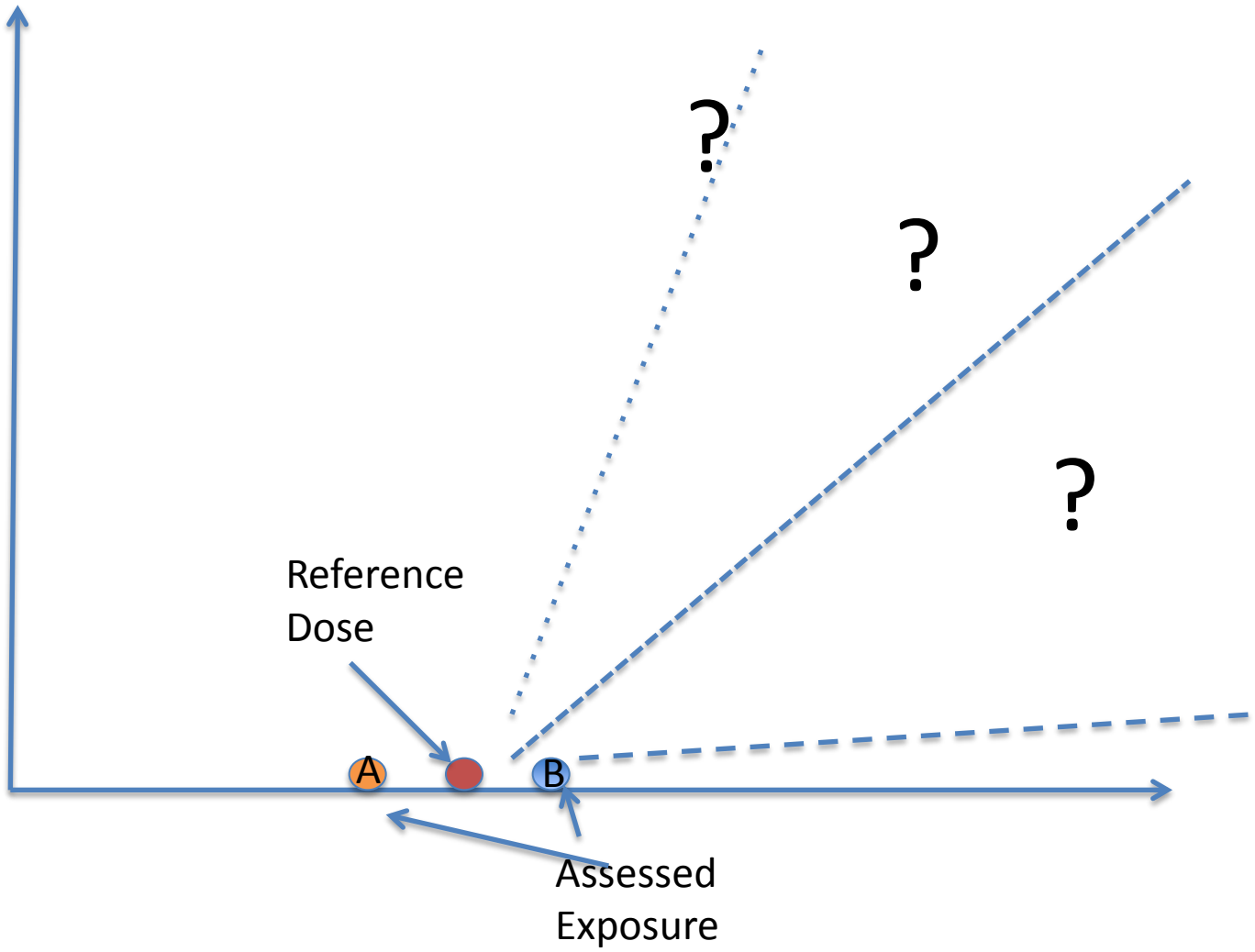
Noncancer Hazard Quotient = E/RfD

where:

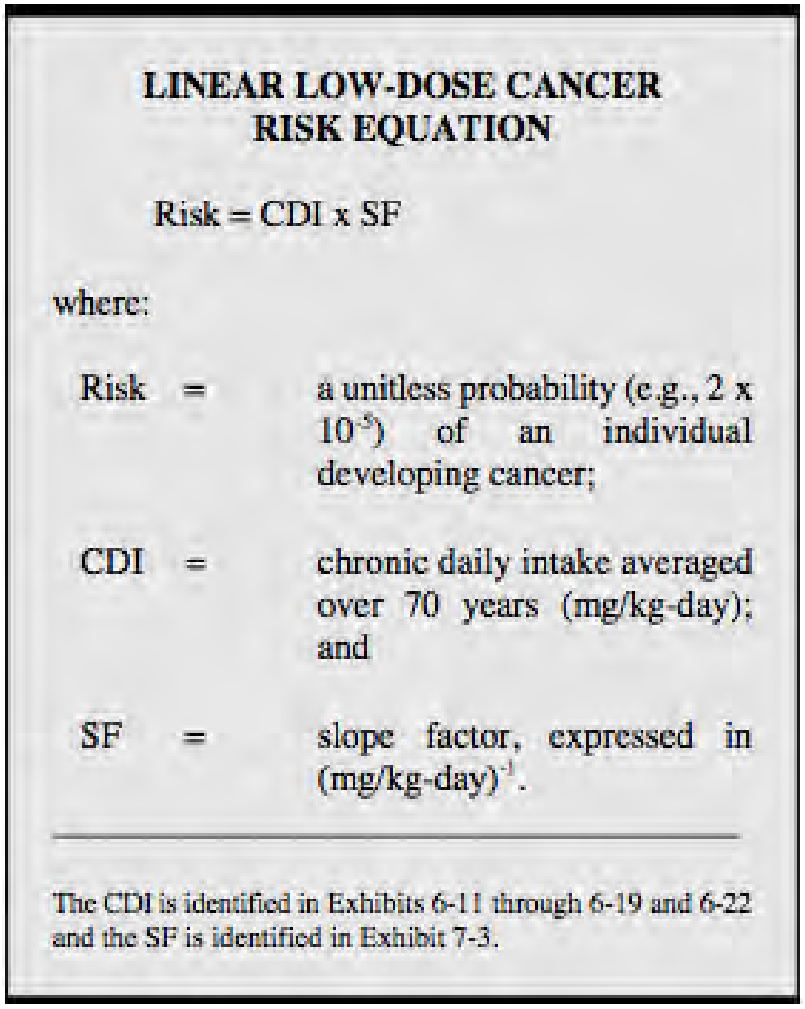
E
= exposure level (or intake);

RfD
= reference dose; and

E and RfD are expressed in the same


?
?
?
Reference
Dose
A
B
Assessed
Exposure

Non-threshold Risk Characterization



LINEAR LOW-DOSE CANCER RISK EQUATION

Risk = CDI x SF

where:

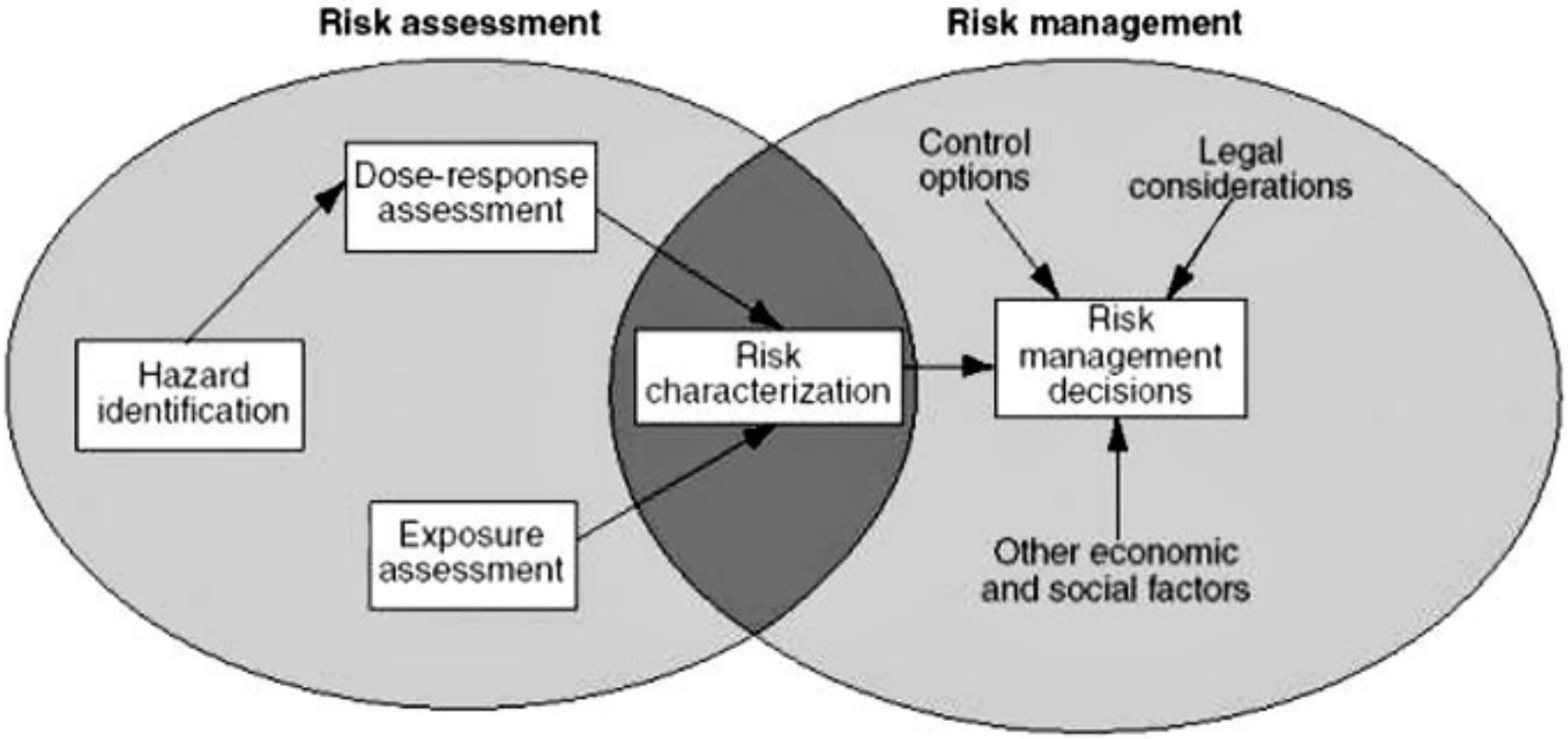
Risk	=	a unitless probability (e.g., 2 x 10^{-5}) of an individual developing cancer;
CDI	=	chronic daily intake averaged over 70 years (mg/kg-day); and
SF	=	slope factor, expressed in $(mg/kg\text{-}day)^{-1}$.

The CDI is identified in Exhibits 6-11 through 6-19 and 6-22 and the SF is identified in Exhibit 7-3.

- Produces a PROBABILITY
  - Assume linear model
  - Assumes lifetime exposure
  - Assumes overall low exposures
    - not always suitable for occupational scenarios
- Acceptable risk? 1-10 in a million
- 1 in 10,000 generally prompts action

Reporting Risk

- Never appropriate to just give the number
  - (1.3 *10-4)
- Risk Assessment results require qualitative accompaniments to be understood
  - Weight of evidence
  - Assumptions, defaults used
  - Limitations of exposure data



http://www.learner.org/courses/envsci/visual/img_lrg/risk_assessment.jpg

Single compound approach: But life's not like that!

- 8 new publications on cumulative risk assessment methods and approaches
  - "combined risks from aggregate exposures"
  - Framework documents available at:
    - http://www.epa.gov/spc/2cumrisk.htm
- What about chemical mixtures? New update:
  - http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533

Microbial Risk Assessment

News Releases By Date

EPA and USDA Announce First-Ever Microbial Risk Assessment Guidance / Guideline will help better determine health risks from food and waterborne pathogens

Release Date: 07/31/2012
Contact Information: Latisha Petteway (News Media Only), petteway.latisha@epa.gov, 202-564-3191, 202-564-4355

WASHINGTON - The Environmental Protection Agency (EPA) and the USDA's Food Safety and Inspection Service (FSIS) today announced the first-ever Microbial Risk Assessment (MRA) Guideline. This new MRA Guideline lays out an overarching approach to conducting meaningful assessments of the risks to Americans posed by pathogens in food and water. Pathogens ingested in food and water can result in acute gastrointestinal-related illnesses; some gastrointestinal-related illnesses can result in long-term and permanent health effects as well as premature death. This new guideline will improve the quality of the data collected by public health scientists charged with protecting Americans from pathogen-related risks in food and water.

Can this model handle Nanotechnology?

Nanomaterials

Research to Support Comprehensive Environmental Assessments of Nanomaterials

Issue:
The U.S. Environmental Protection Agency's mission and mandates call for an understanding of the health and ecological implications of engineered nanomaterials. The Agency uses the comprehensive environmental assessment (CEA) approach as part of its engineered nanomaterial research portfolio. CEA identifies and prioritizes research to support future assessments and risk management decisions.

Recent Updates

- 10/29: Multiwalled Carbon Nanotube Case Study Worshop
- 8/1: Nanomaterial Case Study: Nanoscale Silver in Disinfectant Spray (Final Report)

Contact

Christina Powers
by phone at: 919-541-5504
by email at: powers.christina@epa.gov

Nanomaterials pose special risk assessment challenges due to their diversity, unique properties, and seemingly limitless uses. For example, nanomaterials are so small they may have multiple or unique ways to come in contact with people or ecosystems. And because of their complex physical and chemical properties, it is also a challenge to determine the amount of exposure or dose that will cause an adverse effect. Ongoing research seeks to identify whether the relevant dose metric of a nanomaterial depends on the weight (mass), size, number of particles, shape, surface area, electrical charge, or some combination of these or other characteristics.

But this is Canada!

Health Canada
www.hc-sc.gc.ca

ome | Contact Us | Help | Search | canada.gc.ca

Workplace Health > Reports & Publications > Contaminated Sites

Environmental and Workplace Health

Print | Text Size: S M L XL Help | Share

Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 2.0

2010, Revised 2012
ISBN: 978-1-100-17671-0
Cat.: H128-1/11-632E-PDF

This guidance document (*Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 2.0*) was prepared to provide guidance for custodial departments.

A major emphasis of the FCSAP is to ensure that remediation or risk management is applied to those sites and properties posing significant human health risks. The purpose of a PQRA is to quantify the degree of potential human health risk posed by the presence of contamination at a subject site. The results of a PQRA for federal sites/properties may be used within the FCSAP to rank and prioritize the subject site for remedial funding and priority for action.

Order a copy
Electronic/Accessible

Thank- you

Risk management

In conclusion

- “relatively” new process
- Formal process with many, many guidance documents
  - Continuous work being done in the US
  - Refinement and redefinition
- New scientific knowledge is challenging the original 4 step process
  - Nanotechnology
  - Low dose measures and models

Biologically based response

- For some compounds, there is enough data to determine how compounds react in the body
- Termed: PBPK
  - Physiologically based pharmacokinetic modeling
  - Uses variable such as metabolic rate, blood volume, tissue volumes, etc.
  - Allows for adjustments for processes such as ceullar repair