INTRODUCTION TO CHEMICAL RISK ASSESSMENT FOR FOOD SAFETY

SafeGro Project
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Hanoi, April 2024

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1. Formal Risk Assessment Frameworks and Terminology

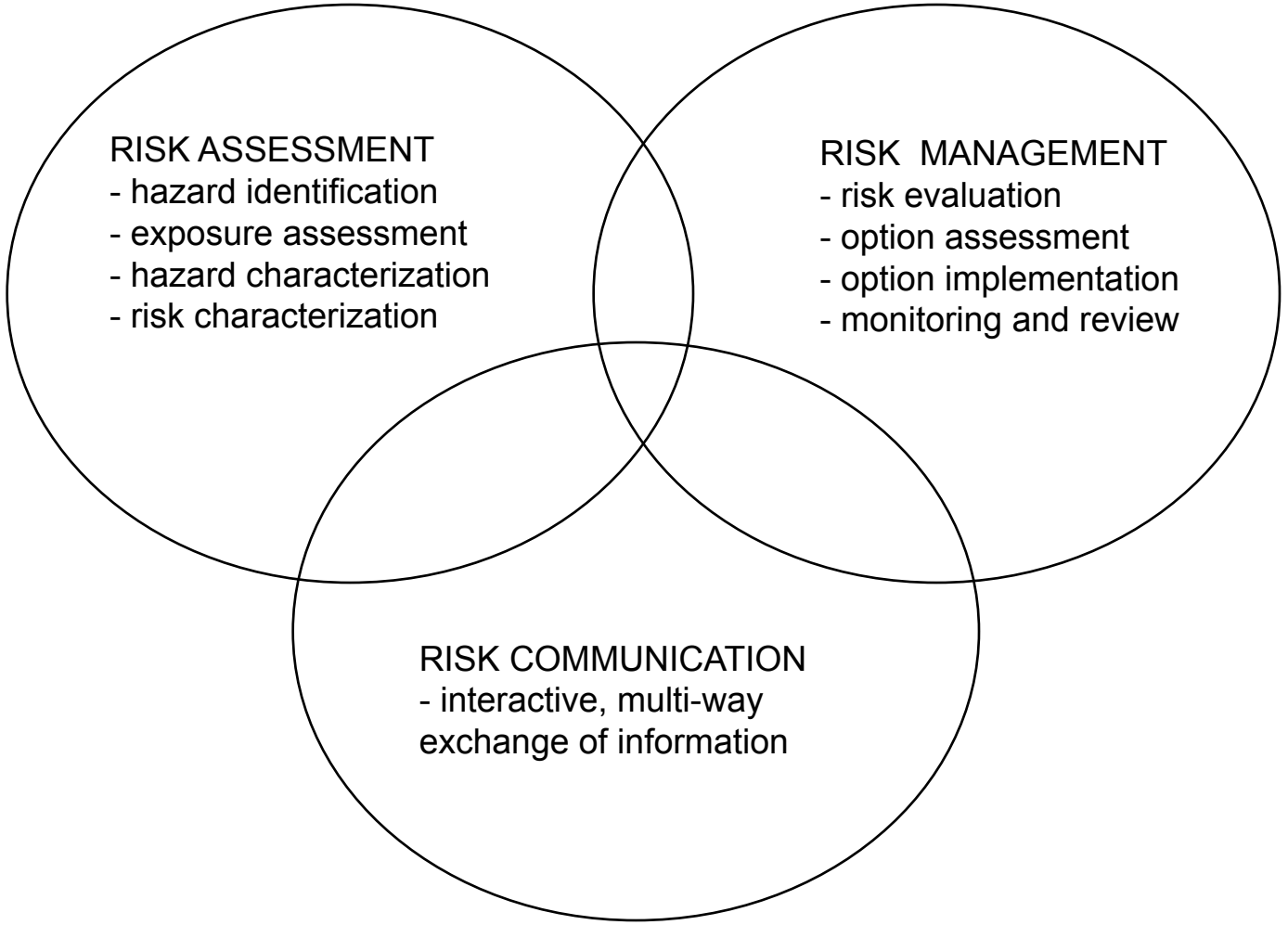
Definitions

Risk: the impact of exposure to a hazard or threat, which integrates the frequency or probability of occurrence of possible outcomes with an estimate of the magnitude of the associated consequences of these outcomes.

Definitions

Risk Assessment: a formal, systematic process of estimating the level of risk for the purpose of informing decision making. It may also include an estimate of the magnitude of a change in risk associated with an option to control risk.

Risk Analysis: An Org-Chart View of Risk Management



Risk Assessment: The Evolution of Major Components

NRC (1983): Red Book

- **Four Steps of Risk Assessment**
- **Later, adopted by WHO as standard terminology**

NRC (1994): Blue Book

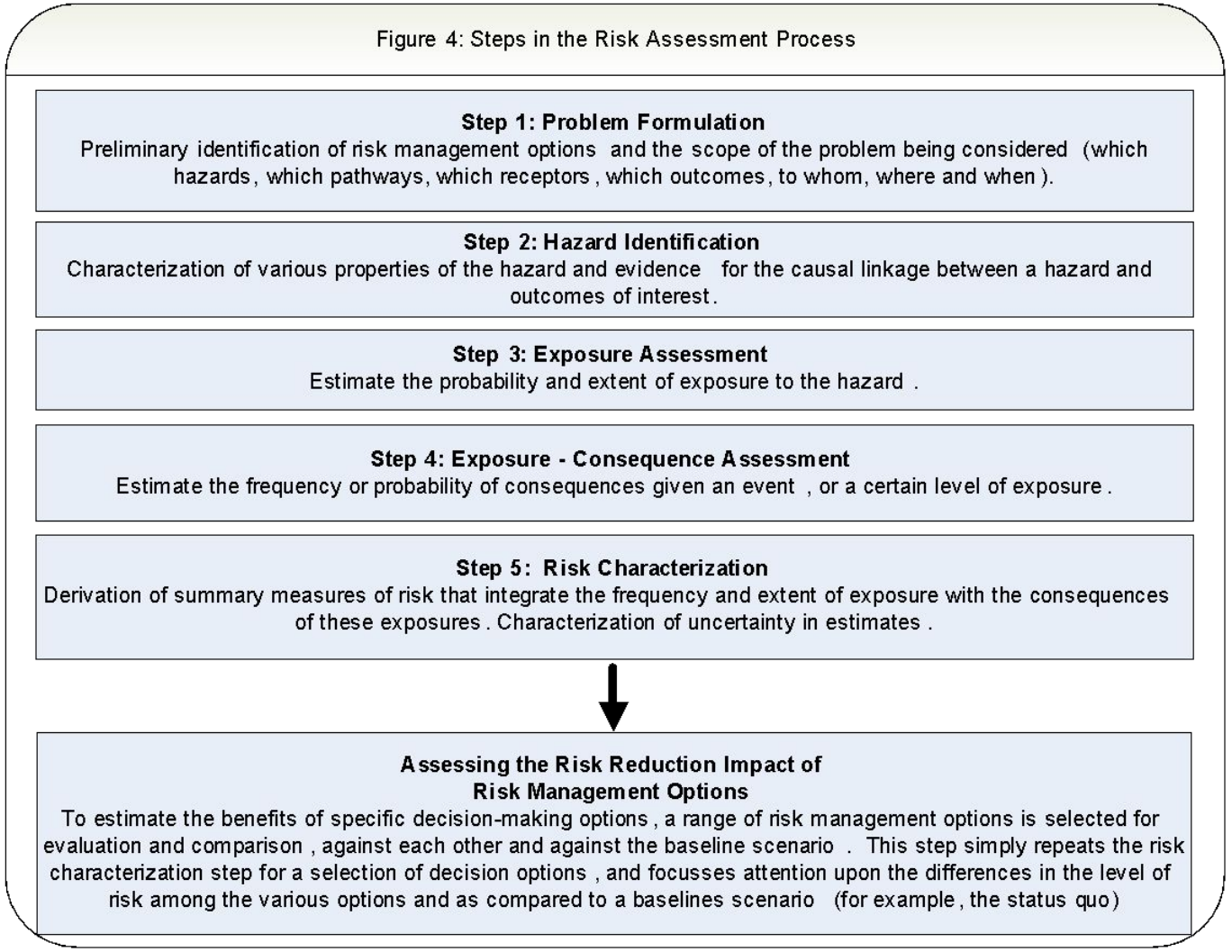
- **Establishing standards for quantitative risk assessment**

NRC (2009): Silver Book, *Science and Decisions: Advancing Risk Assessment*

Embedding RA in Population Health Approach

- **Krewski et al. (2007)**
- **EPA NexGen Framework (2012-13)**

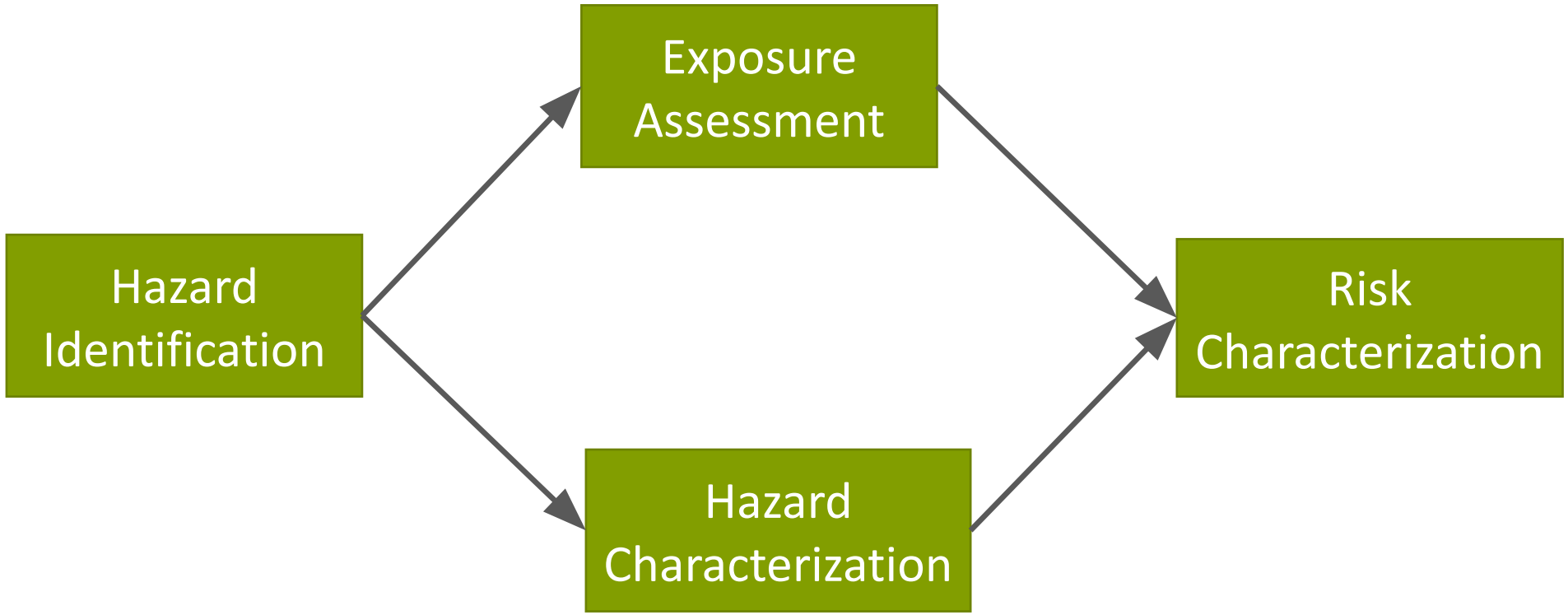
New Treasury Board Guidelines for RA for Regulatory Purposes (2012, forthcoming)



Principles (TBS, 2012)

- Proportionality
- Timeliness
- Evidence-Based and Quality Assured
- Openness and Transparency
- Appropriate Characterization of Variability
- Characterization of Key Uncertainties
- Integration with Related Analyses
- Iteration and Support for Adaptive Risk Management

Risk Assessment consists of Four Distinct Steps



Hazard Identification

The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods

Hazard: A substance, human activity, condition or situation that has the intrinsic or inherent potential for causing injury or loss of life, damage to property, environmental degradation, or a combination of these.

The concept of a hazard is limited to the potential for, or possibility of, harm, as distinct from either the probability or severity of that harm.

Exposure Assessment

The qualitative (?) and/or quantitative evaluation of the extent and likelihood of intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant

Exposure assessment consists of converting the possibility of harm associated with a hazard into estimates of the frequency and extent of the interaction between the hazard and specific targets or receptors of interest.

Hazard Characterization

The qualitative (?) and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food

This step may be called dose-response assessment, concentration-response assessment, damage function assessment, exposure-consequence, or a number of other terms depending on the specific domain.

Despite the differences in terminology, the process derives estimates for the probability, rate and/or extent of damage to the target or receptor *given a level of exposure or a specific type of exposure event*.

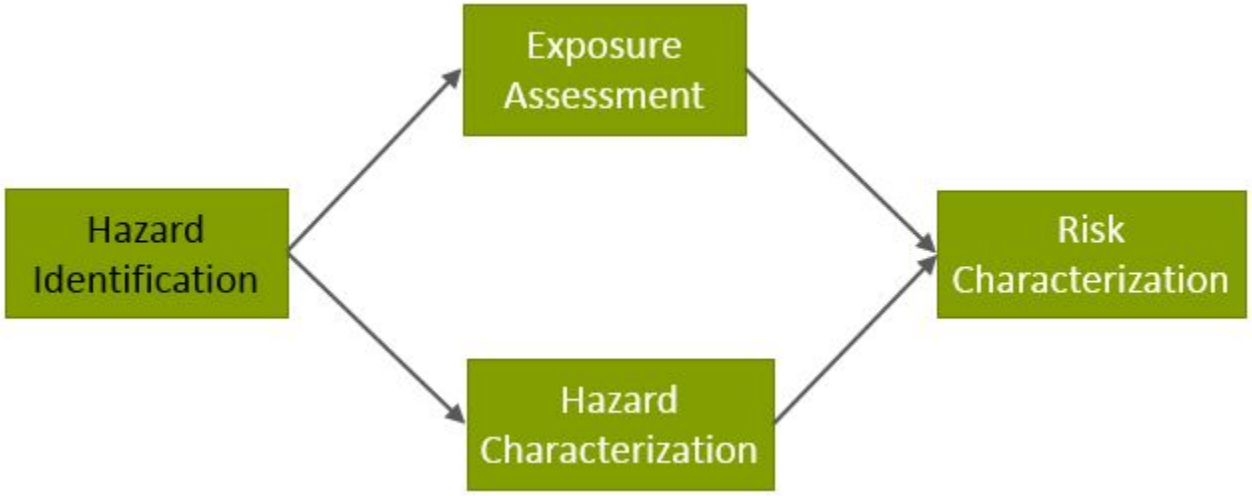
The Final Step: Risk Characterization

The qualitative (?) and/or quantitative estimation of the probability of occurrence and severity of known or potential adverse health effects in a given population

- Including attendant uncertainties
- Uses hazard identification, hazard characterization and exposure assessment
- Contains computational and narrative components

The analytical task is to appropriately combine estimates of the frequency and extent of exposure (resulting from the exposure assessment stage) with the relationship between exposure and consequences to yield estimates of the magnitude of consequences with corresponding estimates of their probability.

2. Hazard Identification



HOW MUCH IS TOO MUCH?

Excess Vitamins and Minerals in Food Can Harm Kids' Health

EWG'S SHOPPER'S GUIDE TO PESTICIDES IN PRODUCE

MANY FAST FOOD WRAPPERS STILL COATED IN PFCS, KIN TO CARCINOGENIC TEFLON CHEMICAL

EWG'S CONSUMER GUIDE TO SEAFOOD

Find healthy seafood picks!

AVOID
Mercury Levels Too High To Eat Regularly

- KING MACKEREL
- MARLIN
- ORANGE ROUGHY
- SHARK
- SWORDFISH
- TILEFISH

Apples Doused with Chemical After Harvest

TUESDAY, APRIL 10, 2018

Few Americans may realize, but most conventionally grown apples are drenched in diphenylamine, an antioxidant chemical treatment to prevent the skins of apples in cold storage from developing brown or black patches known as "storage scald." Tests of raw apples conducted by U.S. Department of Agriculture scientists in 2016, the most recent year for which data are available, found diphenylamine on 80 percent of them, with an average concentration of 0.28 parts per million.[1]

Hazard Identification – Guiding Dose-Response Assessment

Can a chemical cause adverse effects in humans and what would these be?

- Often the most controversial aspect of a chemical risk assessment!

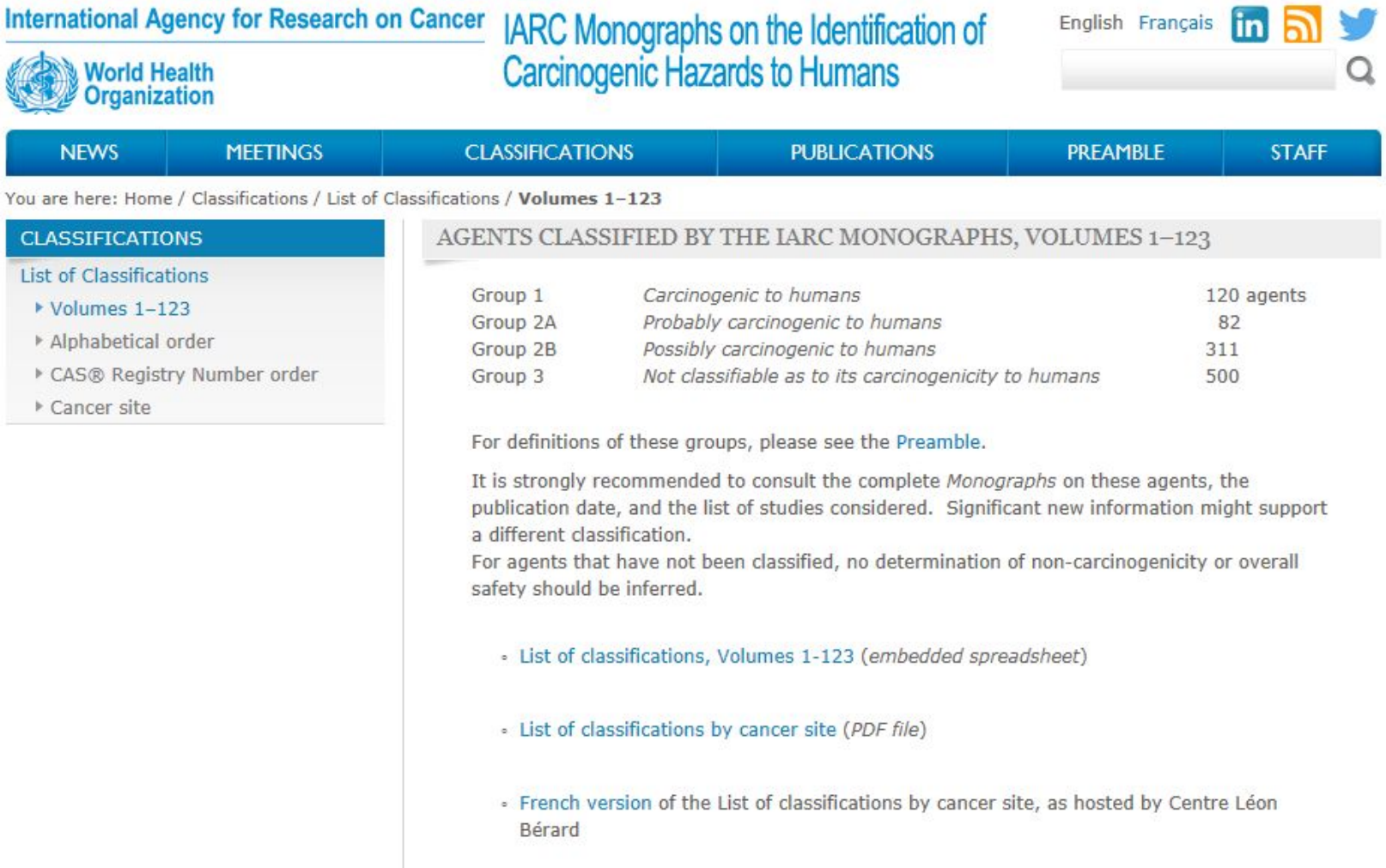
Considering the following characteristics:

- Chemical (forms, organic vs. inorganic, salts, metabolites...)
- Exposure (routes,…)
- Population (site-specific tumours,...)

Considering all data:

- *in vitro*, *in vivo*, *in silico*
- “Weight of evidence” schemes
  - IARC carcinogenicity Classes 1, 2A, 2B, 3 & 4
  - EPA 5-level hierarchy

IARC Assesses Strength of Evidence of Carcinogenicity



International Agency for Research on Cancer
World Health Organization

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

English Français

NEWS | MEETINGS | CLASSIFICATIONS | PUBLICATIONS | PREAMBLE | STAFF

You are here: Home / Classifications / List of Classifications / **Volumes 1–123**

CLASSIFICATIONS

List of Classifications
- Volumes 1–123
- Alphabetical order
- CAS® Registry Number order
- Cancer site

AGENTS CLASSIFIED BY THE IARC MONOGRAPHS, VOLUMES 1–123

Group 1	*Carcinogenic to humans*	120 agents
Group 2A	*Probably carcinogenic to humans*	82
Group 2B	*Possibly carcinogenic to humans*	311
Group 3	*Not classifiable as to its carcinogenicity to humans*	500

For definitions of these groups, please see the Preamble.

It is strongly recommended to consult the complete *Monographs* on these agents, the publication date, and the list of studies considered. Significant new information might support a different classification.
For agents that have not been classified, no determination of non-carcinogenicity or overall safety should be inferred.

- List of classifications, Volumes 1-123 (*embedded spreadsheet*)
- List of classifications by cancer site (*PDF file*)
- French version of the List of classifications by cancer site, as hosted by Centre Léon Bérard

IARC Classes for Strength of Evidence of Carcinogenicity

Group 1: Carcinogenic to Humans:

- "convincing epidemiologic evidence of a causal association between human exposure and cancer" (e.g. aflatoxins, benzene, arsenic, ethanol in alcoholic beverages, cadmium)

Group 2A: Likely to Be Carcinogenic to Humans:

- "the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor [above]" (e.g. acrylamide, creosotes, glyphosate, N-Nitrosodimethylamine)

Group 2B: Suggestive Evidence of Carcinogenic Potential:

- "the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion" (e.g. melamine, ochratoxin A, methyleugenol)

Group 3: Inadequate Information to Assess Carcinogenic Potential:

- "available data are judged inadequate for applying one of the other descriptors" (e.g. d-Limonene, acetaminophen (paracetamol), saccharin, theobromine, eugenol)

Group 4: Not Likely to Be Carcinogenic to Humans:

- "available data are considered robust for deciding that there is no basis for human hazard concern." (the sole representative, caprolactam, was recently reclassed as 3)

EPA's 5-Level Hierarchy of Evidence for Causation

- Causal relationship:
  - "Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures"
- Likely to be a causal relationship:
  - "Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain"
- Suggestive of a causal relationship:
  - "Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited"
- Inadequate to infer a causal relationship:
  - "Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures"
- Not likely to be a causal relationship:
  - "Evidence is suggestive of no causal relationship with relevant pollutant exposures"

Elements of “Weight” assigned to Evidence

Inclusion: Assembly and “Gatekeeping”

- Assigned Weight of Excluded Studies = 0
- What weight to assign to the “Weight of Evidence” of others?

Quality (Reliability) of Evidence

- Does the evidence come from a reliable method or source?

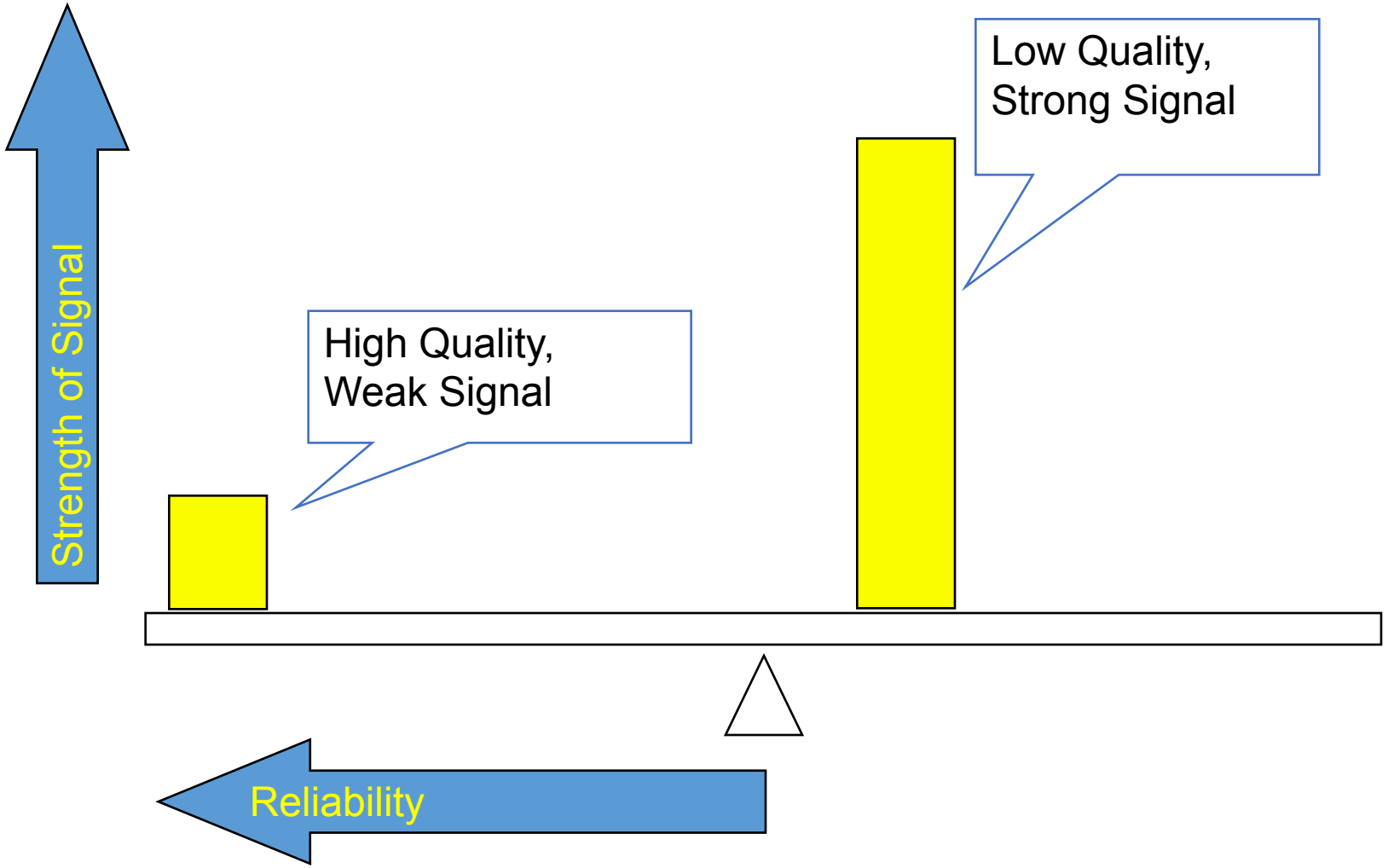
Strength of Evidence

- How strong is the relationship indicated by the evidence?
- Is a strong signal actually a requirement to be considered strong evidence?

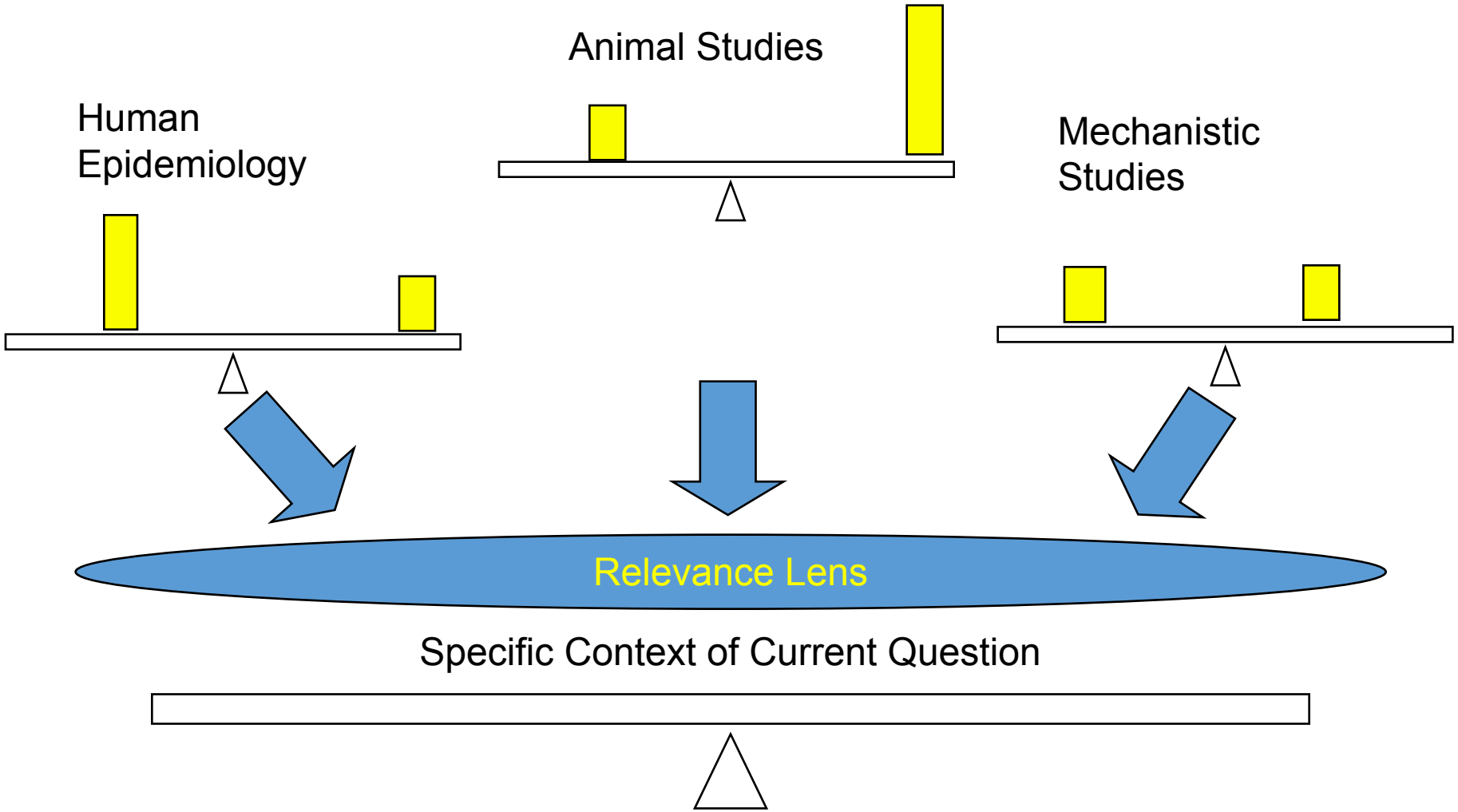
Relevance of Evidence

- What theory supports the claim that the evidence is relevant to the current question?

Elements of “Weight-of-Evidence”



Inter-Context Relevance



Strength of Evidence ≠ Cancer Potency

	IARC Class	Cancer Slope Factor $(mg/kg\text{-}d)^{-1}$
Benzene	1	0.1
Vinyl chloride	1	0.27
Arsenic (inorganic)	1	1.5
Beryllium	1	8.4
Cadmium	1	15
Benzidine	1	500
1,3-Butadiene	2A	0.6
Acrylamide	2A	4.5
N-Nitrosodiethylamine	2A	36

Mode & Mechanism of Action

MECHANISM: Detailed understanding, at the molecular level, of events leading to the endpoint

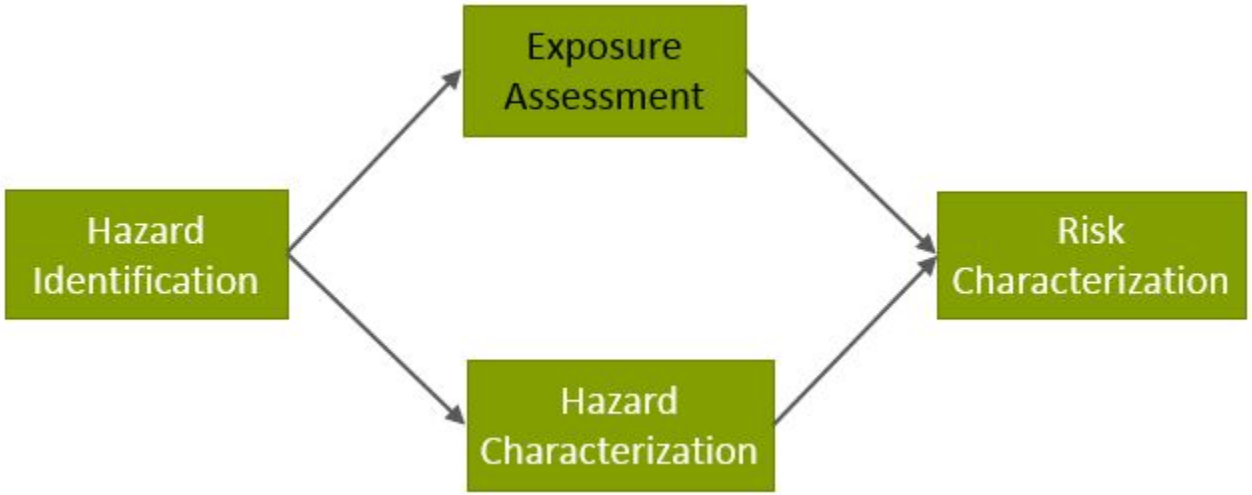
MODE: A sequence of key events leading to cancer

Key events: empirically observable events

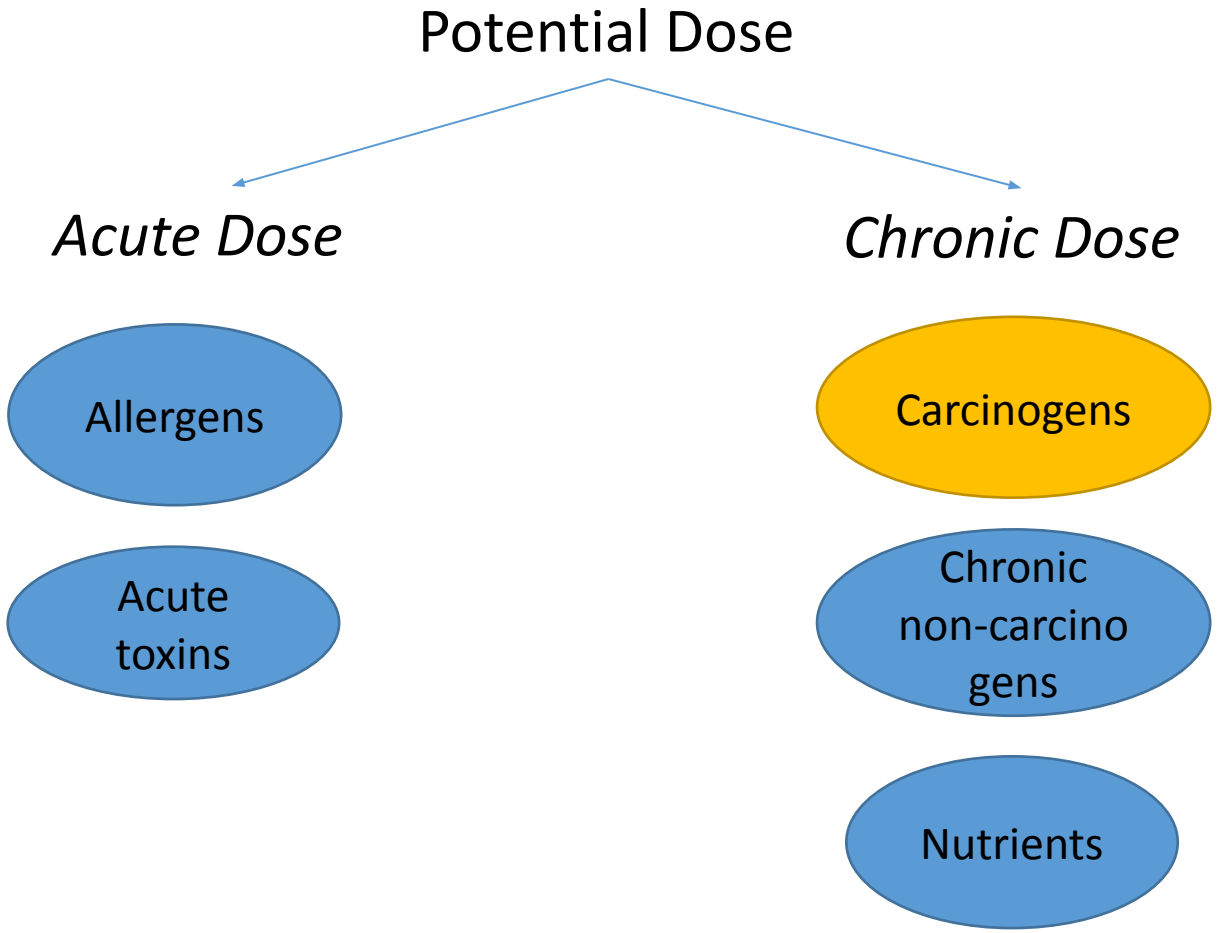
Nature of the toxic moiety, interaction with cellular components, anatomical changes, etc.

- Relevance of animal studies to humans
- Focus on appropriate endpoints for dose-response assessment

3. Exposure Assessment

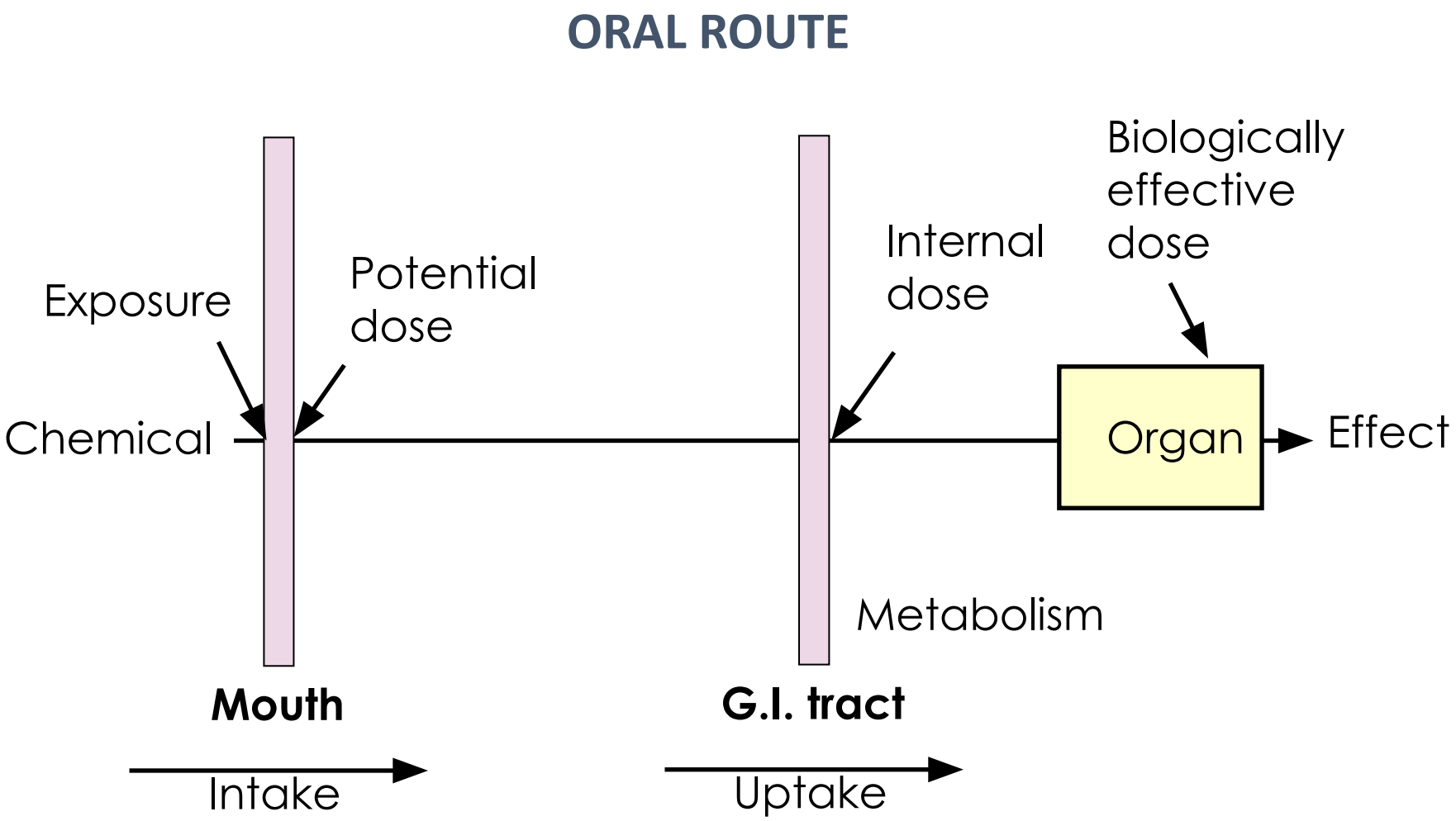


Varieties of Exposure



Legend: Cancer end-point
Non-cancer end-point

Schematic of Dose and Exposure



Potential Dose

Potential dose in humans is comparable to administered dose in experimental animal studies to derive dose-response studies

In the past, the potential dose has been more useful than the absorbed dose since the latter is seldom known in neither animals nor humans

Potential Dose

$$\text{Potential dose} = \frac{C \times IR \times ED}{BW \times AT}$$

C Average concentration (mg/kg food)
IR Intake rate (kg food/d)
ED Exposure duration (days)
BW Body weight (kg)
AT Averaging time (=ED; human environmental exposures)

Carcinogens: Life-time average daily dose (LADD);
Non-carcinogens: Average daily dose (ADD) (mg/kg/d)

Duration of Exposure

Acute exposure

- Assumes illness *can result from any single eating occasion*
- E.g. most chemicals at high levels, or some at lower levels, e.g. allergens
- Individual's dose depends on amount of food eaten per eating occasion, and the level of the chemical in that food

Sub-chronic (less-than-lifetime exposure)

- Applies when a key exposure window exists for the hazard
- E.g. Lead exposure for brain development in children
- E.g. Mercury exposure for women of child-bearing age

Chronic exposure

- E.g. most chemicals at low levels
- Individual's dose depends on average amount of food eaten per day (over lifetime), and the average level of the chemical in that food

Units of Dose for the Three Exposures

Acute exposure

- mg/kg (systemic effects)
- mg (local effects, e.g. allergens)

Sub-chronic

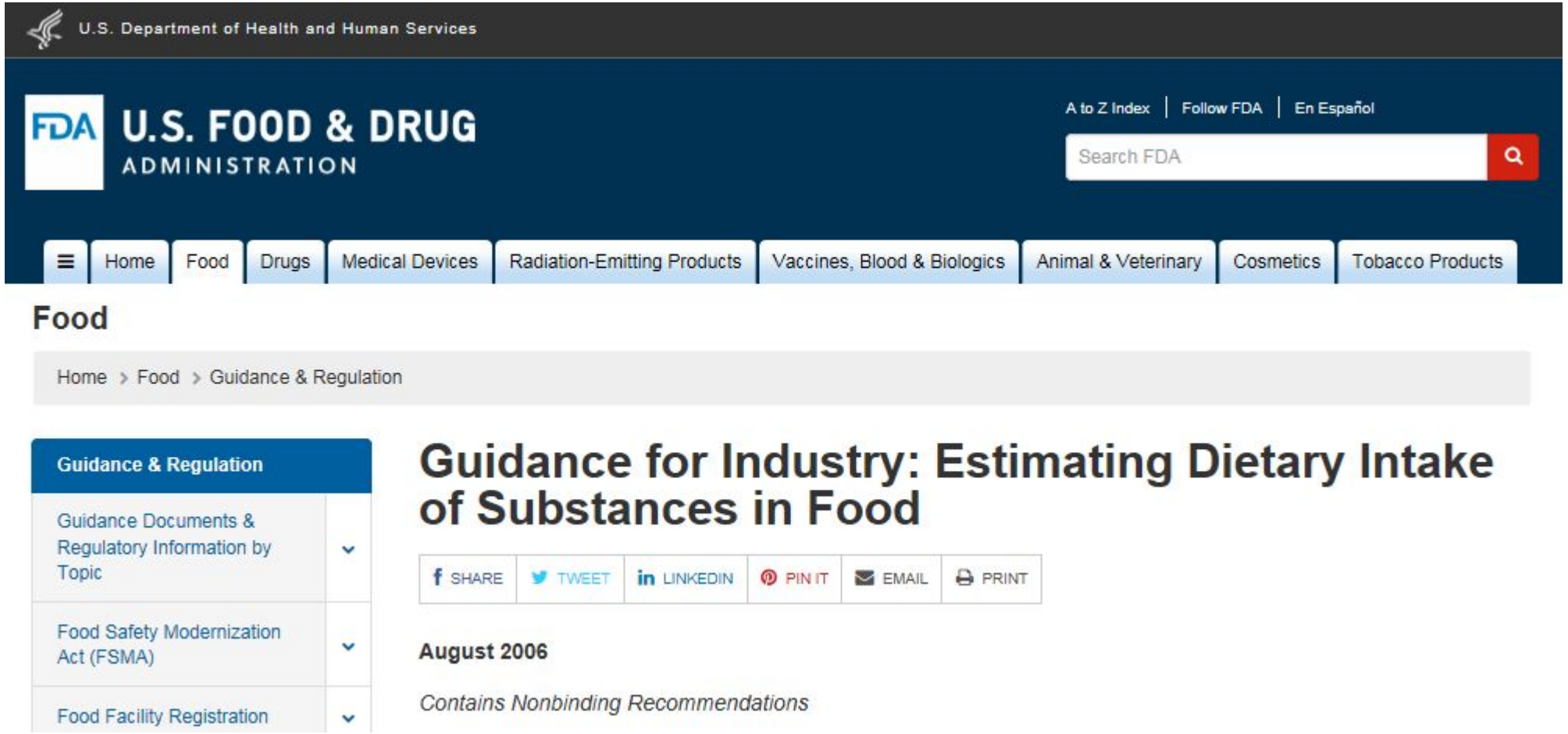
- Average Daily Dose (ADD) in mg/kg-day, during period of interest

Chronic exposure

- Lifetime Average Daily Dose (LADD) in mg/kg-day, during lifetime

Examples of Dose Estimation

Guidance on Dose Estimation is available from FDA



Acute Exposure Dose Estimation

Exposure to Hazelnut Allergen in Chocolate Spread

Estimate of Acute Exposure Dose (with local effects)

- Hazelnut is a tree nut commonly used in foods, particularly in Europe
- In Canada and US the prevalence of allergy to tree nuts is ~ 0.4-1.2%

- Reactions range from mild, such as oral allergy syndrome, to severe (i.e. anaphylaxis).

- The food products most likely to contain undeclared hazelnut proteins include pastries and chocolate

Spanjersberg et al., 2007 Risk Assessment

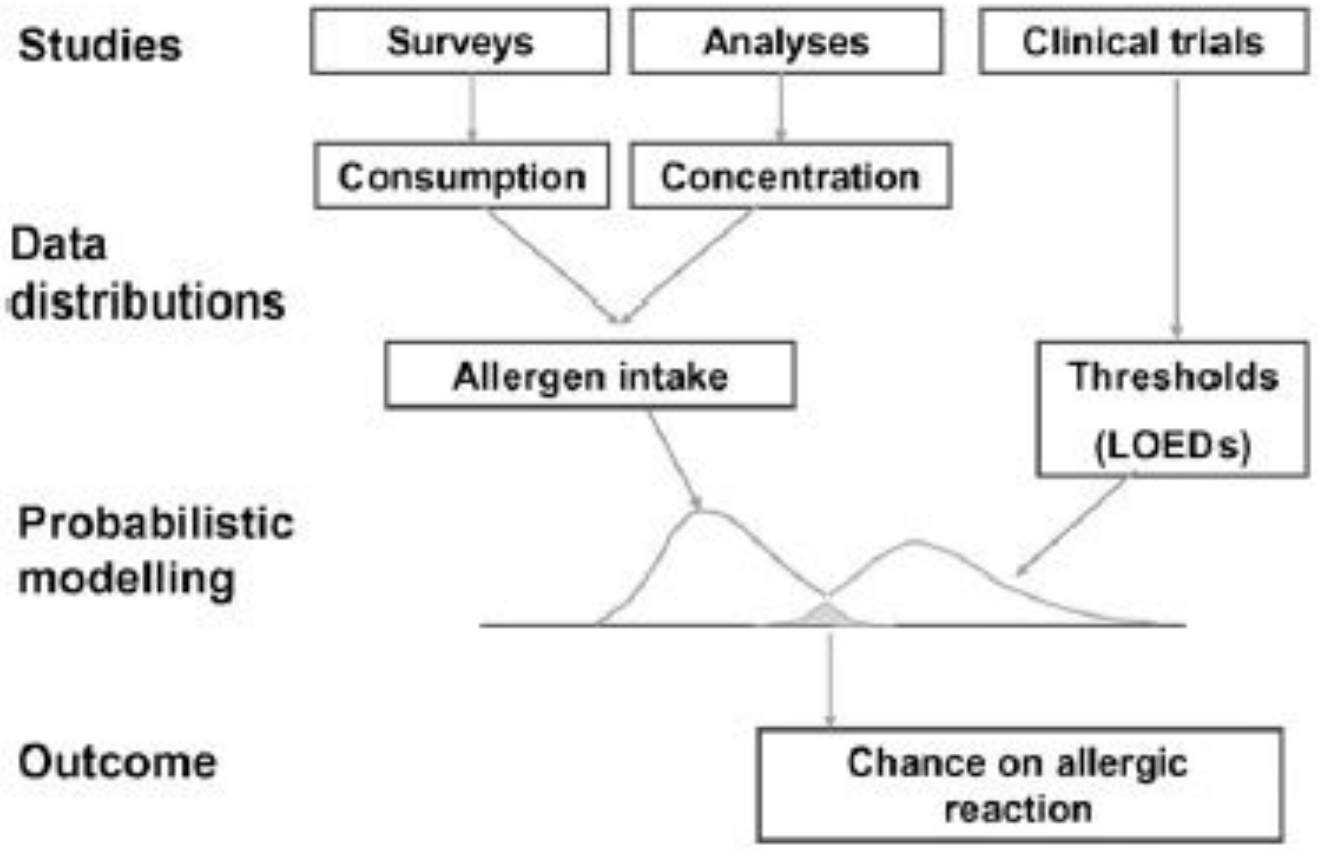


Fig. 1. Schematic presentation of the probabilistic approach in food allergen risk assessment.

"Allergen intake" is the exposure: we will need the amount of food consumed and the concentration of the allergen in the food

"Thresholds" is the dose-response model: we will need the probability of eliciting a response at each dose

Estimating Acute Exposure to Hazelnut Protein

Risk assessment and food allergy: the probabilistic model applied to allergens

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Received 16 December 2005; accepted 14 July 2006

- Concentration in food (chocolate spread)
- Distribution of Eliciting Dose

Risk assessment of dietary acrylamide intake in Flemish adolescents

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Received 18 May 2004; accepted 9 October 2004

- Consumption of food (chocolate spread)

We can estimate risk per serving, and so disregard the frequency of consumption

Estimating Distribution of Consumption of Chocolate Spread

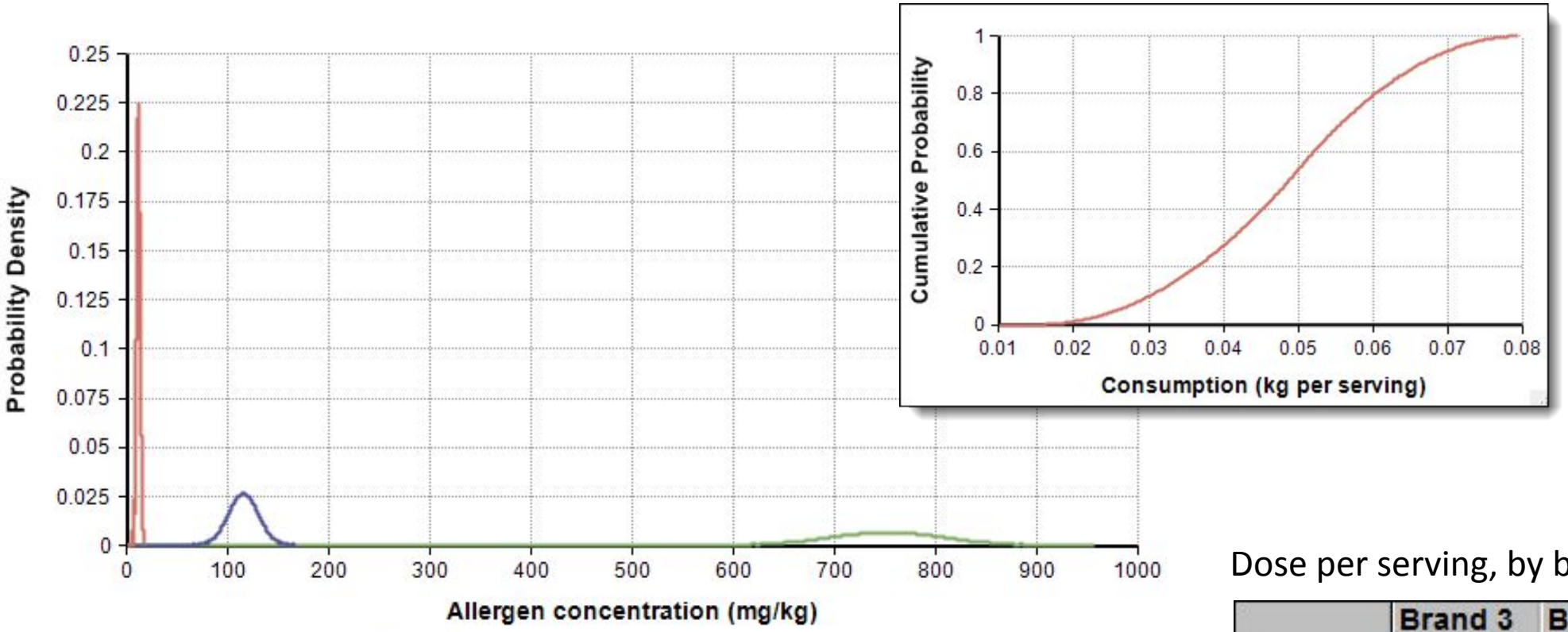
	Consumption data (g/day)		
	All (n = 341)	Boys (n = 129)	Girls (n = 212)
	Mean (P50–P95)	Mean (P50–P95)	Mean (P50–P95)
Baby's biscuits	1.97 (0–15)	1.20 (0–0)	2.44 (0–25)
Bread	119.30 (100–315)	146.45 (135–360)	102.77 (90–265.63)
Small bread type	44.31 (0–200)	47.65 (0–207.60)	42.28 (0–192.50)
Crisps	5.93 (0–45)	7.91 (0–60)	4.72 (0–30)
Chocolate	9.73 (0–50)	12.34 (0–60)	8.14 (0–50)
Choco-spread	7.64 (0–40)	10.30 (0–60)	6.02 (0–30)
French fries	39.88 (0–250)	45.84 (0–300)	36.26 (0–200)

(presence of zeroes is a tip-off that these data are not "consumers only", but average per capita)

Consumption data (from Matthys et al., 2005) describe average daily intake in adolescents, and so underestimate the amount consumed by those who partake daily. The amounts in the high percentiles are likely driven by daily consumers.
We can explore the risk given a simple triangular distribution (min=15g, mode=50g, max=80g)

(30 g is approximately 2 Tbsp)

Combining Concentration and Consumption Gives Dose



Concentration of allergen (mean)
Brand 1: 0.752 ± 0.059 mg/g
Brand 2: 0.115 ± 0.015 mg/g
Brand 3: 0.011 ± 0.002 mg/g

Dose per serving, by brand (mg allergen)

	Brand 3	Brand 2	Brand 1
Min	0.1602	1.441	12.49
Median	0.5238	5.539	36.31
Mean	0.5309	5.571	36.35
Max	1.237	11.81	64.83
Std. Dev	0.1705	1.737	10.46

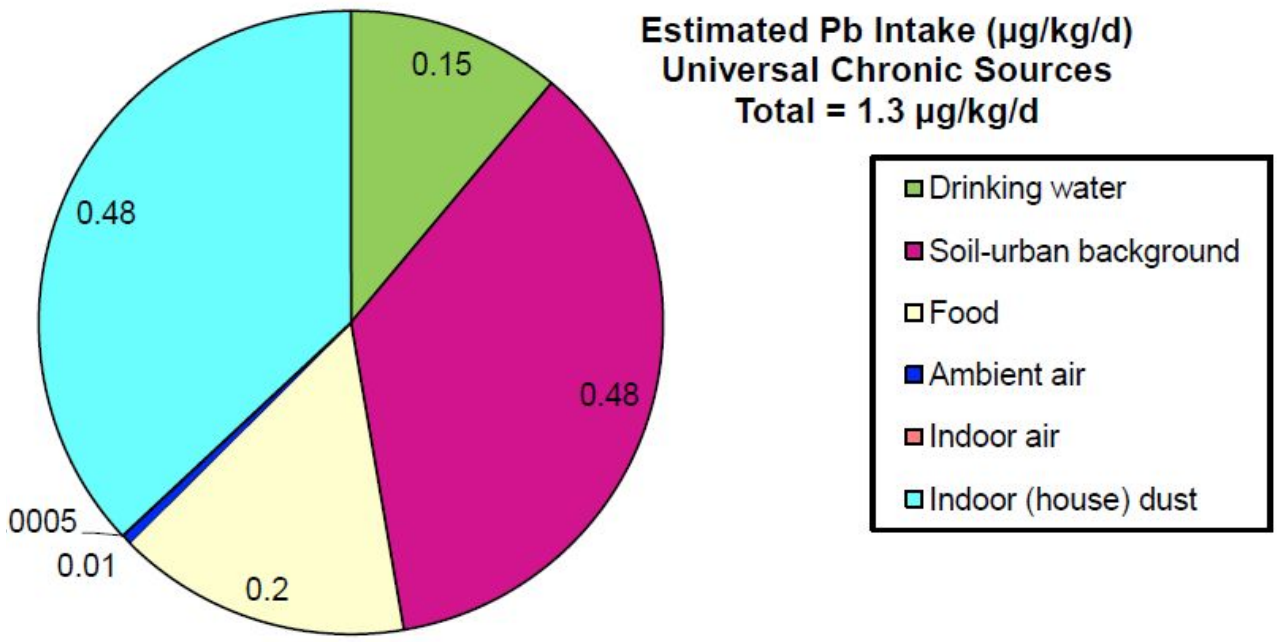
Sub-Chronic Exposure Dose Estimation

Dietary Lead Exposure in Children

The Canadian Total Diet Study

Dietary Exposure to Lead

Age Category	Median (µg/kg bw/day)	90th Percentile (µg/kg bw/day)	95th Percentile (µg/kg bw/day)
0-6 months	0.076	0.343	0.435
0.5-4 years	0.195	0.363	0.431
5-11 years	0.124	0.253	0.314
+12 years	0.069	0.148	0.180



We can focus exclusively on the excess risk contributed by lead in the diet, since the dose- response model displays a linear relationship. The sensitive stage is up to ~ 7 years.

The Canadian Total Diet Study

Dietary Exposure to Lead

Age Category	Median (µg/kg bw/day)	90th Percentile (µg/kg bw/day)	95th Percentile (µg/kg bw/day)
0-6 months	0.076	0.343	0.435
0.5-4 years	0.195	0.363	0.431
5-11 years	0.124	0.253	0.314
+12 years	0.069	0.148	0.180

Calculation of average daily dose (dietary) over 0 to 7 years:

0.5/7 * Dose at 0-6 months
+ 4.5/7 * Dose at 0.5-4 years
+ 2.0/7 * Dose at 5-11 years

Median = 0.166 mg/kg bw/day
90^{th} %ile = 0.330 mg/kg bw/day
95^{th} %ile = 0.398 mg/kg bw/day

Chronic Exposure Dose Estimation

Arsenic Exposure from Rice Consumption

Estimate of Chronic Exposure: Inorganic Arsenic in Rice

Consider inorganic arsenic in rice

- Inorganic Arsenic (iAs) is the harmful form
- iAs is naturally occurring in the earth's crust and other media
  - Also a contaminant from mining and smelting activities
  - Contaminant in groundwater, and a component of agricultural pesticides used up until the 1970s

Chronic exposure to chemicals is measured as a lifetime average daily dose, in units of mass per kilogram of body weight

Calculation of Lifetime Average Daily Dose (LADD)

The dose is the average daily intake of chemical per kg body weight

Can be based on:

- Average amount of food consumed daily in g/day
  - E.g. “Foods Commonly Eaten in the United States” (2002)
  - What We Eat in America
- Body weight in kg
  - E.g. Exposure Factors Handbook (USEPA, 2011)

Or:

- Data integrating daily food consumption and body weight
  - E.g. Continuing Survey of Food Intake by Individuals (CFSII)

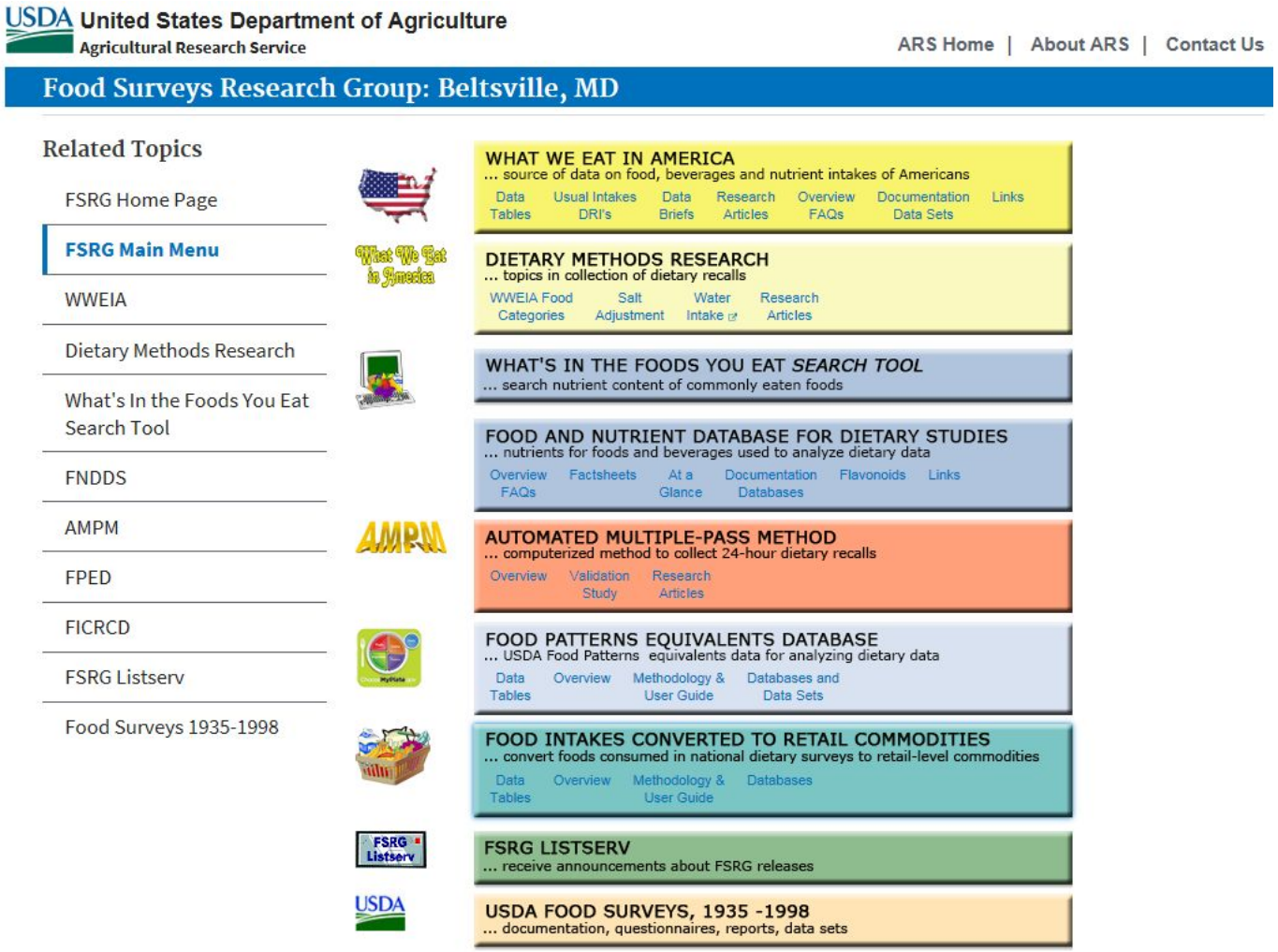
And we need average concentration of chemical in the food in mg/kg food

Rice Consumption Data by Age (USDA, 2002)

Table 2.016. Total Rice: Percentage of persons using food in 2 days and quantities consumed in a day.

Statistic	All individuals age 2 and over	Age (years) and sex									
		2-5	6-11	12-19		20-39		40-59		60 and older	
		Males and females	Males and females	Males	Females	Males	Females	Males	Females	Males	Females
Number in sample	14,262	2,109	1,432	696	702	1,543	1,449	1,663	1,694	1,545	1,429
Percent of persons using					%						
at least once in 2 days	31.1	32.7	28.0	26.4	31.9	33.1	35.0	32.3	32.2	27.6	25.4
on 1 of 2 days	23.9	24.5	22.1	19.3	25.6	25.7	26.8	24.4	24.4	21.4	19.3
on both days	7.3	8.2	5.9	7.1	6.3	7.5	8.2	7.9	7.8	6.3	6.1
Quantity consumed in a day (1/2 cup regular rice = 79 g)					g						
Mean	152	86	124	207	156	209	139	176	129	138	113
SEM	4	4	6	20	9	11	7	7	5	9	6
5th percentile	13	9	12	20 *	11 *	22	12	18	7	8	9
10th percentile	24	18	22	39	17	40	21	32	19	18	13
25th percentile	58	39	51	78	51	82	58	75	59	49	39
50th percentile	117	76	99	156	118	156	115	153	109	104	78
75th percentile	183	111	156	239	229	297	161	234	156	162	156
90th percentile	312	159	245	462	341	416	312	328	236	311	241
95th percentile	397	206	312	621 *	464 *	610	345	461	313	319	313

Consumption Data Available from USDA



WWEIA: Food Intakes Converted to Retail Commodities

Retail Commodity Intakes: Mean Amounts of Retail Commodities per Individual, 2007-08

Only provides mean amount per capita, but includes all sources

Table 4. Grains: Mean Amounts of Retail Commodities Consumed per Individual[1], Estimated From Dietary Intake Data, by Gender and Age, in the United States, WWEIA, NHANES 2007-2008

Gender and Age (years)	Sample size	†Total Grains		Corn Flour and Meal		Oats and Oat Flour		Rice (dry)		Wheat Flour	
		Mean (SE) in grams									
Males:											
2 - 5	455	86	(2.3)	10	(0.8)	6	(0.9)	8	(1.4)	61	(2.4)
6 - 11	550	122	(3.5)	15	(1.0)	4	(0.7)	9	(1.4)	92	(3.3)
12 - 19	607	146	(5.1)	16	(2.0)	4	(0.5)	13	(1.8)	110	(4.8)
2 - 19	1612	124	(2.5)	14	(1.0)	5	(0.4)	11	(1.4)	93	(2.4)
20 - 29	409	156	(5.6)	18	(1.5)	4	(0.9)	21	(3.8)	113	(6.0)
30 - 39	451	144	(4.6)	21	(3.3)	6	(0.9)	16	(2.6)	100	(5.5)
40 - 49	412	142	(6.2)	15	(1.4)	4	(1.1)	19	(2.7)	103	(4.9)
50 - 59	431	131	(5.5)	13	(1.8)	5	(1.0)	13	(2.7)	96	(5.0)
60 - 69	459	119	(4.4)	10	(1.2)	6	(1.0)	12	(1.8)	87	(3.9)
70 and over	500	106	(4.2)	9	(0.6)	9	(1.0)	6	(1.0)	79	(3.3)
20 and over	2662	137	(2.8)	15	(1.0)	5	(0.5)	16	(1.7)	99	(2.7)
Females:											
2 - 5	377	83	(3.7)	9	(1.2)	4	(0.7)	8	(1.2)	61	(2.9)
6 - 11	571	110	(2.8)	13	(1.3)	4	(0.7)	8	(1.8)	83	(3.6)

Body Weights from Exposure Factors Handbook (USEPA, 2011)

Chapter 8—Body Weight Studies

Table 8-4. Mean and Percentile Body Weights (kg) for Male Derived from NHANES (1999–2006)

Age Group	*N*	Mean	Percentiles								
			5th	10th	15th	25th	50th	75th	85th	90th	95th
Birth to <1 month	88	4.9	3.6	3.6	4.0	4.4	4.8	5.5	5.8	6.2	6.8
1 to <3 months	153	6.0	4.6	5.0	5.1	5.4	6.1	6.8	7.0	7.2	7.3
3 to <6 months	255	7.6	5.9	6.4	6.6	6.9	7.5	8.2	8.6	8.8	9.1
6 to <12 months	472	9.4	7.3	7.9	8.2	8.5	9.4	10.3	10.6	10.8	11.5
1 to <2 years	632	11.6	9.0	9.7	10.0	10.5	11.5	12.6	13.2	13.5	14.3
2 to <3 years	558	14.1	11.4	12.0	12.2	12.8	14.0	15.2	15.9	16.4	17.0
3 to <6 years	1,158	18.8	13.5	14.4	14.9	15.9	18.1	20.8	22.6	23.8	26.2
6 to <11 years	1,795	31.9	20.0	21.8	22.9	24.8	29.6	36.4	41.2	45.2	51.4
11 to <16 years	2,593	57.6	33.6	36.3	38.9	44.2	55.5	66.5	75.5	81.2	91.8
16 to <21 years	2,462	77.3	54.5	57.6	60.0	63.9	73.1	86.0	96.8	104.0	113.0
21 to <30 years	1,359	84.9	58.7	63.0	66.2	70.7	81.2	94.0	103.0	111.0	123.0
30 to <40 years	1,445	87.0	61.1	65.7	68.7	73.8	84.0	96.5	104.0	110.0	124.0
40 to <50 years	1,545	90.5	64.9	69.5	73.0	77.7	87.4	99.7	109.0	114.0	125.0
50 to <60 years	1,189	89.5	64.1	68.8	71.4	77.0	87.8	99.8	107.0	112.0	123.0
60 to <70 years	1,360	89.1	63.4	67.5	71.6	77.2	86.9	99.4	108.0	113.0	120.0
70 to <80 years	1,079	83.9	60.6	64.6	68.3	73.1	82.1	93.8	98.6	104.0	113.0
Over 80 years	662	76.1	56.7	60.6	63.9	67.2	75.1	84.0	89.4	92.5	100.0

Source: U.S. EPA Analysis of NHANES 1999–2006 data.

Concentration of iAs in Rice: FDA, 2016

Arsenic in Rice and Rice Products

Risk Assessment Report

Table 4.5. Estimated Inorganic Arsenic Concentrations in All Brown Rice, All White Rice, and All Rice Combined

Rice Type (uncooked/ unprepared)	Number of Inorganic Arsenic Data Samples	Inorganic Arsenic Concentration Weighted Mean[a] (ppb)	Inorganic Arsenic Concentration Weighted SEM (ppb)
All	573	96.0	1.2
Brown	144	153.8	3.2
White	429	92.3	1.3

[a] Determined based on inorganic arsenic data on individual rice types from FDA (2013) and Consumer Reports (2012); weighted based on market share from the USDA Economic Research Service (ERS) and USA Rice Federation (Appendix 9.7; additional personal communications, Nathan Childs, ERS).

[b] ppb = µg/kg or ng/g

RSI

Estimating Lifetime Average Daily Dose (LADD)

1. Calculate the average amount of the food consumed daily during the lifetime, per kg body weight (bw).

Lifetime Average Daily Dose (LADD) Calculation	Rice intake (g/day)	Body weight (kg)	Rice intake (g/kg-day)	Lifestage duration (years)	"weights"	Weighted daily rice intake
males 2 to 5 (50th %ile)	76	18.1	4.2	4	0.05	0.21
males 6 to 11 (50th %ile)	99	29.6	3.3	6	0.08	0.25
males 12 to 19 (50th %ile)	156	62	2.5	8	0.10	0.25
males 20 to 39 (50th %ile)	156	82.5	1.9	20	0.25	0.47
males 40 to 59 (50th %ile)	153	87.6	1.7	20	0.25	0.44
males 60+ (50th %ile)	104	82	1.3	22	0.28	0.35
				80		1.97 Lifetime average rice (cooked) intake (g/kg-day)

2. Divide by 3.4 to get the weight of dry rice consumed: 0.60 g/kg-day
3. Combine the lifetime average rice intake with the mean concentration of arsenic in rice (96 µg/kg) to get LADD:

0.0006 kg rice/kg bw-d * 96 µg/kg rice = 0.06 µg/kg-d

i.e. 0.06 µg arsenic per kg body weight per day, for lifetime

USEPA Food Consumption Data: *per capita*, per kg bw

United States Environmental Protection Agency

CSFII Analysis of Food Intake Distributions

"per capita" data include those not consuming the food (zero values are giveaway)

Table 3-33. Per capita intake of rice (g/kg-day as consumed)

Group	Percent consuming	Mean	SE	Percentile									
				1st	5th	10th	25th	50th	75th	90th	95th	99th	100th
TOTAL	17.6	0.424	0.029	0	0	0	0	0.000	0.000	1.306	2.567	6.799	42.990
Age													
0–5 months	0.2	0.011	0.239	0	0	0	0	0.000	0.000	0.000	0.000	0.000	5.197
6–12 months	9.2	0.345	0.418	0	0	0	0	0.000	0.000	0.000	1.989	8.063	14.514
< 1 years	4.4	0.167	0.283	0	0	0	0	0.000	0.000	0.000	0.000	6.699	14.514
1–2 years	19.2	0.905	0.166	0	0	0	0	0.000	0.000	3.225	5.805	12.011	27.921
3–5 years	17.0	0.795	0.179	0	0	0	0	0.000	0.000	2.292	4.838	12.493	42.990
6–11 years	15.8	0.492	0.098	0	0	0	0	0.000	0.000	1.935	3.516	7.187	12.493
12–19 years	17.1	0.462	0.105	0	0	0	0	0.000	0.000	1.501	2.898	7.565	20.019
20–39 years	19.2	0.435	0.058	0	0	0	0	0.000	0.000	1.493	2.756	6.029	24.383
40–69 years	18.4	0.336	0.038	0	0	0	0	0.000	0.000	1.078	1.923	5.528	14.151
70 + years	13.3	0.236	0.078	0	0	0	0	0.000	0.000	0.645	1.366	3.928	15.833

USEPA Food Consumption Data: per consumer, per kg bw

United States Environmental Protection Agency

CSFII Analysis of Food Intake Distributions

data describe only those people consuming the food

Table 3-33a. Consumer-only intake of rice (g/kg-day as consumed)

Group	Percent consuming	Mean	SE	Percentile 1st	5th	10th	25th	50th	75th	90th	95th	99th	100th
TOTAL	100	2.409	0.054	0.133	0.374	0.528	0.889	1.513	2.895	5.278	7.213	13.330	42.990
Age													
0–5 months	100	5.197	0.000	5.197	5.197	5.197	5.197	5.197	5.197	5.197	5.197	5.197	5.197
6–12 months	100	3.765	0.960	0.573	0.573	1.452	1.797	1.989	6.699	8.063	14.514	14.514	14.514
< 1 years	100	3.801	0.915	0.573	0.573	1.452	1.797	1.989	6.699	8.063	14.514	14.514	14.514
1–2 years	100	4.710	0.271	0.374	0.936	1.382	2.073	3.349	5.898	8.892	13.854	23.222	27.921
3–5 years	100	4.670	0.334	0.432	0.654	1.177	1.742	2.837	5.842	10.926	12.963	30.713	42.990
6–11 years	100	3.111	0.157	0.032	0.505	0.898	1.451	2.354	4.147	6.699	8.021	11.875	12.493
12–19 years	100	2.694	0.198	0.073	0.352	0.581	1.089	1.639	3.317	5.688	7.917	19.351	20.019
20–39 years	100	2.267	0.099	0.156	0.380	0.581	0.898	1.540	2.855	4.750	6.123	11.551	24.383
40–69 years	100	1.827	0.070	0.128	0.344	0.466	0.741	1.161	1.996	3.888	5.584	12.116	14.151
70 + years	100	1.785	0.177	0.118	0.205	0.341	0.670	1.123	1.785	3.483	5.225	14.760	15.833
Season													
Fall	100	2.539	0.114	0.173	0.396	0.564	0.920	1.555	3.163	5.805	7.213	13.854	24.383

Estimating Average Lifetime Dose (LADD) at 50th Percentile

Lifetime Average Daily Dose (LADD) Calculation	Rice intake (g/kg-day)	Lifestage duration (years)	"weights"	Weighted daily rice intake	
persons 3 to 5 years (50th %ile)	2.837	3	0.04	0.11	
persons 6 to 11 years (50th %ile)	2.354	6	0.08	0.18	
persons 12 to 19 years (50th %ile)	1.639	8	0.10	0.17	
persons 20 to 39 years (50th %ile)	1.54	20	0.25	0.39	
persons 40 to 69 years (50th %ile)	1.161	30	0.38	0.44	
persons 70+ years (50th %ile)	1.123	12	0.15	0.17	
		79		1.45	Lifetime average rice (cooked) intake (g/kg-day)

Divide by 3.4 to get the weight of dry rice consumed: 0.43 g/kg-day

$$0.43 \frac{g\ dry\ rice}{kg\ body\ weight\ per\ day} \times 96 \frac{\mu g\ arsenic}{kg\ dry\ rice} \times 0.001 \frac{kg}{g} = 0.04 \frac{\mu g\ arsenic}{kg\ body\ weight\ per\ day}$$

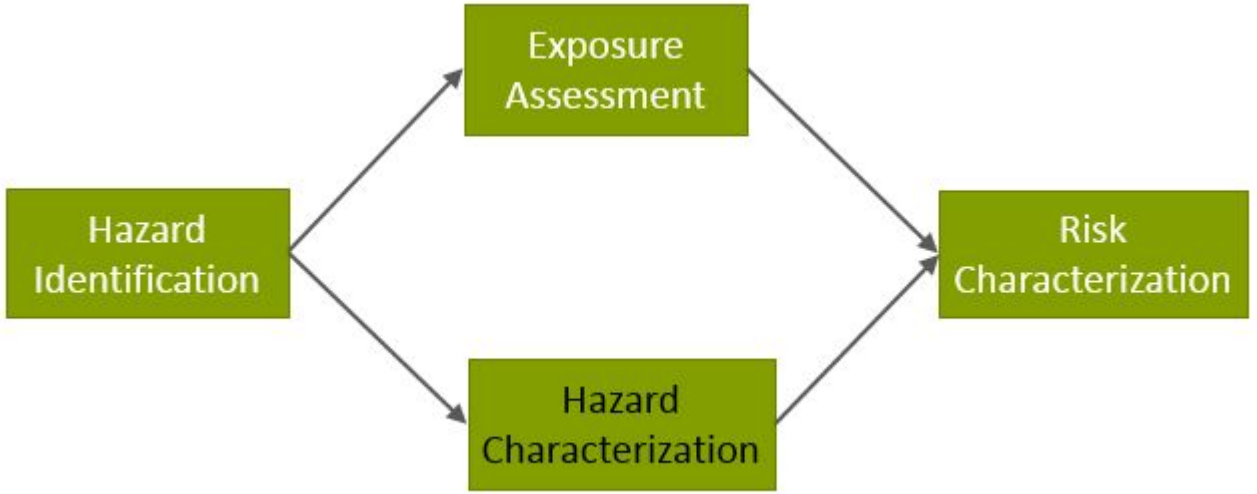
Estimating Average Lifetime Dose (LADD) at 99th Percentile

Lifetime Average Daily Dose (LADD) Calculation	Rice intake (g/kg-day)	Lifestage duration (years)	"weights"	Weighted daily rice intake
persons 3 to 5 years (99th %ile)	30.713	3	0.04	1.17
persons 6 to 11 years (99th %ile)	11.875	6	0.08	0.90
persons 12 to 19 years (99th %ile)	19.351	8	0.10	1.96
persons 20 to 39 years (99th %ile)	11.551	20	0.25	2.92
persons 40 to 69 years (99th %ile)	12.116	30	0.38	4.60
persons 70+ years (99th %ile)	14.76	12	0.15	2.24
		79		13.80 Lifetime average rice (cooked) intake (g/kg-day)

Divide by 3.4 to get the weight of dry rice consumed: 4.06 g/kg-day

$$4.06 \frac{g\ dry\ rice}{kg\ body\ weight\ per\ day} \times 96 \frac{\mu g\ arsenic}{kg\ dry\ rice} \times 0.001 \frac{kg}{g} = 0.39 \frac{\mu g\ arsenic}{kg\ body\ weight\ per\ day}$$

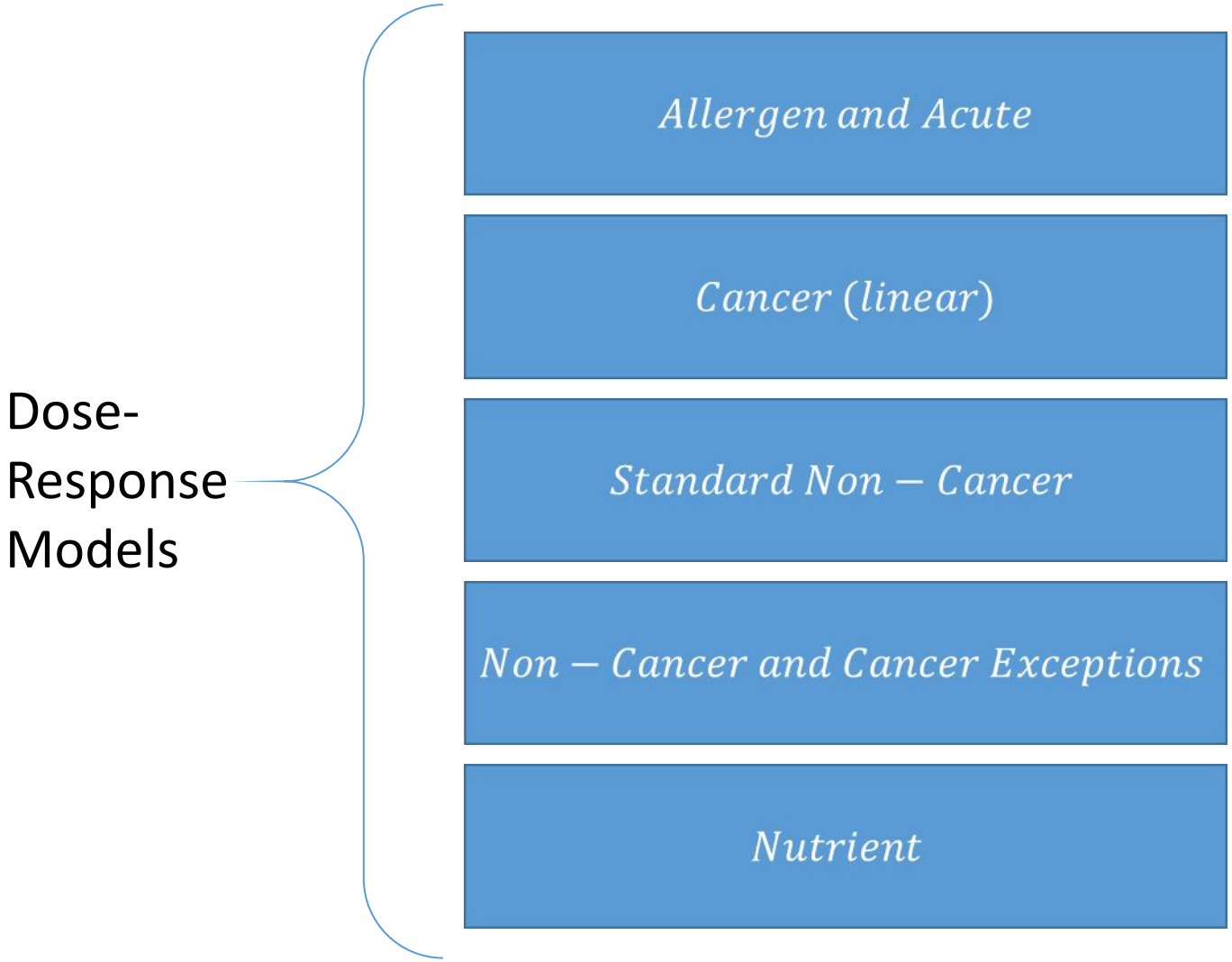
4. Hazard Characterization (Dose-Response Assessment)



Chemical Dose-Response Models

- May be for acute or chronic exposure
- Dose is expressed as mg/day or mg/kg body weight per day
- Human data (occupational exposures, or highly exposed populations) or animal data with appropriate adjustments incorporated
- Both linear and non-linear forms

Varieties of Dose-Response Models



Examples of Dose-Response Models

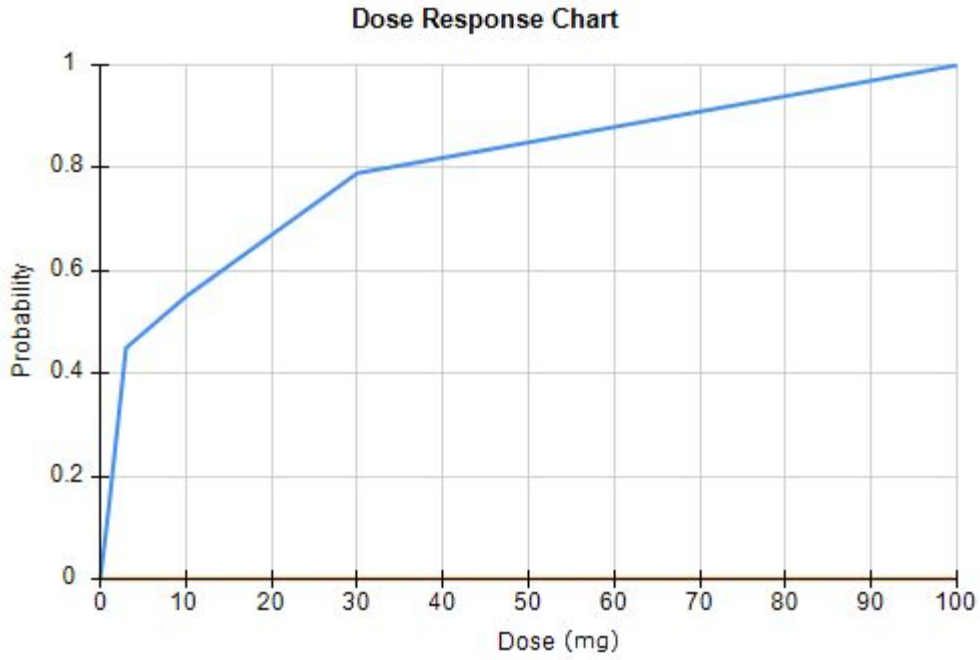
4a. Dose-Response Model for Acute Exposure with a Local Effect

Acute Exposure to Hazelnut Allergen

Dose-Response for Allergen: Acute Exposure, Local Response

Spanjersberg et al. (2007) reported the threshold of sensitivity for 29 patients as follows:

- four patients responded to 1 mg,
- nine to 3 mg,
- three to 10 mg,
- seven to 30 mg and
- six to 100 mg of hazelnut protein



From this an empirical distribution can be constructed based on the cumulative fraction of subjects responding at each intake (above right).

Example of Acute Exposure with Systemic Effect

- Measured in mg chemical/ kg body weight
- E.g glycoalkaloids (as in potatoes)

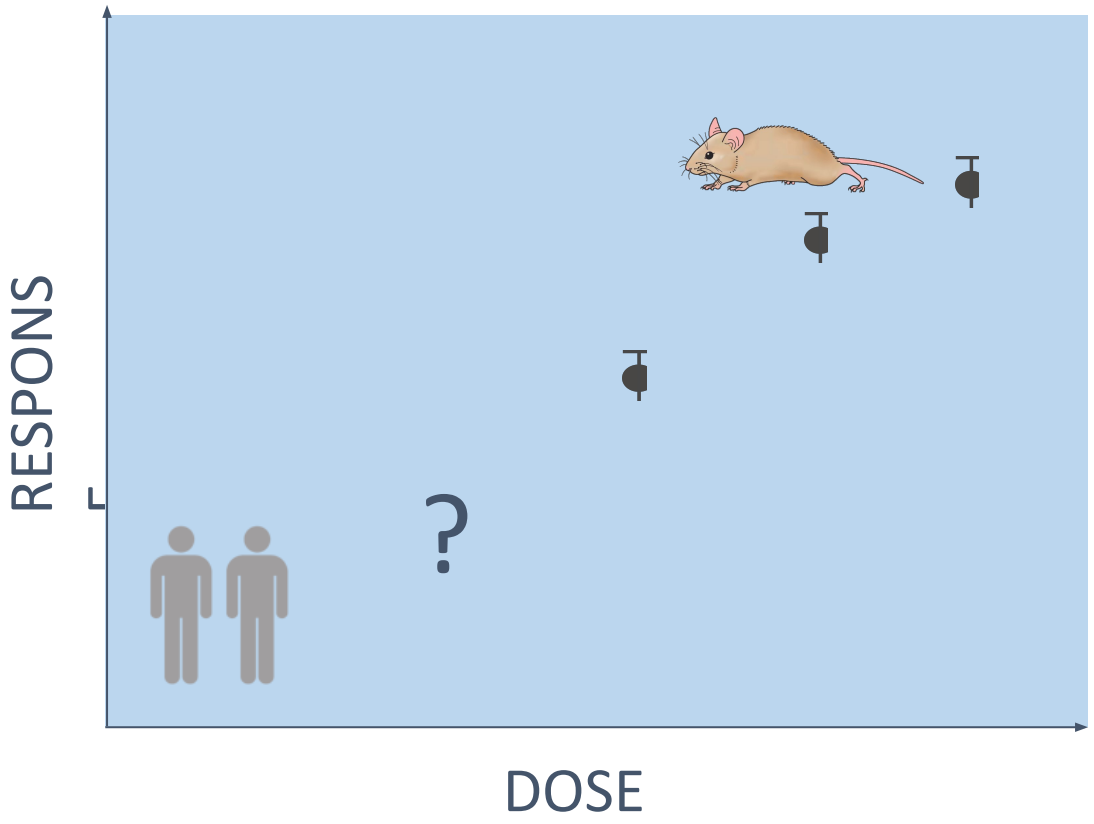
Information from Health Canada:

- “Adverse health effects from higher intakes of glycoalkaloids are usually related to consumption of potatoes that show signs of physical change or damage (e.g. sprouting, greening, bruising).
- Symptoms associated with glycoalkaloid poisoning from potatoes include a bitter or burning sensation in the mouth and flu-like symptoms such as nausea, vomiting, stomach and abdominal cramps, and diarrhea.
- More severe cases of glycoalkaloid poisoning may be accompanied by a variety of neurological effects (i.e. drowsiness, apathy, restlessness, shaking, confusion, weakness, and disturbed vision).
- There are a few reports of deaths being attributed to glycoalkaloid exposure from the consumption of potatoes, potato leaves, and potato berries.”

4b. Dose-Response Model for Chronic Exposure to a Carcinogen

Chronic Exposure to Arsenic

Cancer Risk Assessment Extrapolations



Dose-Response Assessment: Cancer

Experiments demonstrate increased risk of cancer over the lifetime

- In humans, through epidemiological studies at « real doses »
- In animals, through the lifetime of the test animal at artificially high doses in animal's feed or water

High to low doses extrapolations

- Experimental to low exposure levels
- Slope characterization

Animal- Human extrapolations

- Slope conversion
- Based on equivalent dose in human

1×10^{-6} Lifetime Cancer Risk Level

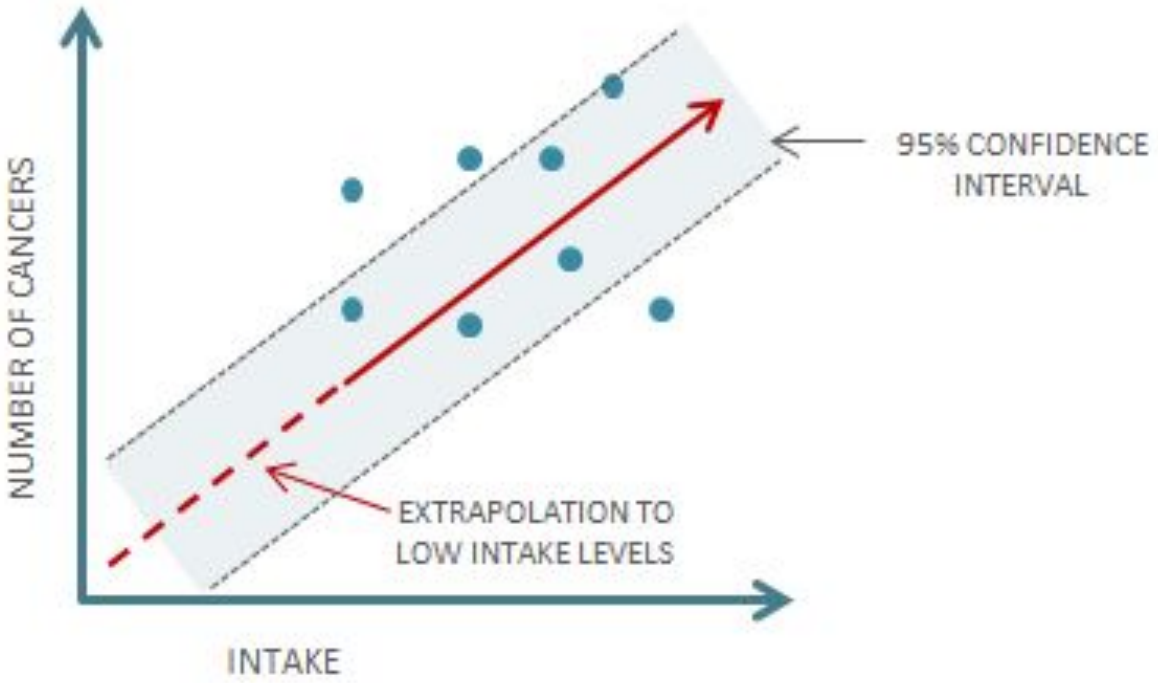
- Mantel & Bryan (1961) introduced the concept of virtual safety: 1 in 100 million

- *de minimis* risk; Acceptable risk socially determined
- Target risk range: 1×10^{-5} to 1×10^{-6}

- The dose associated with 1×10^{-6} risk level has been called a Virtually Safe Dose (VSD)

Cancer Slope Factors

There is a lot of uncertainty in predicting excess cancer risk in humans, but by using standard cancer potency factors, we can make relative comparisons between substances and exposure routes.



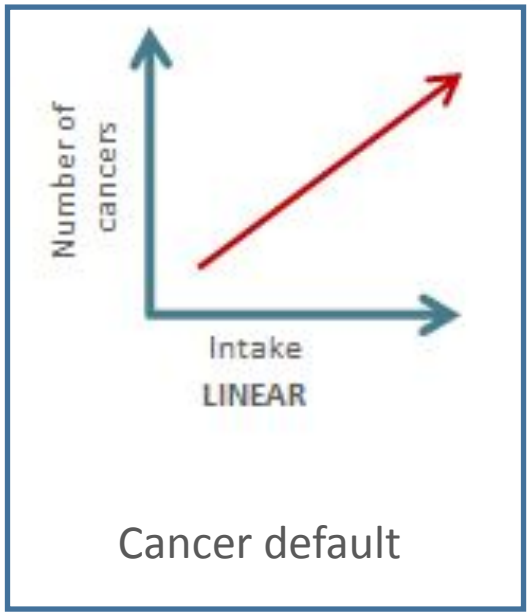
When the number of cancers increases in direct proportion to the intake (dose), it is possible to predict the number of cancers expected for any given intake, using the slope of the line that is the best fit for the data. Cancer potency factors are also called oral or inhalation slope factors.

Cancer potency factors are often developed using data that reflect relatively high intake levels. When intake levels are low, the best fit line must be extrapolated below the point of any observed data.

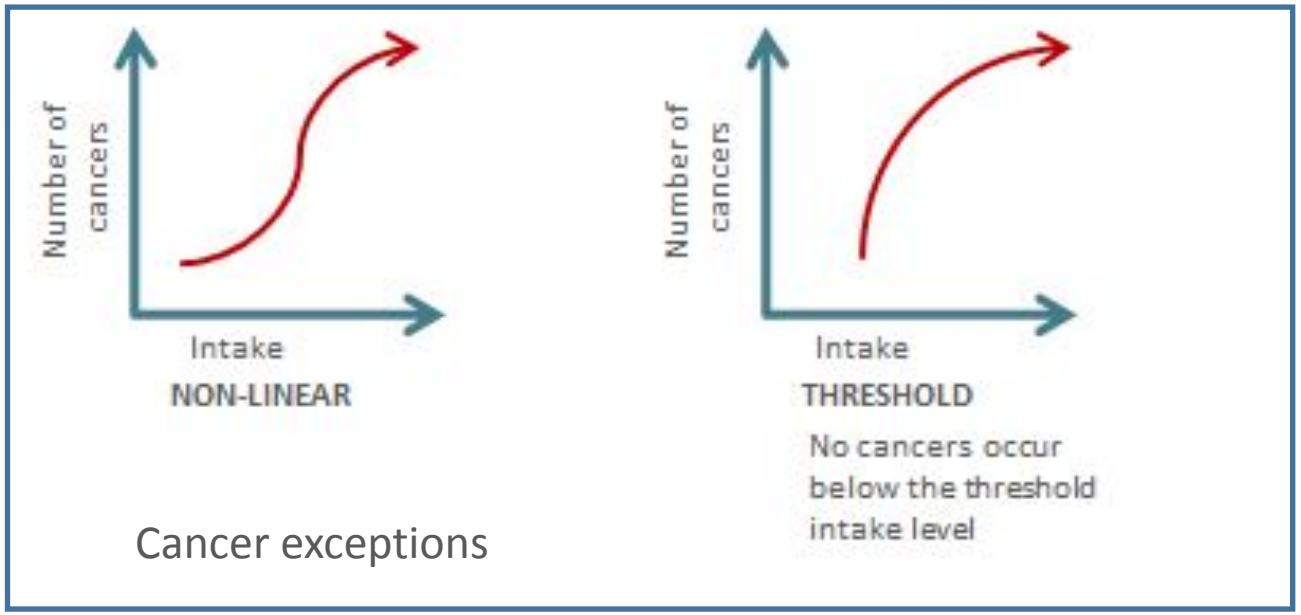
Cancer Slope Factors

The cancer potency factors used by Health Canada, US EPA and California OEHHA assume a linear relationship and reflect the slope of the upper bound of the 95% confidence interval.

The real relationship between intake and the number of cancers may not always be linear. This adds uncertainty to the extrapolation of the cancer potency factor to intakes lower than those observed in the existing studies.



Cancer default



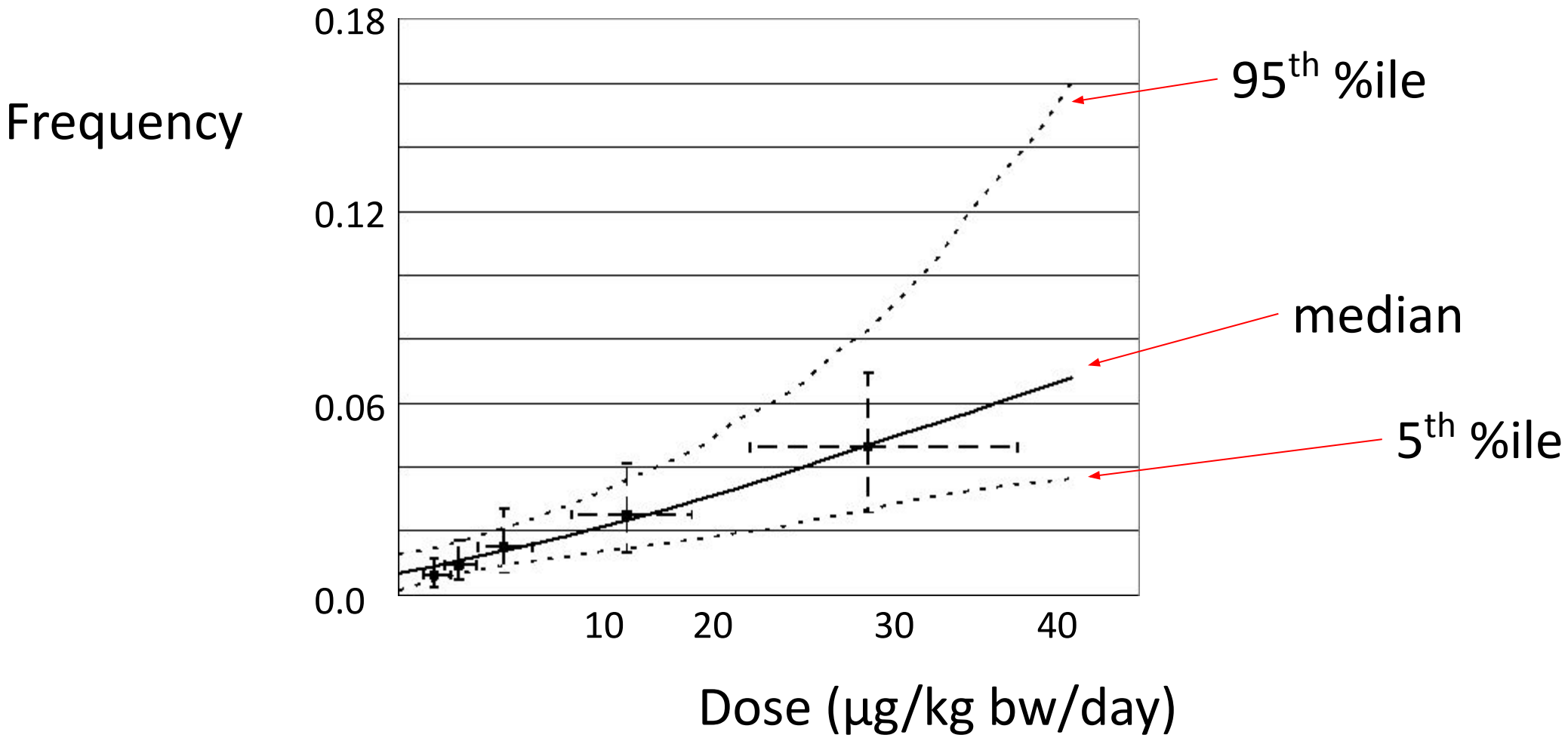
Cancer exceptions

Describing Cancer Potency

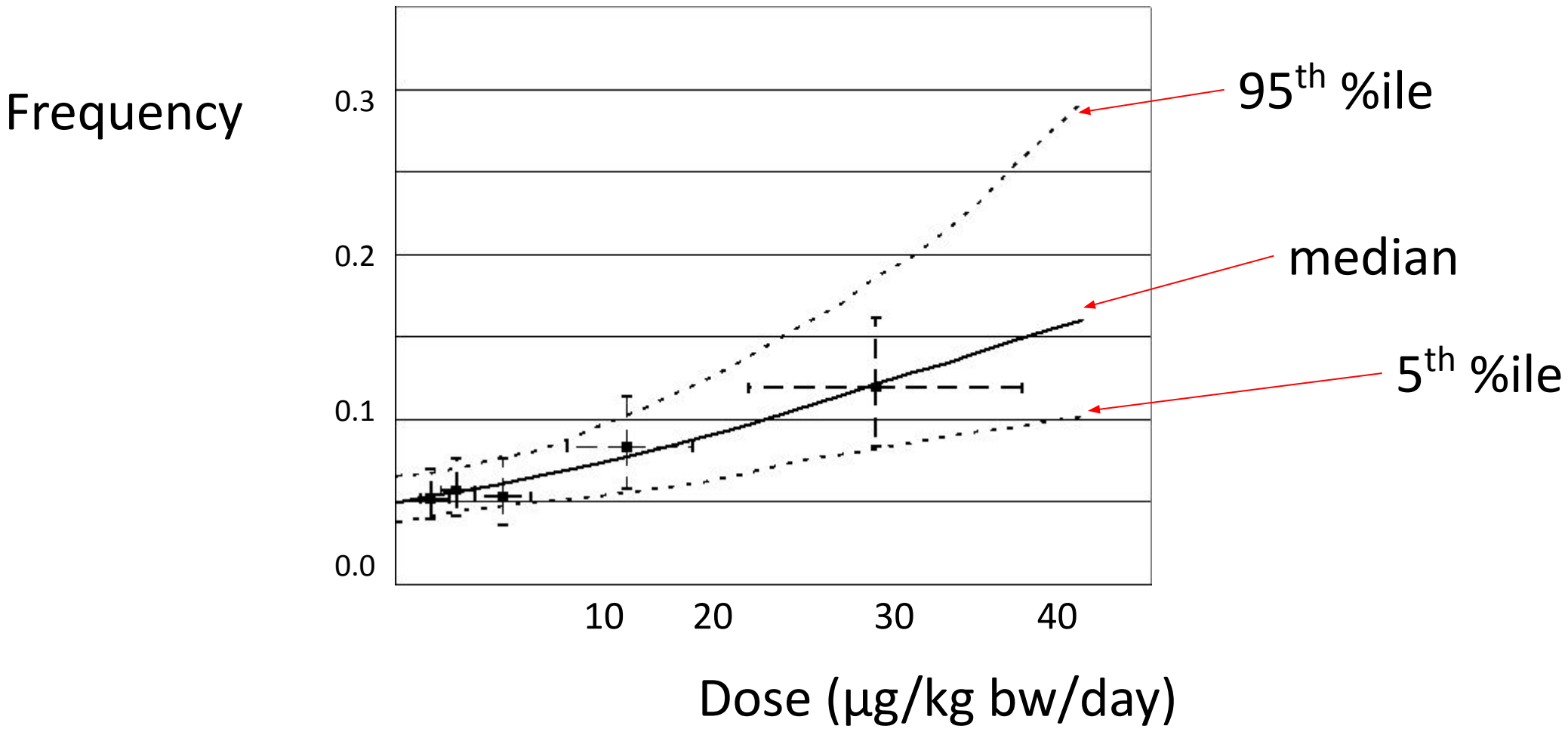
Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
Acetaldehyde		75-07-0	TAC	2.7 E-6	1.0 E-2	B2	2B
Acetamide		60-35-5	RCHAS-E	2.0 E-5	7.0 E-2	NC	2B
Acrylamide		79-06-1	IRIS	1.3 E-3	4.5 E+0	B2	2A
Acrylonitrile		107-13-1	RCHAS-S	2.9 E-4	1 .0 E+0	B1	2A
Allyl chloride		107-05-1	RCHAS-S	6.0 E-6	2.1 E-2	C	3
2-Aminoanthraquinone		117-79-3	RCHAS-E	9.4 E-6	3.3 E-2	NC	3
Aniline		62-53-3	IRIS	1.6 E-6	5.7 E-3	B2	3
Arsenic (inorganic)	(inhalation)	7440-38-2	TAC	3.3 E-3	1.2 E+1	A	1
	(oral)		IRIS		1.5 E+0		
Asbestos		1332-21-4	TAC	6.3 E-2	2.2 E+2	A	1
				1.9 E-4[#]			

Urinary Tract Cancer from iAs



Lung Cancer from iAs



Cancer Slope Factors (oral) for Inorganic Arsenic

Table 3.4 Linear Slope Estimates and ED01 from Morales *et al.* (2000) Model 1

Endpoint	Sex	ED01 (µg/L)[a]	SEM[b]	Linear Slope[c] (cases per mg/kg bw/day)
Bladder cancer	M	395 (326)	35	0.89 (0.76, 1.02)
Bladder cancer	F	252 (211)	21	1.39 (1.20, 1.58)
Bladder cancer	M+F	324 (267)	29	1.08 (0.92, 1.24)
Lung cancer	M	364 (294)	36	0.96 (0.81, 1.12)
Lung cancer	F	258 (213)	23	1.36 (1.16, 1.56)
Lung cancer	M+F	311 (252)	30	1.13 (0.95, 1.30)

[a] Effective Dose for 1% (ED01) is equivalent to a BMD1 for a quantal endpoint. The lower bound, equivalent to a $BMDL_1$, is given in parentheses. The values reported in Morales *et al.* (2000) were converted to dietary equivalents using the standard values used by the authors; a water consumption value of 2 liters and a body weight of 70 kg.

[b] The standard error of the mean (SEM) was calculated for the lower bound, assuming a normal distribution of the ED01.

[c] The values provided are the median and in parentheses are the 5^{th} and 95^{th} percentiles of the uncertainty distribution (CI90%).

4c. Dose-Response Model for Chronic Exposure with a Non-Cancer Endpoint

Non-Cancer Safety Assessment

For most chemicals that do not cause cancer, toxicologists often assume that there is a chronic dose level below which the human body will not experience adverse effects (this level is often referred to as a threshold).

As a result, the management of the risk associated with such chemicals is based on whether exposure is above or below the estimated threshold.

- This creates a binary outcome: safe vs. unsafe
- There is no risk estimate associated with exposure at the threshold dose
- For this reason the assessment is sometimes called a safety assessment rather than a risk assessment
- This situation is an area of methodological research to convert non-cancer safety assessment into risk assessment (IPCS, 2015, to be discussed later)

Non-cancer Assessment

- Acceptable Daily Intake (ADI) was coined by FAO/WHO Expert Committee on Food Additives in 1961

- The daily intake of a chemical which, during the entire lifetime, appears to be without deleterious risk on the basis of all the known facts at that time.

- Toxicity Reference Values (TRV):
- = ADI, TDI, PTWI, RfD, RfC, VTR, …

Which effects are adverse effects ?

- Not all biological effects are signs of toxicity
- Alter the normal functioning and growth of the exposed organism (physical, biochemical, physiological, histopathological)
- Whenever there is doubt about the significance of a particular effect, it should be considered as an adverse one (WHO)

Dose *vs* Response

- Biological responses are closely related to the chemical present in the target tissue, rather than the amount administered to the animal (i.e., dose in mg/kg/d)
- Blood concentrations *vs* tissue responses long been recognized in pharmacology and drug development
- In toxicology and risk assessment, the target tissue dose or the internal dose that most closely relates to an adverse response is referred to as a *dose metric*

Establishment of TDI

- Dose to which humans can be exposed daily during lifetime without developing adverse effects
- Human chronic study (other effects ?)
  - Critical study
  - Critical effect
  - A dose to serve as the Point of departure (POD)
  - Uncertainty Factors (UF, also called “Adjustment Factors”) to adjust POD to final Reference Value

Uncertainty Factors Used In Dose-response Assessment

UNCERTAINTY FACTORS	TO ADDRESS UNCERTAINTY RELATED TO….
Inter & intra species ($UF_{H,}$ UF_{A})	Interspecies and intraspecies variation in toxicokinetics and toxicodynamics
Subchronic (UF_{S})	Duration-dependent extrapolation of the point of departure
LOAEL (UF_{L})	To extrapolate to NOAEL
Adequacy of study (UF_{D})	Inability of existing studies to account for all critical adverse effects (modifying/database factor)

Dose-Response Assessment for endpoints with a threshold

$$\text{Reference dose (ARfD, ADI)} = \frac{\text{POD}}{\text{CAF}}$$

$$UF_{total} = UF_A \times UF_H \times (UF_L \times UF_S \times UF_{DB})$$

$$CAF = UF_{total} \times \text{PCPA factor}$$

Greater than 3000 – low confidence in database;
refrain from deriving reference values ?!

The PCPA factor is a legally-mandated margin of safety intended to afford particular protection of infants and children (Health Canada, 2008); the default value is 10-fold.

Example of a Toxicity Reference Value (TWI)

"On the basis of the **lowest observed adverse effect level** (LOAEL) of 8 µg/kg body weight (b.w.) per day for early markers of renal toxicity **in pigs** (the most sensitive animal species),

and applying a composite uncertainty factor of 450* for the uncertainties in the extrapolation of experimental data derived from animals to humans as well as for intra-species variability,

a Tolerable Weekly Intake (TWI) of 120 ng/kg b.w. was derived for OTA."

(EFSA 2006 Opinion on Ochratoxin A)

*UF_A = 15, UF_H = 10, UF_L = 3

Selection of Critical Study

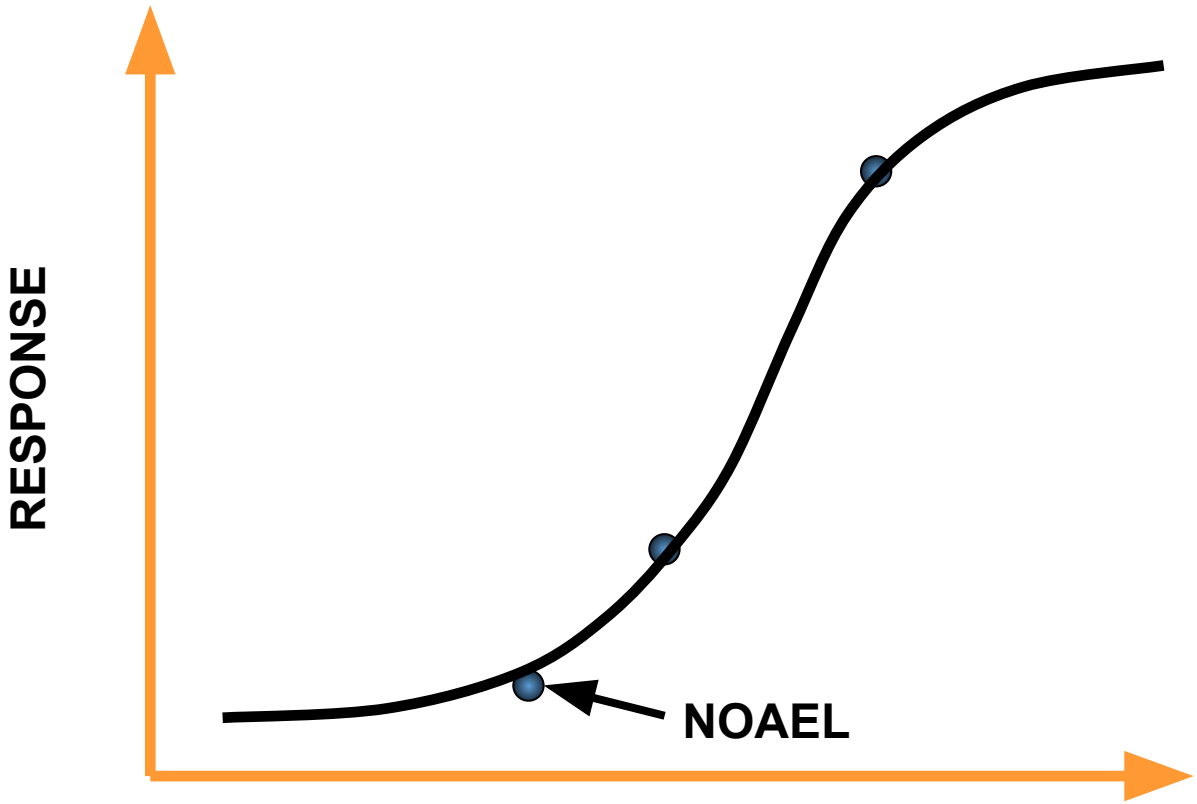
Critical study: the study forming the basis of TDI derivation

Human data ?

Animal model that is most relevant to humans

If not, the most sensitive animal species

Point of Departure



POINT OF DEPARTURE (POD):
The dose-response point that marks the beginning of a low-dose extrapolation

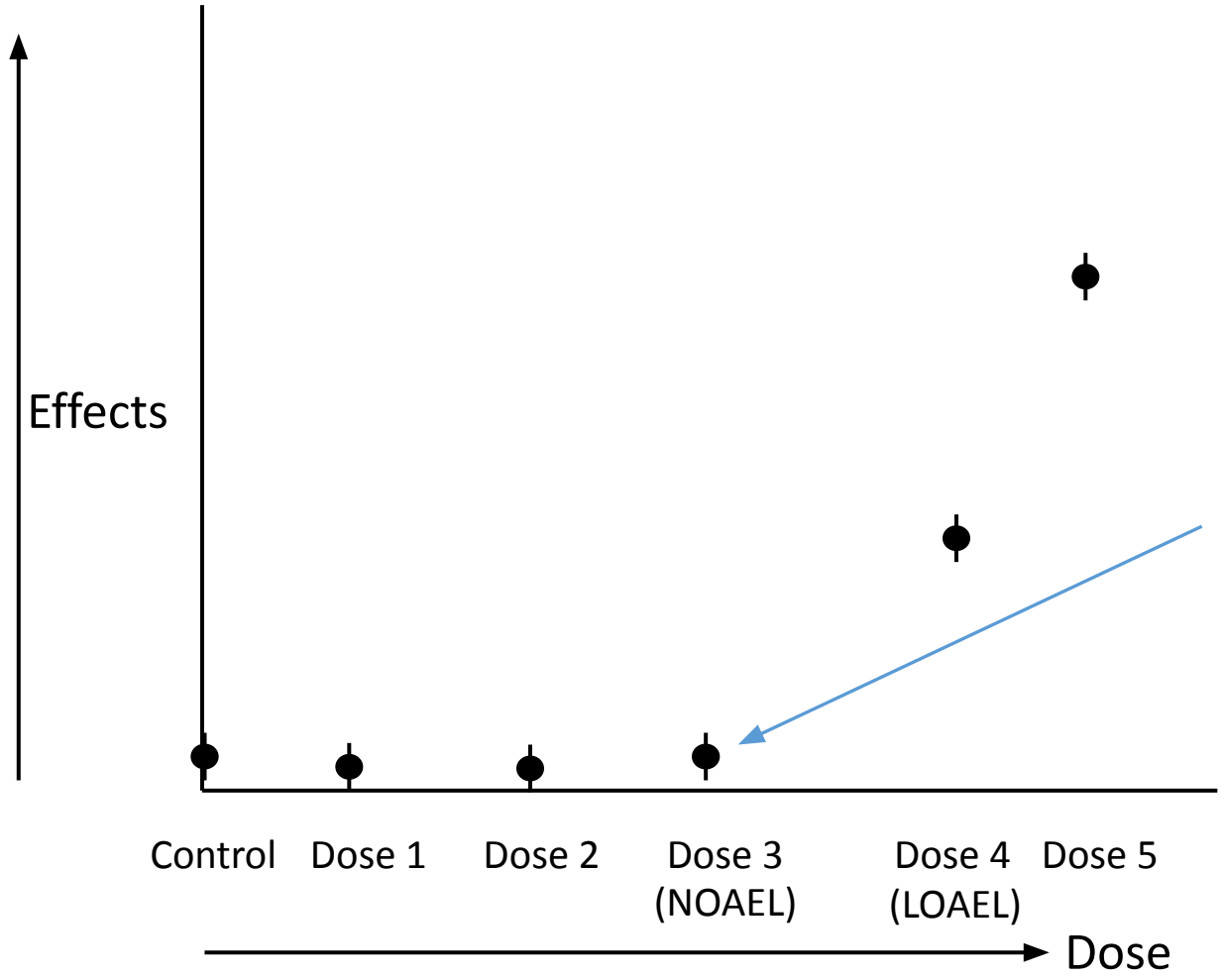
Selection of NOAEL

Dose 1	0 mg/kg	no effect
Dose 2	10 mg/kg	no effect
Dose 3	25 mg/kg	some effect
Dose 4	50 mg/kg	severe effect

Dose 1 and 2 are not statistically different.

Dose 2 is NOAEL and Dose 3 is LOAEL

Selection of NOAEL



The NOAEL may be truly "no effect" or may be an effect that is not significantly different from the response to the control dose.

Selection of POD (mg/kg/d)

OBSERVATION	DOG	RAT	MOUSE
Severe effect	280	150	400
Some effect	140	100	200
No effect	70	50	100
No effect	35	25	50
No effect	0	0	0

Small Number of Animals to Larger Number of Humans

Animals are homogenous and inbred

Human populations are heterogeneous

Animal NOEL to acceptable intake for humans: factor of 100 (Lehman & Fitzhugh 1954)

100-fold Margin of Safety

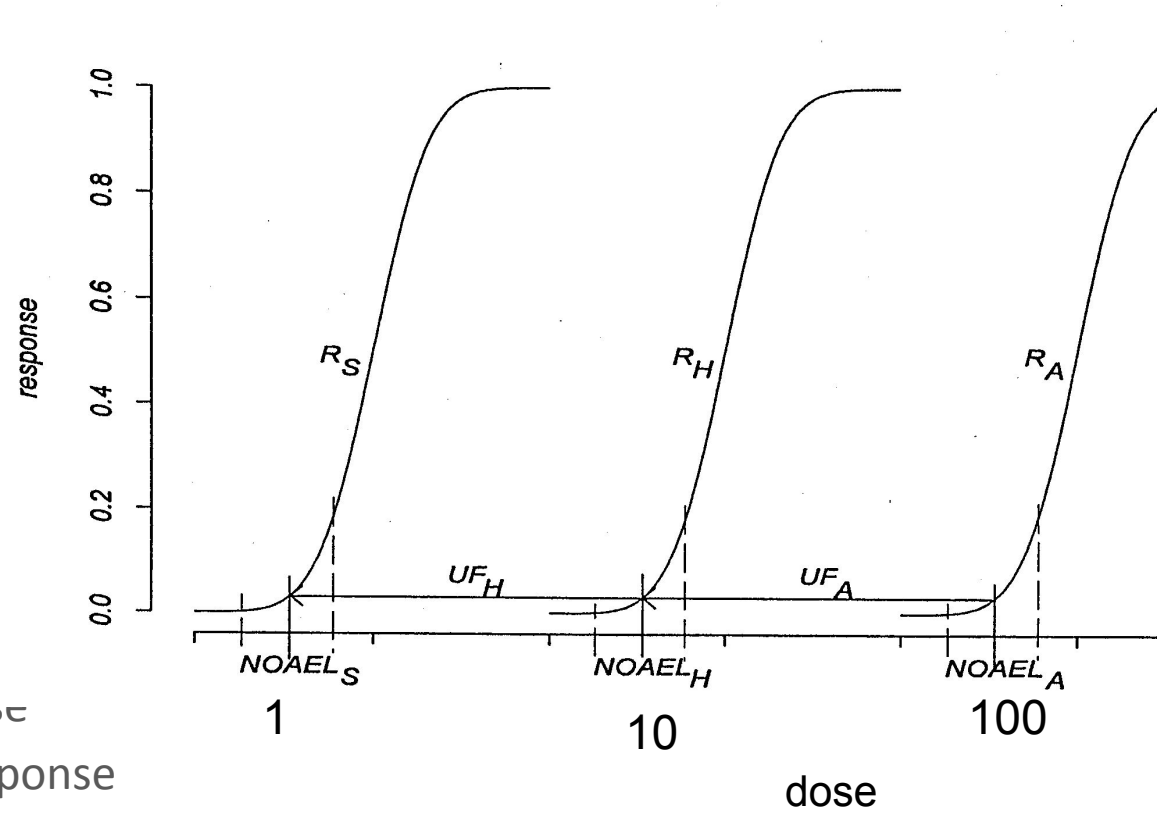
Safety of food additives for humans

Fluoride in diet: safe for people at 1 ppm but rat tolerates up to 10 ppm

Arsenic in diet: dog tolerates up to 127 ppm but humans show signs of toxicity at 30 ppm

Variability between and within animals (age, sex, strain) and humans: **100 ?**

Use of Uncertainty Factors in Non-Cancer Assessment (average rat to average human to sensitive human)

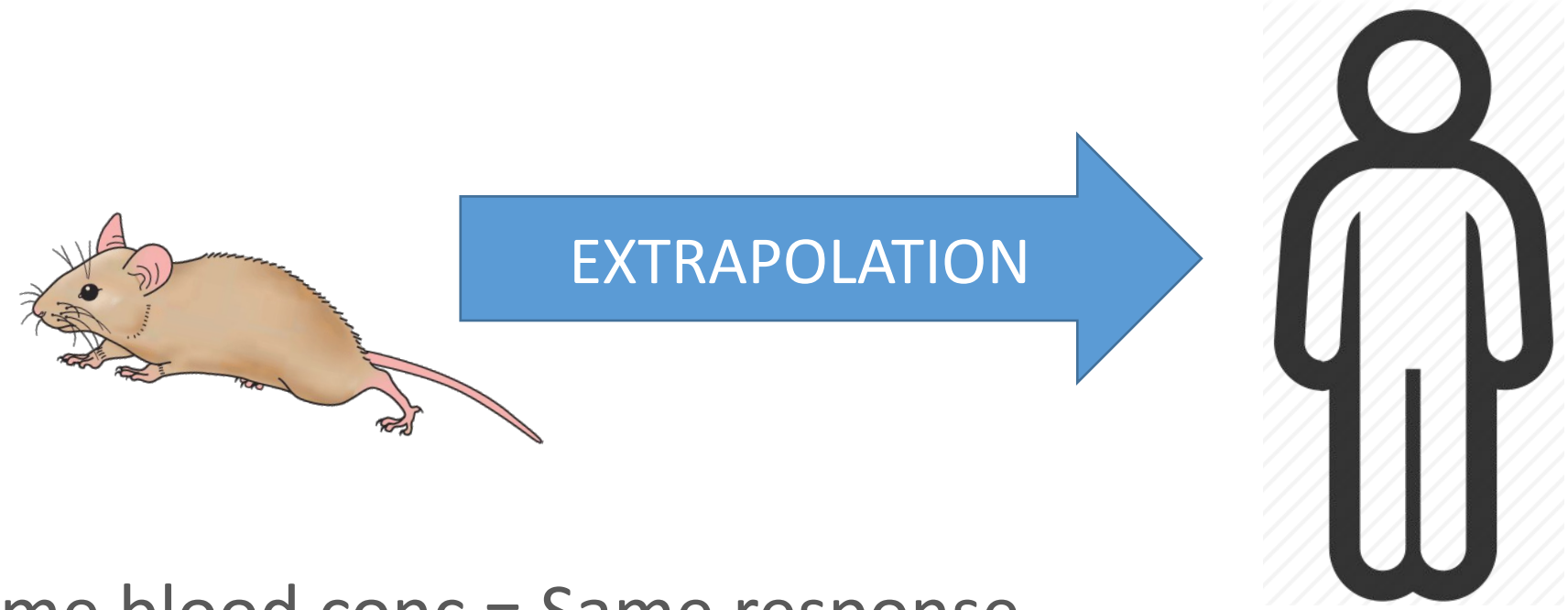


R_A = test animal response

R_H = average human response

Rs = sensitive human response

INTERSPECIES: UF_A



- Same blood conc = Same response
- Blood conc. ~ Dose/BSA; BSA = $BW^{0.7}$
- Interspecies (animal) UF_A = 10 as a common default

SUBCHRONIC to CHRONIC: UF_S

- Difference in exposure duration should be accounted for
- (lifetime vs less-than-lifetime)

- Based on Haber's law (Dose x Duration = Constant)

- Use of a factor of 10

INTRASPECIES: UF_H

- Interindividual variation in toxicokinetics and toxicodynamics
- Individual factors may vary but should be analyzed collectively
- Age, Sex, Physical activity, Disease conditions, Genetic polymorphism,etc.
- Describes the distance between the individuals at the 50^{th} and 95^{th} percentile

LOAEL to NOAEL : UF_L

- Weil and McNamara (1963): 10 or less
- 95 % of chemicals within a factor of 5
- If the LOAEL is for less severe effects, then the use of a lower factor is justified
- More recent data suggest that 91% data are within a factor of 6 and 100% are within a factor of 10
- Therefore the common default is UF_L of 10

DATABASE UNCERTAINTY FACTOR: UF_{DB}

May be applied in the absence of any one of the following requirements:

- Two mammalian chronic (lifetime) toxicity studies in two different species
- Two mammalian developmental toxicity studies in different species
- One mammalian 2-generation reproductive toxicity study

N/LOAEL Approach: Issues

- Should be a dose tested experimentally
- Depends upon dose spacing
- Influenced by the number of animals and variability in the data; doesn’t do anything about it
- Does not take into account the shape or slope of the dose-response curve
- No consistency across chemicals or endpoints

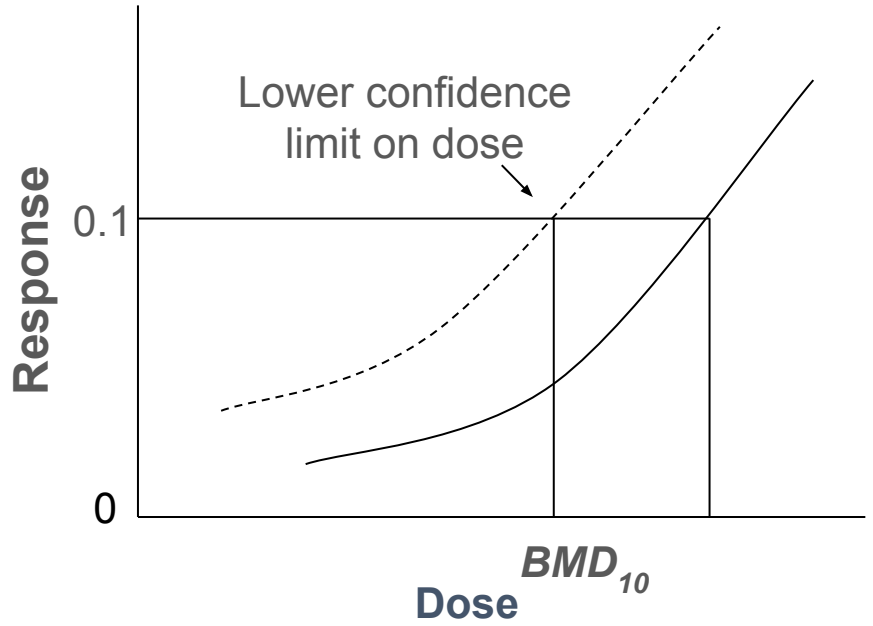
BMD

Benchmark dose

- Dose that is associated with a predetermined level of response
- Determined by mathematical modeling; 95% lower confidence interval on the dose that causes a pre-determined percent increase in the response level compared to controls
- BMD = central estimate; BMDL = 95% lower confidence limit on the dose

Benchmark Dose (BMD)

- Uses all data in developing the model
- Accounts for the slope of the DR curve
- Takes into account variability in data
- Is not limited to one experimental dose
- Usually BMD (5-10%) is close to NOAEL

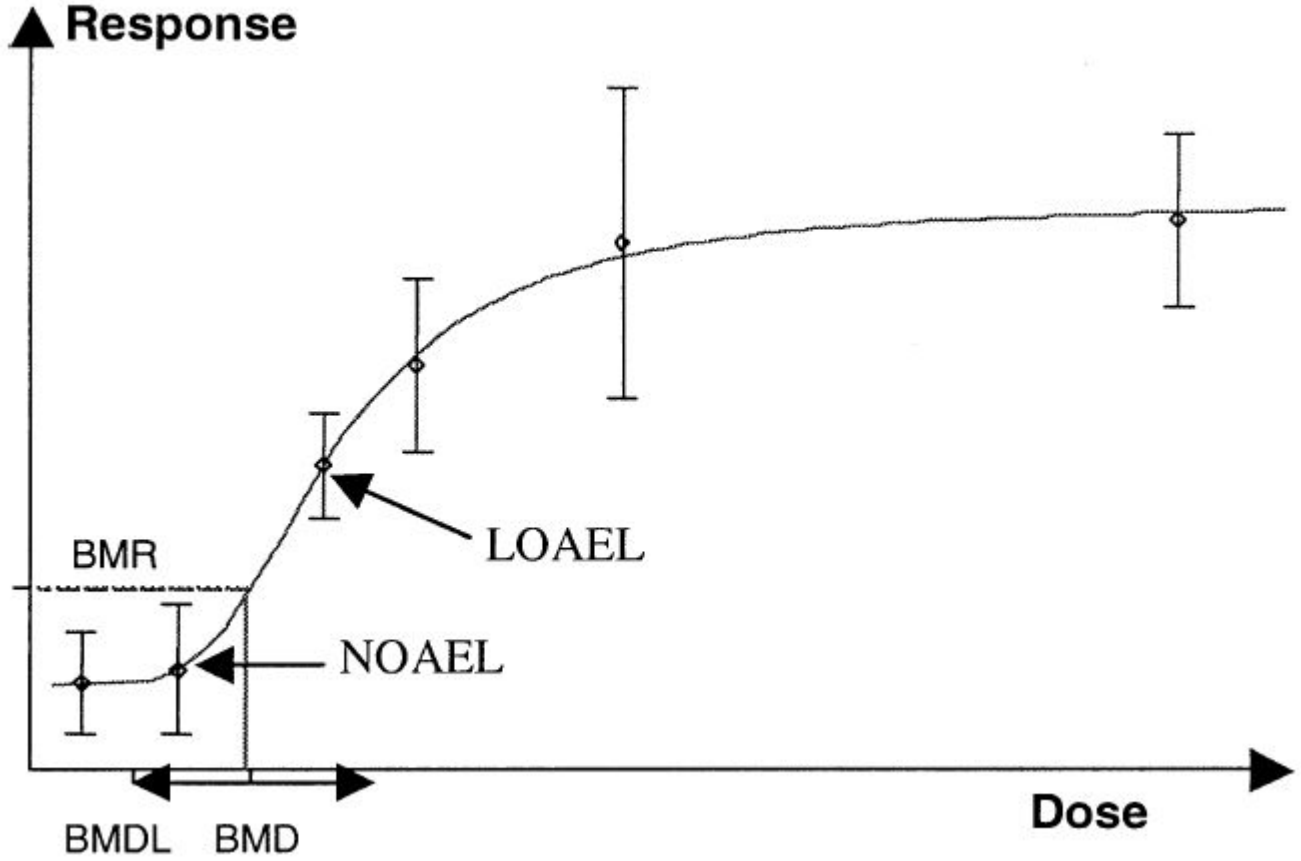


Benchmark Dose is associated with a measurable response

BMR = Benchmark Response (e.g. 5% reduction in body weight)

BMD = Benchmark Dose: the dose at which the BMR would be predicted (central estimate)

BMDL = the lower bound of the confidence interval around the BMD

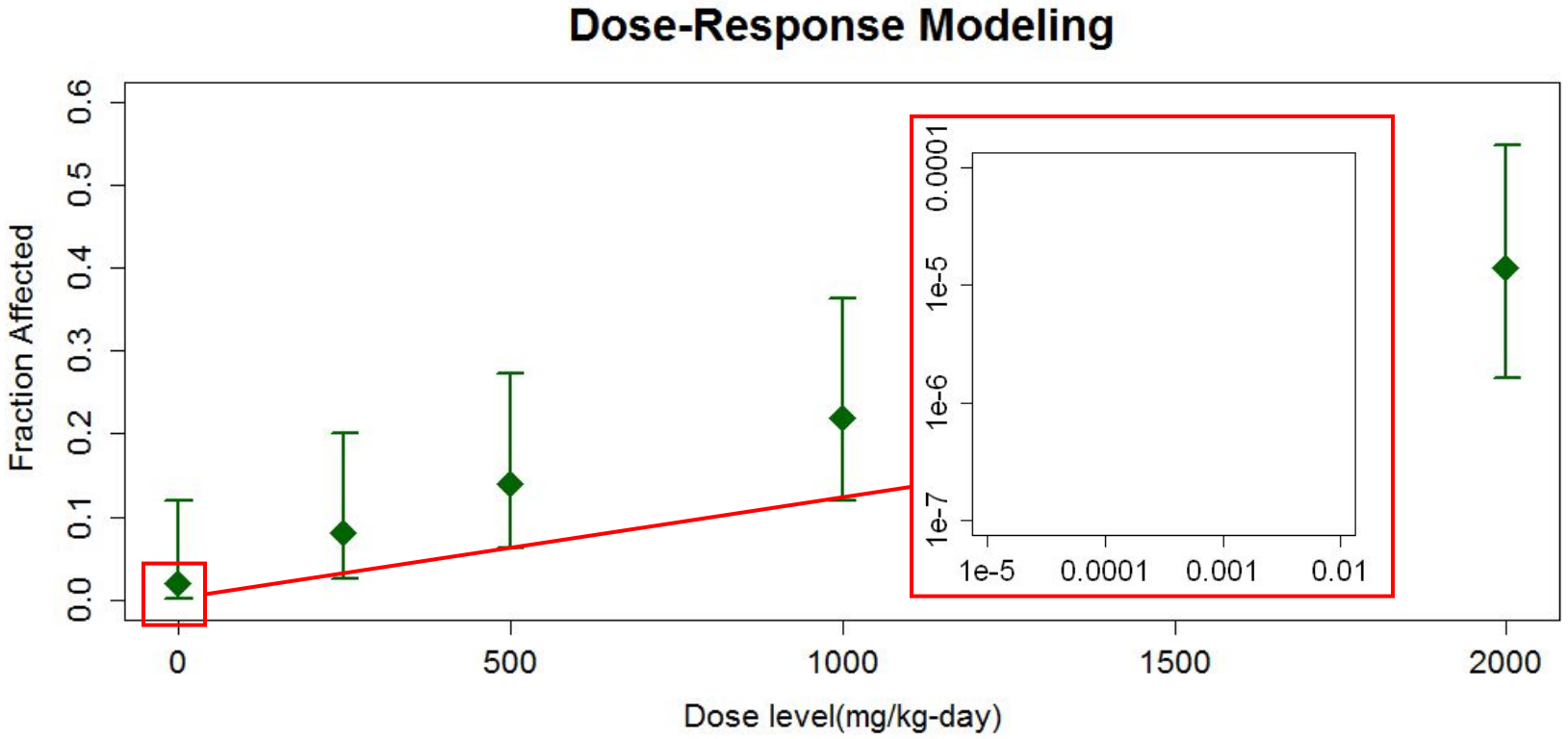


Source: Filipsson et al., 2003

BMD models

- Linear or power linear model
- Weibull or log-logistic model
- Exponential model
- Probit model
- Polynomial model
- Hill model
- Gamma model

Dose-Response Analysis



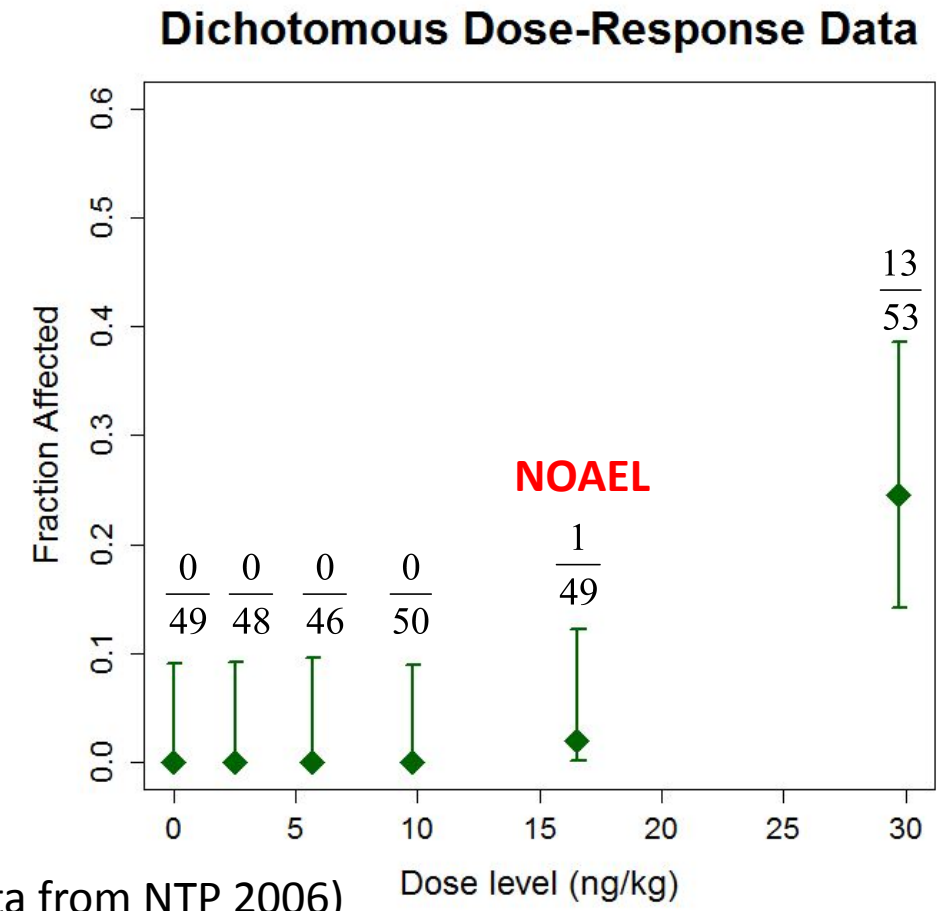
Step 1: Deriving Point of Departure (POD)

Step 2: Inference (or "Extrapolation")

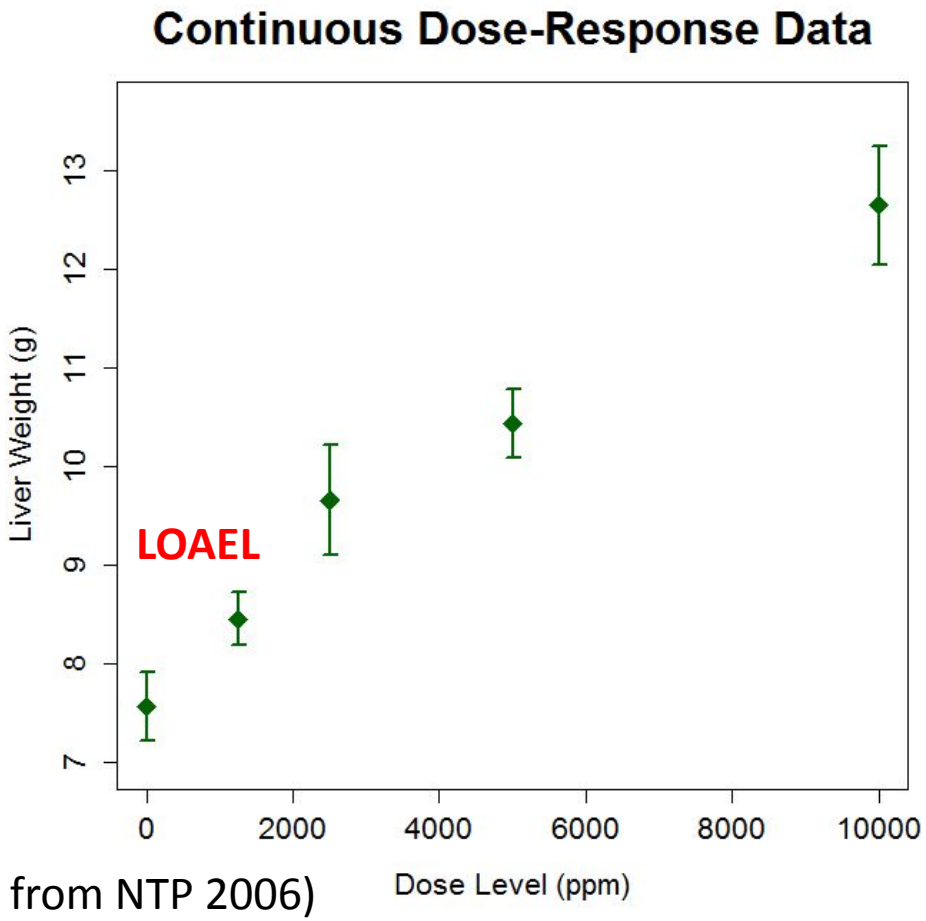
Source: Kan Shao, Indiana University

POD Derivation – Traditional Method

NOAEL/LOAEL



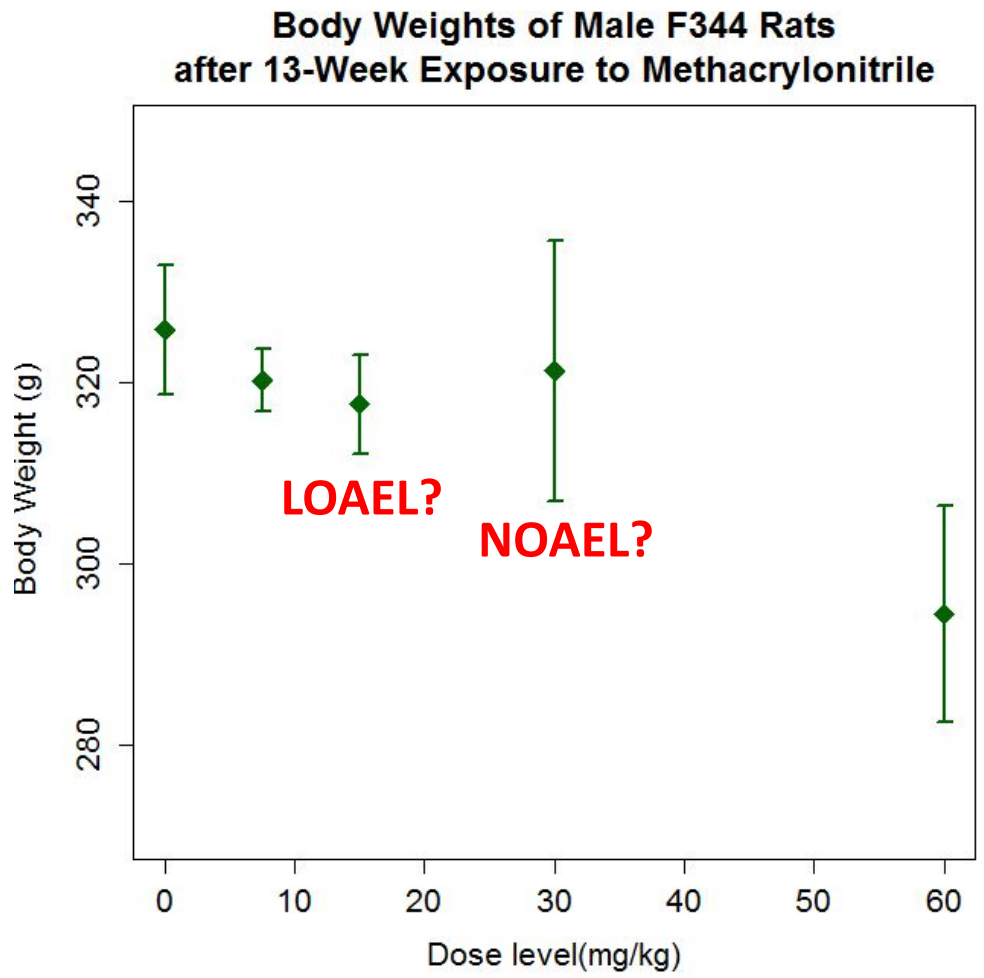
(Data from NTP 2006)



(Data from NTP 2006)

Source: Kan Shao, Indiana University

Limitations of NOAEL/LOAEL



(Data from NTP, 2000)

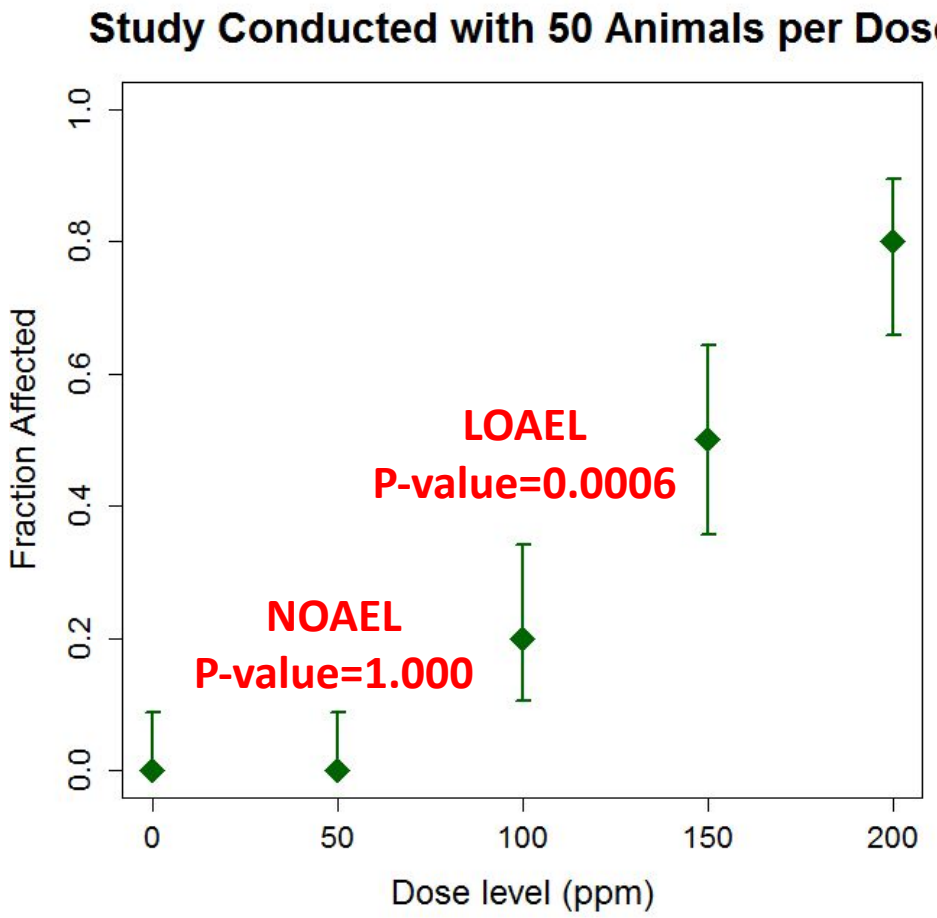
Highly depends on study design

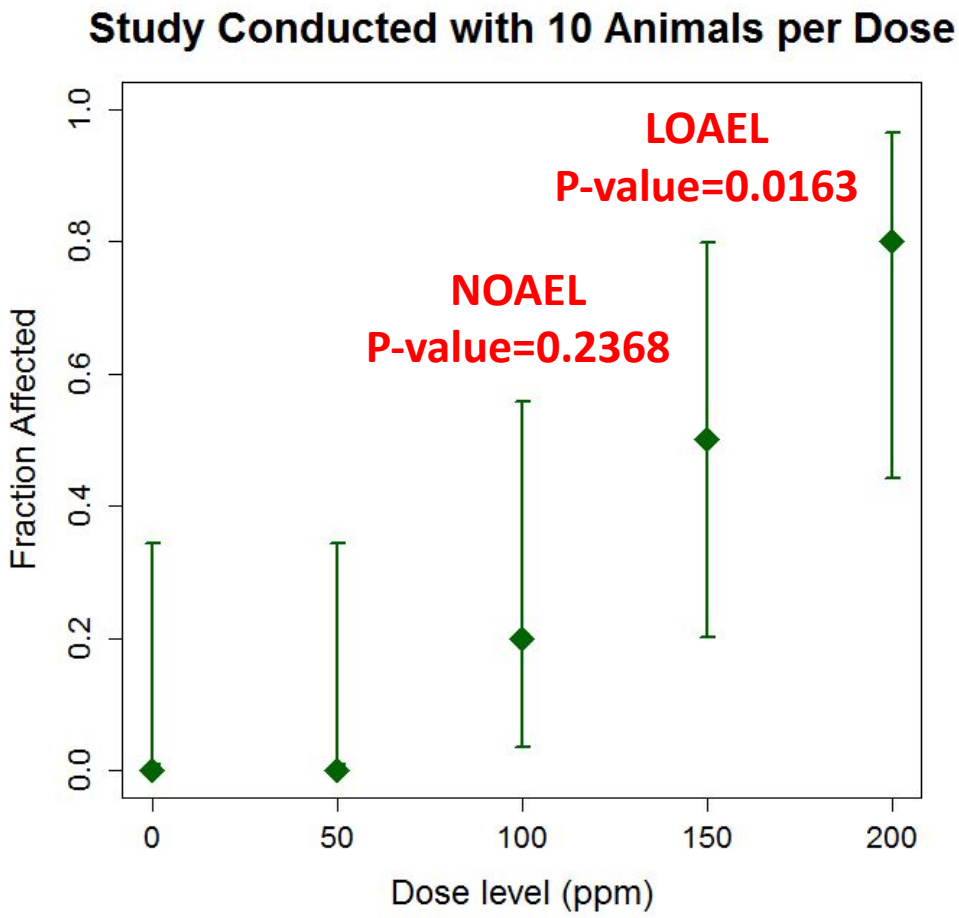
Partially uses the information in toxicity study

Improperly characterizes the uncertainty in responses

Source: Kan Shao, Indiana University

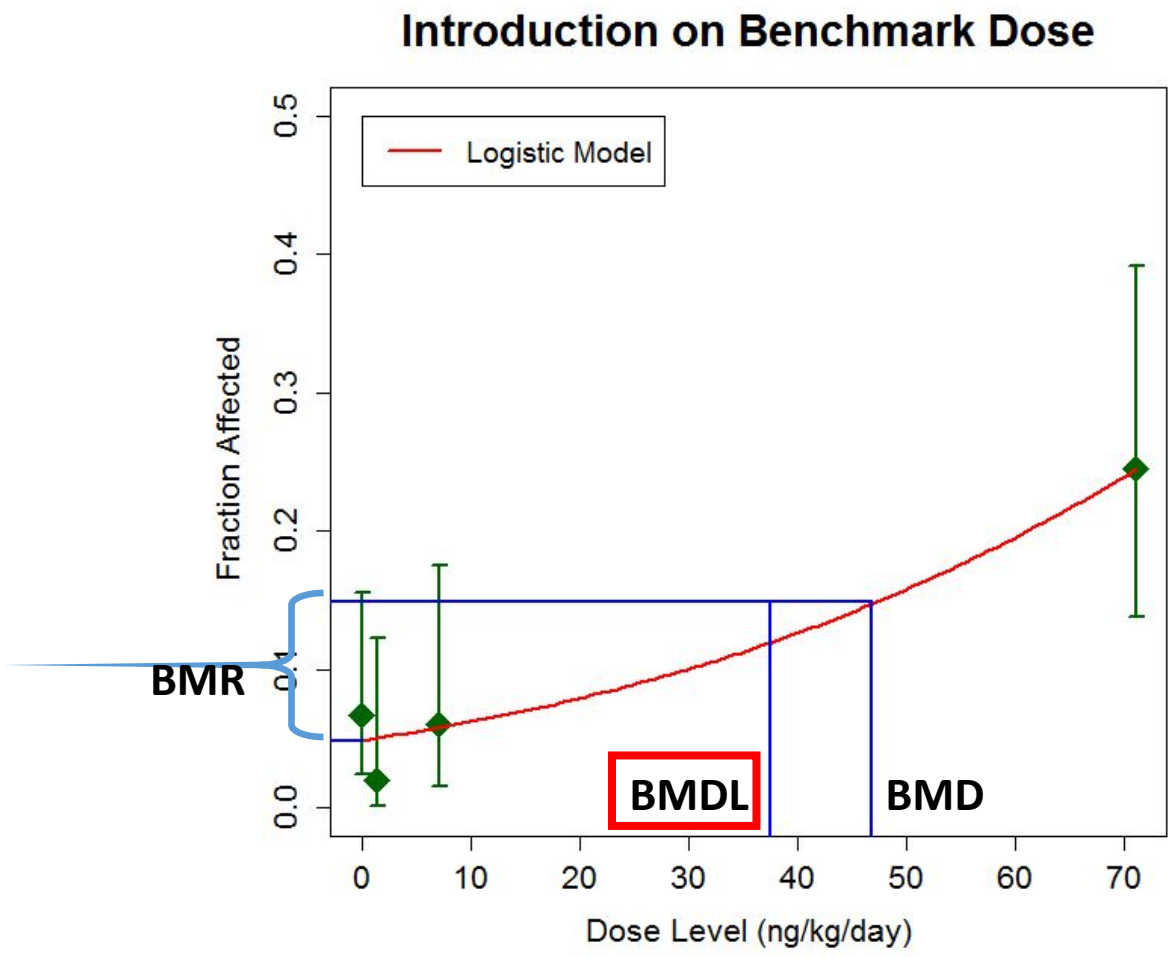
NOAEL's Inappropriateness in Quantifying Uncertainty





Source: Kan Shao, Indiana University

Benchmark Dose Methodology



BMD Steps:

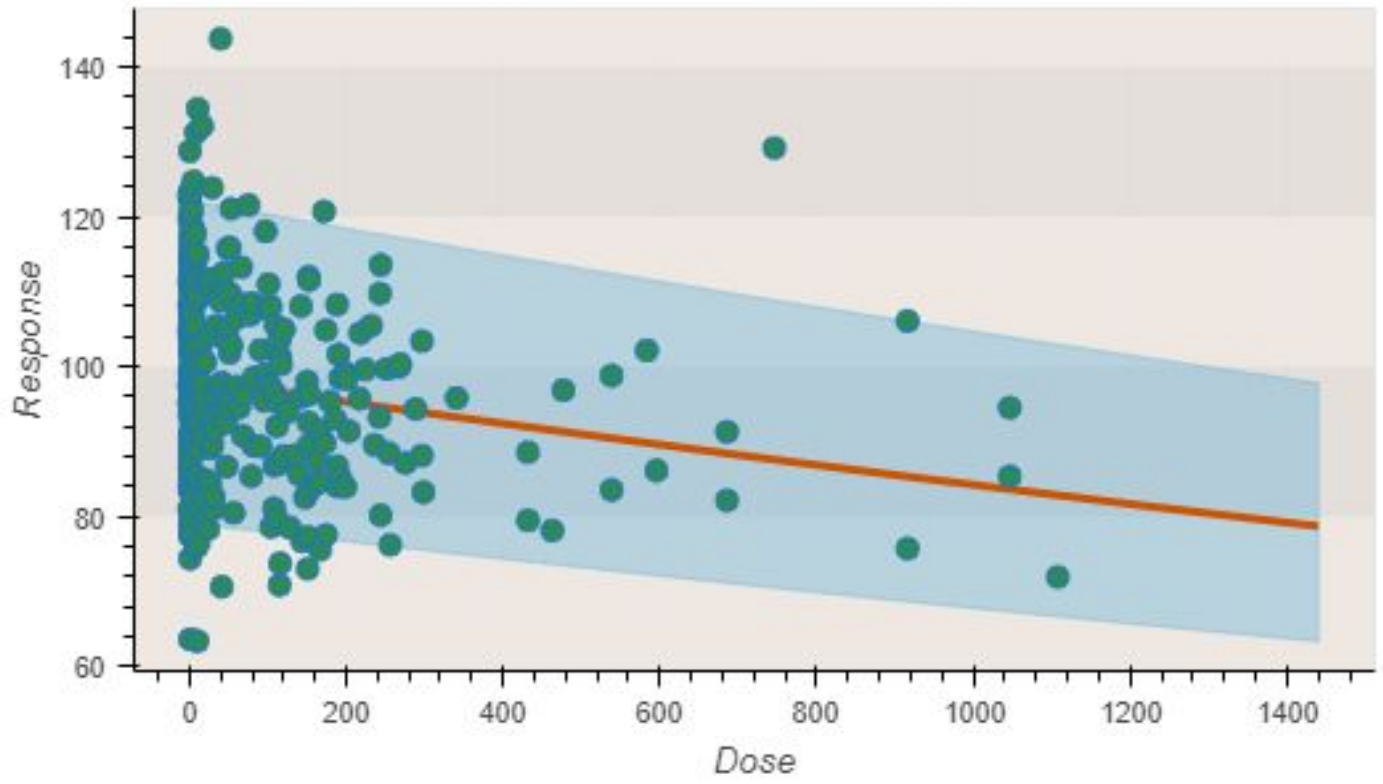
- Fit a DR model
- Define Benchmark Response (BMR)
- Calculate BMD/ BMDL

BMD recognized

- FAO/WHO (2006)
- EFSA (2009)
- US EPA (2012)

Source: Kan Shao, Indiana University

BMD can also be applied to epidemiological data



Subjects have a unique exposure and response level

Advantages of BMD Approach

Subject	BMD Approach
Dose selection	BMD and BMDL not constrained to be a dose used in study
Sample size	Appropriately considers sample size: as sample size decreases, uncertainty in true response rate increases (i.e., ↓ N = ↓ BMDL)
Cross-study comparison	Observed response levels at a selected BMR are comparable across studies (recommended to use BMD as point of comparison)
Variability and uncertainty in experimental results	Characteristics that influence variability or uncertainty in results (dose selection, dose spacing, sample size) are taken into consideration
Dose-response information	Full shape of the dose-response curve is considered
NOAEL not identified in study	A BMD and BMDL can be calculated even when a NOAEL is missing from the study

Benchmark Dose Software Available: USEPA

Benchmark Dose Tools

Staying Connected

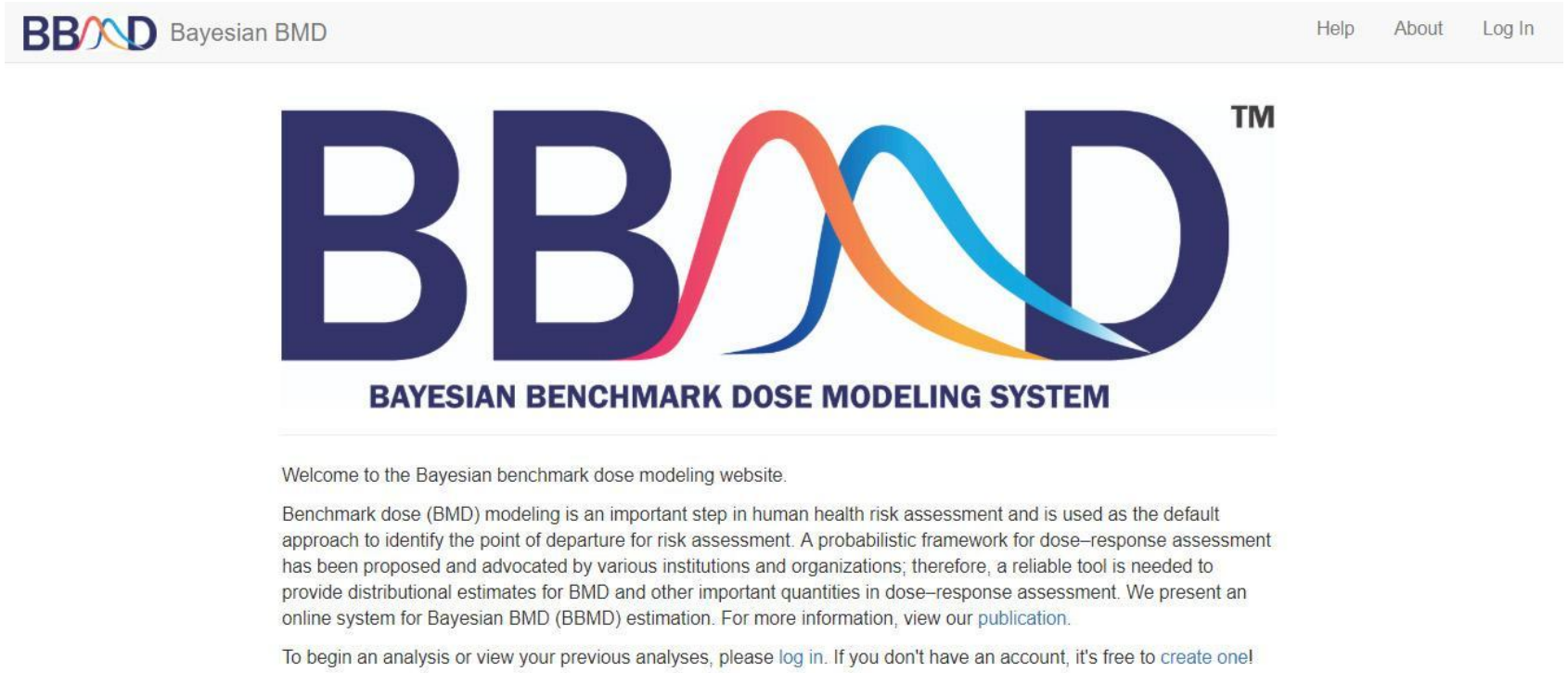
- Sign up for the BMDS mailing list for the latest updates, training announcements, and more.

Latest Updates

- Learn about BMDS happenings from the Announcement List

Benchmark dose (BMD) methods are used by the U.S. EPA and throughout the world for dose-response analyses to support chemical risk assessments and regulatory actions. The primary BMD tools developed by the U.S. EPA for this purpose are the Benchmark Dose Software (BMDS) and Categorical Regression (CatReg) software.

Bayesian Benchmark Dose Modeling System



Available at:

https://benchmarkdose.com (or https://benchmarkdose.org)

Comparison of TRVs for Dietary Cadmium

There have been three dietary reference values published by major authoritative bodies in the past decade:

- European Food Safety Authority (EFSA), 2009
- Joint Expert Committee on Food Additives (and contaminants) (JECFA), 2011
- Agency for Toxic Substances and Disease Registry (ATSDR), 2012

The three TRVs vary across a factor of 8

Comparison of TRVs for Dietary Cadmium

What is the overall influence of all of the differences that have been identified on the EFSA, JECFA and ATSDR values?

	EFSA	JECFA	ATSDR
PoD µg/g creatinine	**4**	**5.24**	**0.5**
Adjustment Factor (applied to biomarker)	3.9		
PoD after adjustment	1	5.24	0.5
Dietary to urinary ratio (median)	0.36	0.23	0.66
Equivalent Intake ug/kg bw/day	0.36	1.2	0.33
Choice of 5th percentile		0.8	
"Diabetic" factor (applied to dietary)			3
Daily TI or MRL µg/kg bw/day	**0.36**	**0.8**	**0.1**

- ATSDR: most conservative urinary PoD (European populations, and pHC)
- JECFA: most conservative overall adjustment to urinary PoD. Dietary to urinary adjustment includes TD and TK within a simulation model and choice of 5th %ile.
- ATSDR: least conservative dietary to urinary ratio despite choosing only females.
- ATSDR: additional uncertainty factor of 3.

Comparison of Toxicity Reference Values for Ochratoxin A

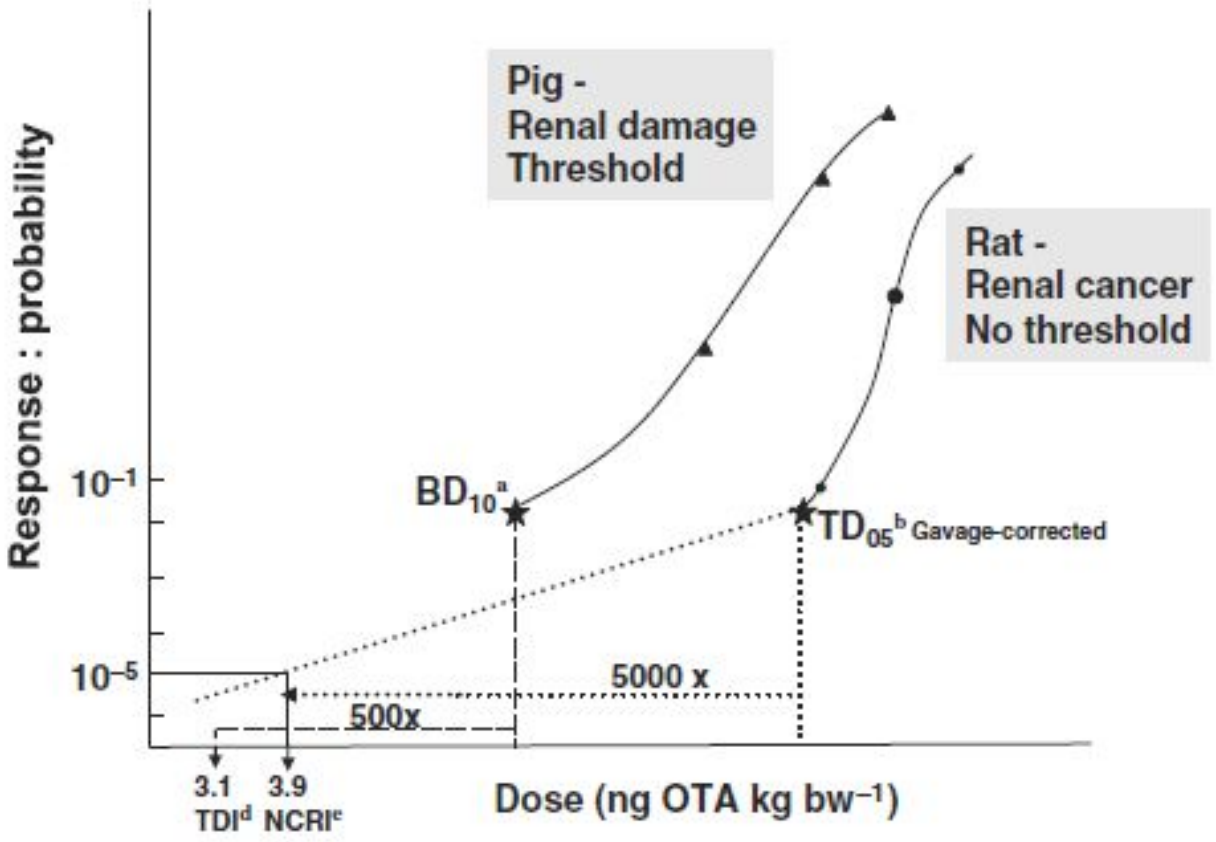
Table 2. Uncertainty factors used in the derivation of risk metrics for OTA from the 90-day pig study.

	EFSA (2006)[a] Lowest dose tested: 8 µg kg bw^{-1} day^{-1}	Health Canada[a] Derived benchmark dose: BD_{10} = 1.56 µg kg bw^{-1} day^{-1}
Source of uncertainty:		
Intraspecies	10	10
Interspecies	15[b]	25[c]
LOAEL to NOAEL	3	
90-Day subchronic to chronic		2
Overall uncertainty	450	500
Resulting TDI (ng kg bw^{-1} day^{-1})	17	3.0

Notes: [a]Uncertainty factors applied to lowest dose tested (8 µg OTA kg bw^{-1} day^{-1}) or BD_{10} (data from Krogh et al. 1974).
[b]Toxicodynamics (2.5×); toxicokinetics related to OTA half-life (6×) as estimated by EFSA.
[c]Toxicodynamics (2.5×); toxicokinetics related to OTA half-life (10×) (see Table 3).

Source: Kuiper-Goodman et al., 2010

Derivation of Non-Cancer and Cancer Risk Metrics for OTA



A Toxicity Reference Value is derived from the pig study (non-cancer), while a Negligible Cancer Risk Intake (NCRI) is derived from the rat (cancer) study

Source: Kuiper-Goodman et al., 2010

4d. Dose-Response Model for Sub-Chronic Exposure (Non-Cancer Exception)

Sub-Chronic Exposure to Lead (during childhood)

Dose-Response Model for Lead in Children

A meta-analysis done in 1994

Schwartz concluded that a doubling of blood-lead concentration from 10 µg/dL to 20 µg/dL results in a loss of 2.57 IQ (SE = 0.41) points, on average.

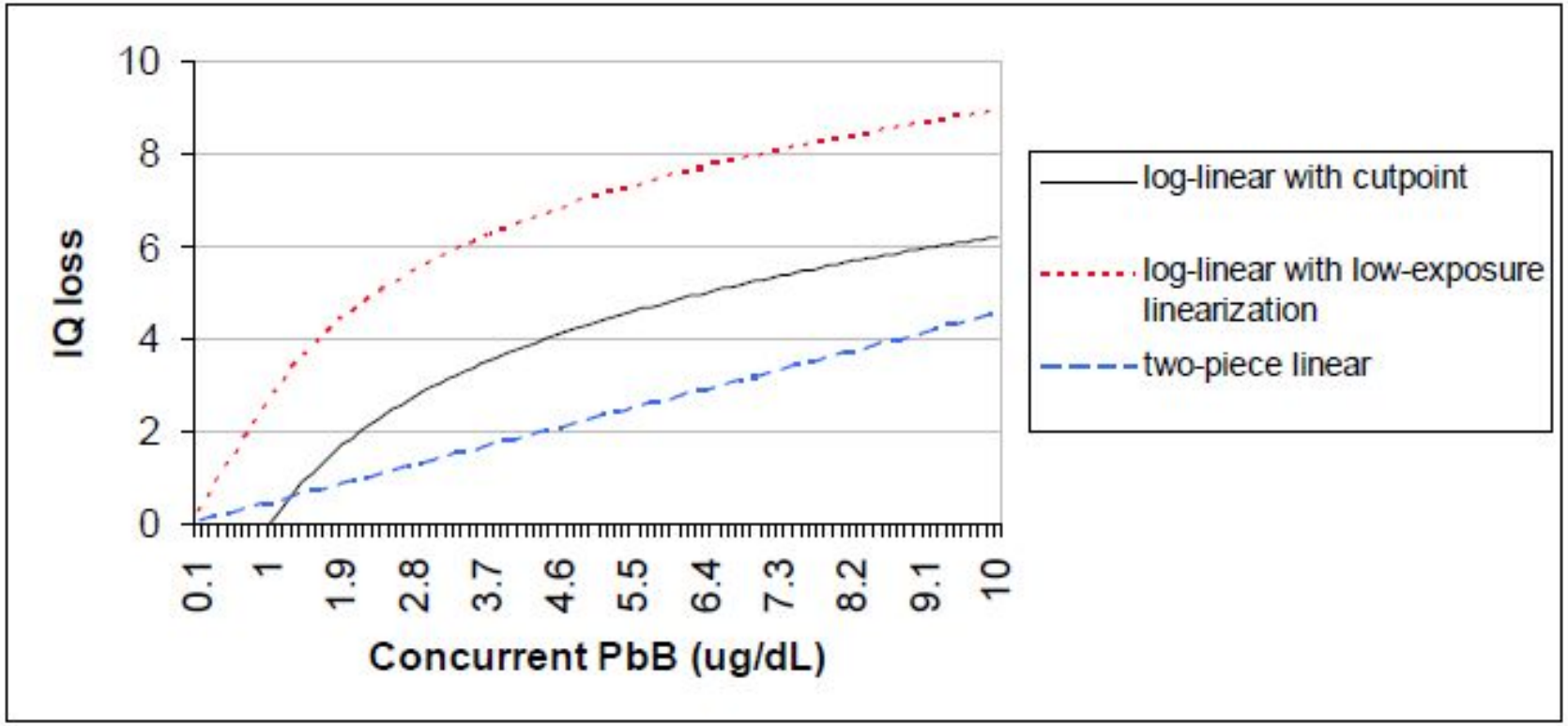
It follows that, a 1 µg/dL increase in blood-lead concentration results in a loss of 0.257 IQ points, on average

Benchmark Dose studies indicate

- a 1 IQ point loss at 1 µg/dL blood lead
- a 1% increase in average systolic blood pressure at 1.7 µg/dL blood lead

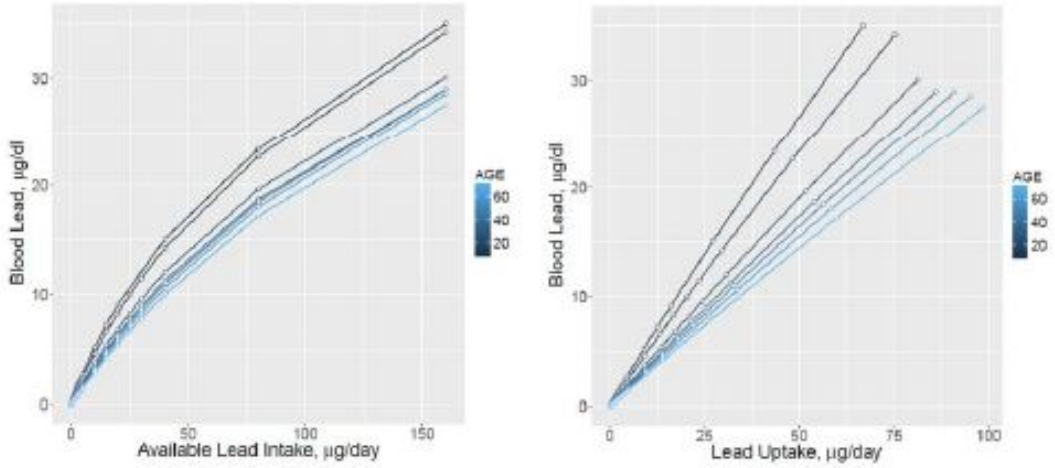
Neurological Endpoint for Lead Exposure: IQ Loss by Blood Level

Figure 4-1. Comparison of three concentration-response functions for concurrent blood Pb levels < 10 µg/dL.



Predicting Blood Lead Levels from Intake

Exhibit 35. IEUBK Batch Model Output



Notes: Left Panel: For each age (months), there is a deterministic non-linear relationship between available intake (µg/day) and blood lead (µg/dL).
Right Panel: By accounting for saturable process in the GI, a linear relationship between uptake (mg/day) and blood lead (µg/dL) is observed.

The relationship between lead uptake and blood lead was shown to be linear (Exhibit 35, right panel), although not perfectly linear. Therefore, polynomial regression was used to address slight departures from linearity thought to arise from non-linear binding of lead to red blood cells. Additionally, there is a small intercept, because in running IEUBK to develop the regression equations, the default value of maternal blood lead of 1 µg/dL was not modified.

Exhibit 36 shows age-specific regressions used to describe an age-dependent relationship relating lead uptake to blood lead. The coefficients pertain to a third-order polynomial regression of the form:

$$\text{Blood Lead } (\mu g/dL) = \beta o + \beta_1 \text{ Uptake} + \beta_2 \text{ Uptake}^2 + \beta_3 \text{ Uptake}^3 + e$$

Coefficients for the month that represents the mid-point of the age range of interest were used in the analyses.

Exhibit 36. Polynomial Regressions Fit for Specific Months

IEUBK Age Interval (Year)	Age (Months)	β_0	β_1	β_2	β_3
0.5-1	9	0.00786	0.547	-0.00131	6.01E-6
1-2	18	-0.000311	0.447	-0.000637	1.53E-6
2-3	30	0.00123	0.379	-0.000429	8.45E-7
3-4	42	0.000658	0.355	-0.000371	6.24E-7
4-5	54	0.000636	0.336	-0.000338	5.44E-7
5-6	66	0.00165	0.313	-0.000278	3.57E-7
6-7	78	0.000132	0.288	-0.000230	3.08E-7
$R^2 > 0.995$					

With the lead uptake distribution calculated in SHEDS through probabilistic modeling of lead uptake and regression modeling relating lead uptake to BLLs, EPA was able to develop distributions of BLLs to determine the concentration of lead in drinking water that would result in a specified percentile of blood lead being equal to 3.5 or 5 µg/dL.

Dose-Response Models for Lead in Children

"The respective BMDLs derived from blood lead levels in µg/L (corresponding dietary intake values in µg/kg b.w. per day) were:

- developmental neurotoxicity BMDL01, 12 (0.50);
- effects on systolic blood pressure BMDL01, 36 (1.50);
- effects on prevalence of chronic kidney disease BMDL10, 15 (0.63)."

- At an intake of 0.50 µg/kg-day, expect decrease of 1 IQ point

4e. Dose-Response for Nutrients

Background

- A harmonized approach to nutrient risk assessment is needed given the face of increasing use of ‘fortified’ foods, ‘functional foods’, and supplements

- Nutrients have been defined as biologically active dietary substances whose absence alone results in adverse health effects

- This definition emphasizes the distinction between nutrients in foods and contaminants (microbial or chemical)
  - In contrast to nutrients, contaminants and additives in food are deemed be devoid of any beneficial effect on health

- For nutrient risk assessment, two risks may be described:
  - Deficiency (inadequacy)
  - Toxicity

Issues Unique to Nutrients

- U-shaped relationship for nutrient risks
  - There is risk of adverse effects associated with inadequate intakes as well as with excessively high intakes of nutrients
  - This differs from the single-curve relationship traditionally used for most substances for which risk assessments have been conducted (e.g. pesticides, microbial pathogens, and food additives)

- The nature of the evidence available for evaluating nutrient risk is generally incomplete and may be difficult to use
  - Most available animal and in vitro studies were not designed to evaluate the safety of high nutrient intakes
  - Studies often don't fully collect or report the more complete dose-response data and wide range of potential adverse effects normally included in systematic safety studies for example for food additives and contaminants

Dietary Reference Intakes (DRIs)

- Dietary Reference Intakes (DRIs) represent a common set of reference intake values used
- in Canada (and the United States) in planning and assessing diets of apparently healthy
- individuals and population groups

Recommended Dietary Allowance

- The RDA is the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life-stage and gender group

- The RDA is the goal for usual intake by an individual

- Also referred to as the Recommended Nutrient Intake (RNI)
  - For example by FAO/WHO

Estimated Average Requirement (EAR)

- The EAR is the median daily intake value that is estimated to meet the requirement of half the healthy individuals in a life-stage and gender group.
  - At this level of intake, the other half of the individuals in the specified group would not have their needs met
- The EAR is based on a specific criterion of adequacy, derived from a careful review of the literature
  - Reduction of disease risk is considered along with many other health parameters in the selection of that criterion
- The EAR is used to calculate the RDA
- EAR is also used to assess the adequacy of nutrient intakes, and can be used to plan the intake of group

Adequate Intake (AI)

- If sufficient scientific evidence is not available to establish an EAR on which to base an RDA, an AI is derived instead
- The AI is the recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people who are assumed to be maintaining an adequate nutritional state
- The AI is expected to meet or exceed the needs of most individuals in a specific life-stage and gender group
- When an RDA is not available for a nutrient, the AI can be used as the goal for usual intake by an individual
- The AI is not equivalent to an RDA

Tolerable Upper Intake Level (UL)

- The UL is the highest average daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in a given life-stage and gender group

- The UL is not a recommended level of intake

- As intake increases above the UL, the potential risk of adverse effects increases.

Assessing Inadequacy

2 common methods:

1. Cut-point Method

2. Probability Approach

(reference: DRI Dietary Reference Intakes: Applications in Dietary Assessment. Institute of Medicine (US) Subcommittee on Interpretation and Uses of Dietary Reference Intakes)

Cut-Point method

- Estimates the proportion of individuals in a group whose usual intakes do not meet their requirements

- Underlying assumptions:
- Intakes and requirements are independent
  - (an example where they are dependant would be food intake and calories)
- Distribution of requirements is symmetrical around the EAR
  - A skewed example would be iron in menstruating women
- Variance of distribution of requirements is smaller than the distribution of usual intakes

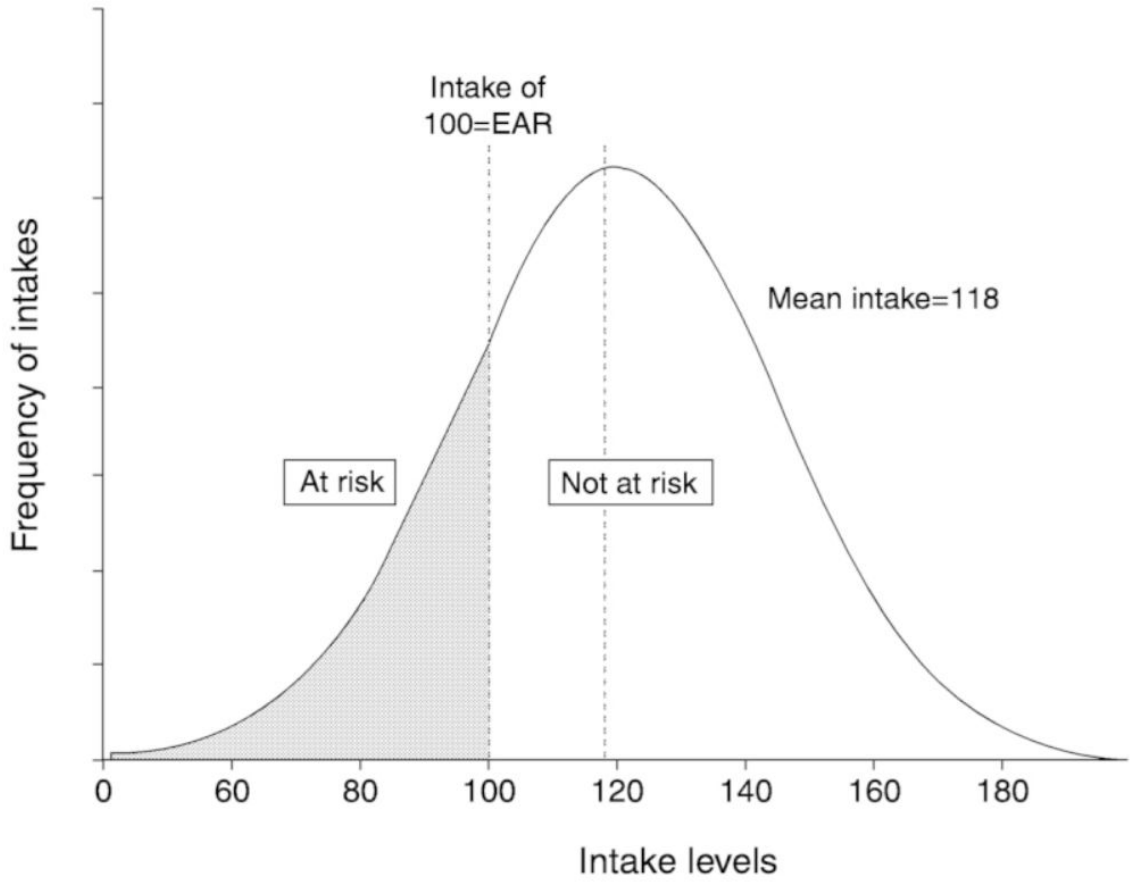
- As prevalence of inadequacy approaches 0 or 100 percent, the performance of the EAR cut-point method declines (works best at a prevalence of 50%)

Cut-Point method (2)

The population prevalence of inadequate intakes is the proportion of population with intake below the median requirement, the EAR

Shaded area represents the proportion of individuals in the group whose intakes are below the EAR

Unshaded area represents the proportion with usual intakes above the EAR



The Probability Approach

- Relates individual intakes to the distribution of requirements

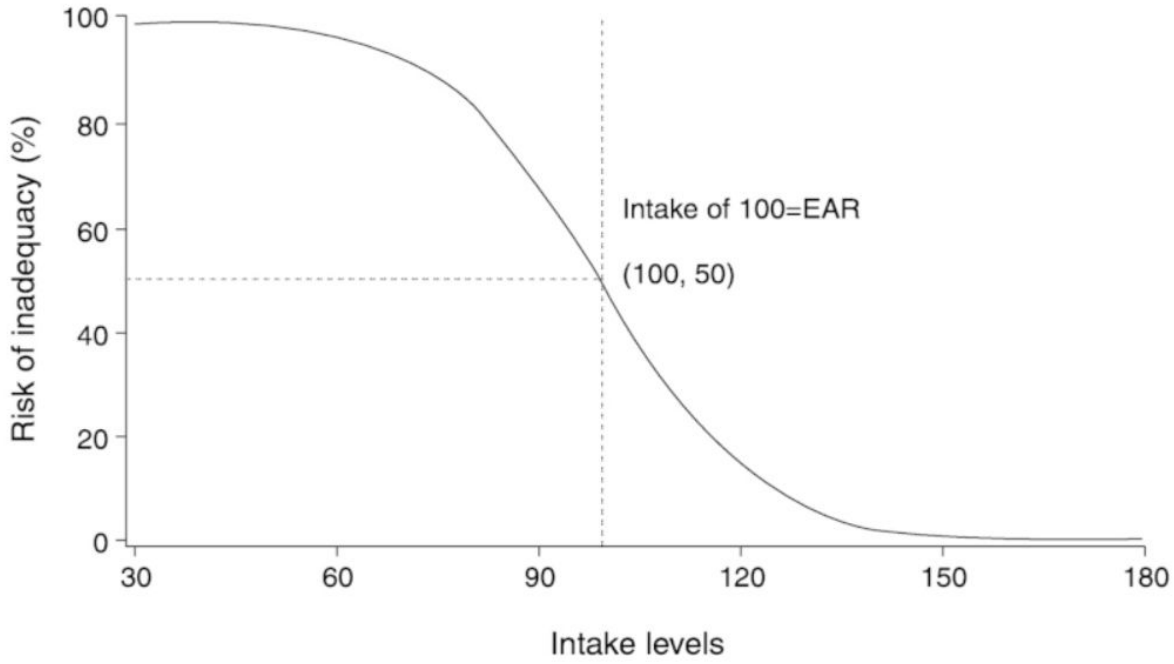
- The probability approach applies a continuous risk-probability function to each individual's estimated intake and then averages the individual probabilities across the population or group

Inadequacy Risk Curve

Step 1: Construct a risk curve using the information on the requirement distribution of the group (median and variance)

The risk curve specifies the probability that any given intake is inadequate for the individual consuming that intake

An intake at the level of the average requirement has a probability of inadequacy of approximately 50 percent for all nutrients whose requirements follow a normal distribution.

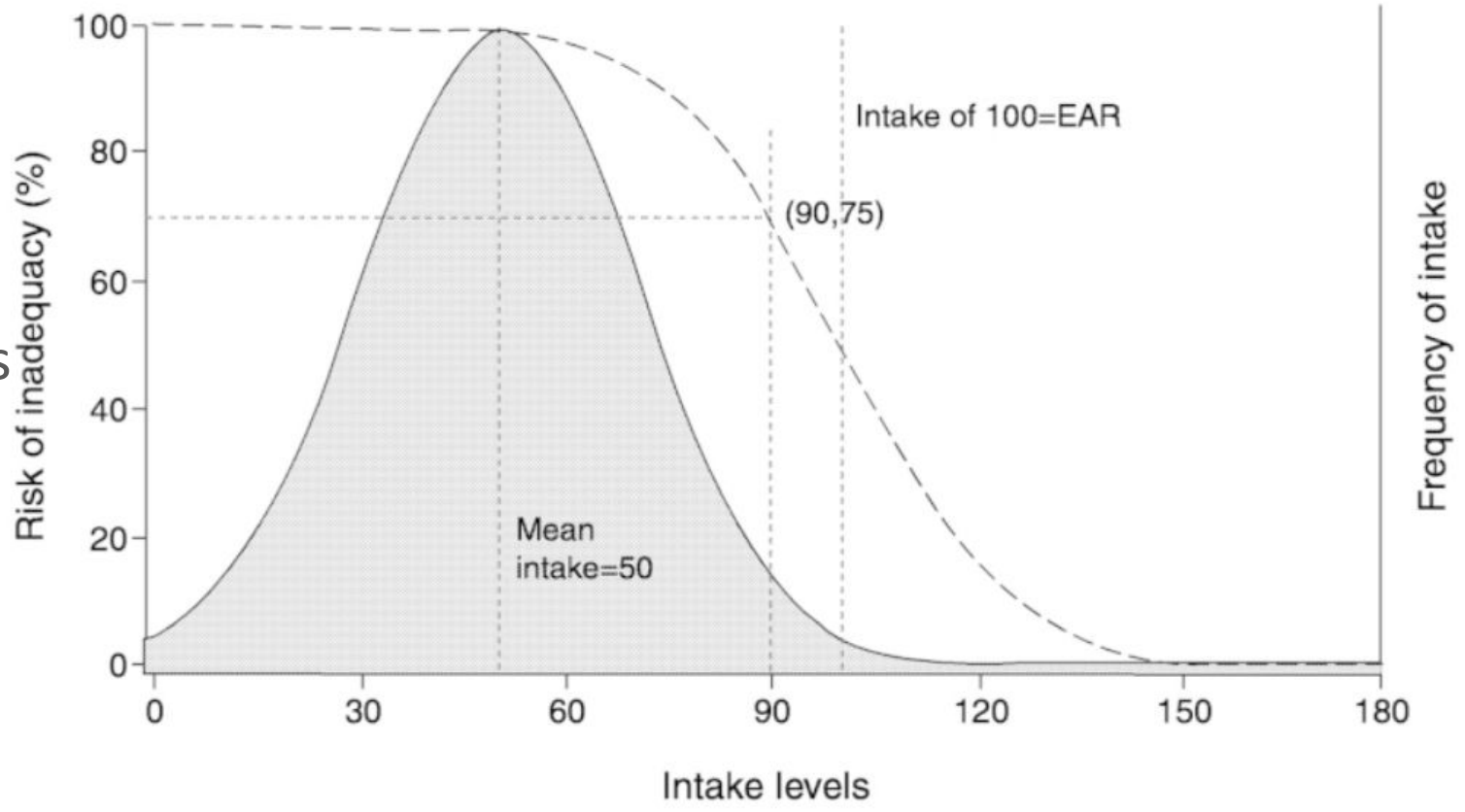


Determine Proportion of the Population With Inadequate Intake

Step 2: Compare the risk curve to the distribution of usual intakes for the population to determine what proportion of the population has an inadequate intake

The mean of the usual intake distribution is 50 units and the majority of the intake values are less than 90 units

At 90 units, the risk of inadequacy is about 75 percent. Therefore, in this population, the probability of inadequacy is high

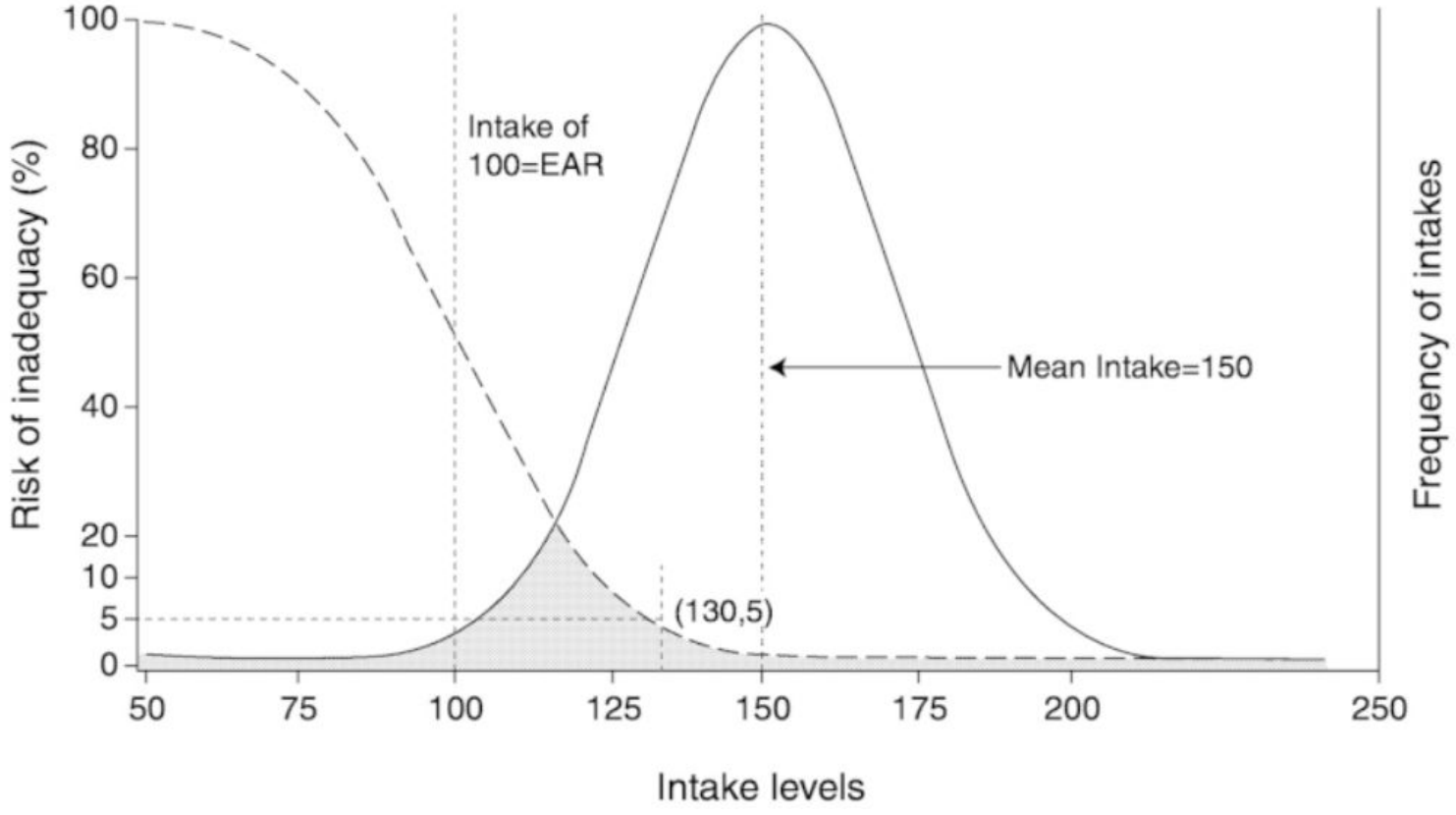


Mean Intake 'Much' Higher than EAR

Mean intake is much higher than the EAR

Nearly the entire intake distribution falls to the right of the risk curve

Only those with intakes below 130 units have a risk of inadequate intake (shaded area).



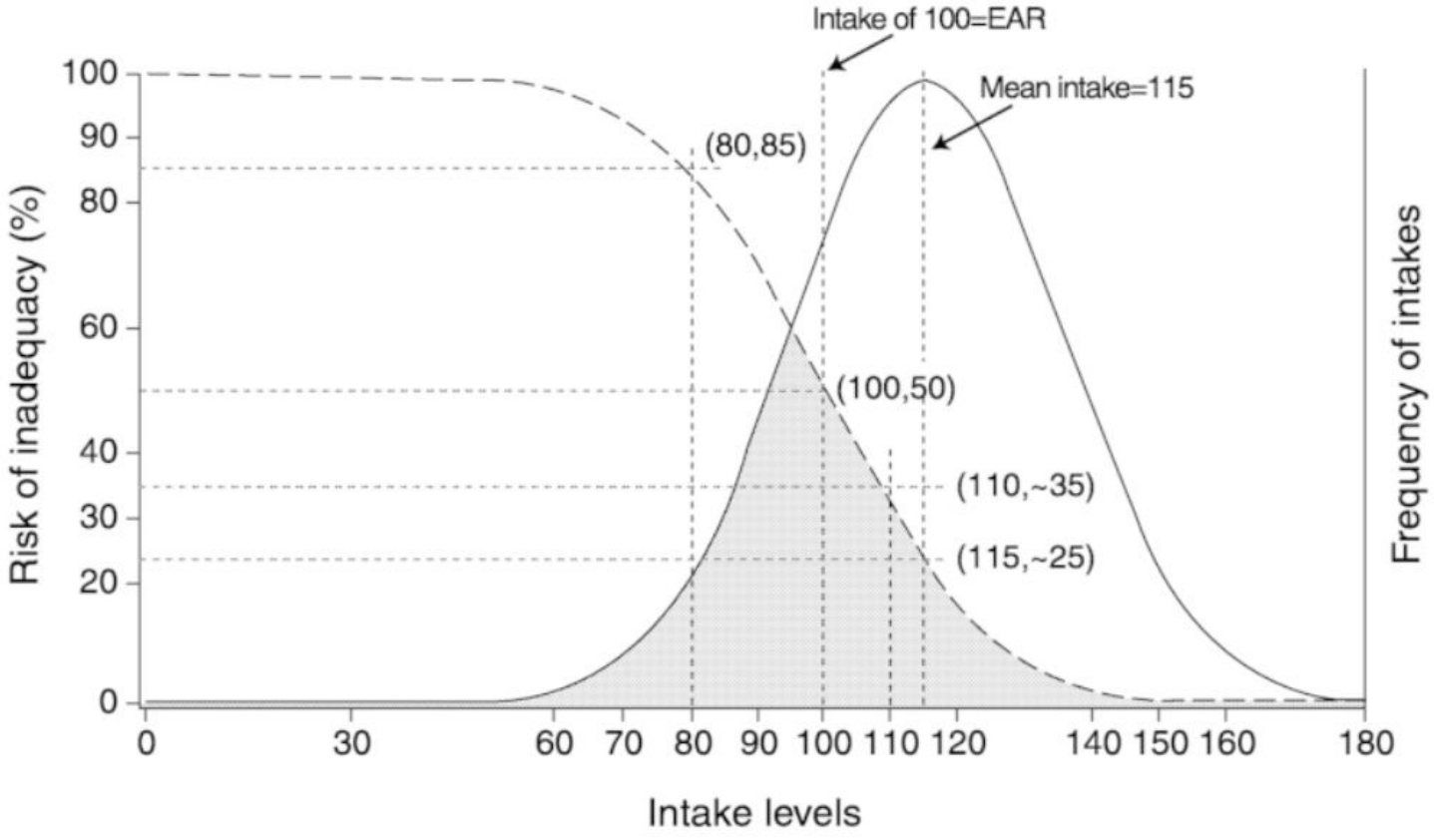
Mean Intake ‘Slightly’ Higher than EAR

Mean intake (115 units) is slightly higher than the Estimated Average Requirement (EAR) (100 units)

The risk curve and usual intake distribution have significant overlap

The proportion of individuals at risk of inadequacy (shaded area) at the mean intake is about 25 percent

The risk of inadequacy increases as intake becomes closer to the EAR



Assessing Toxicity

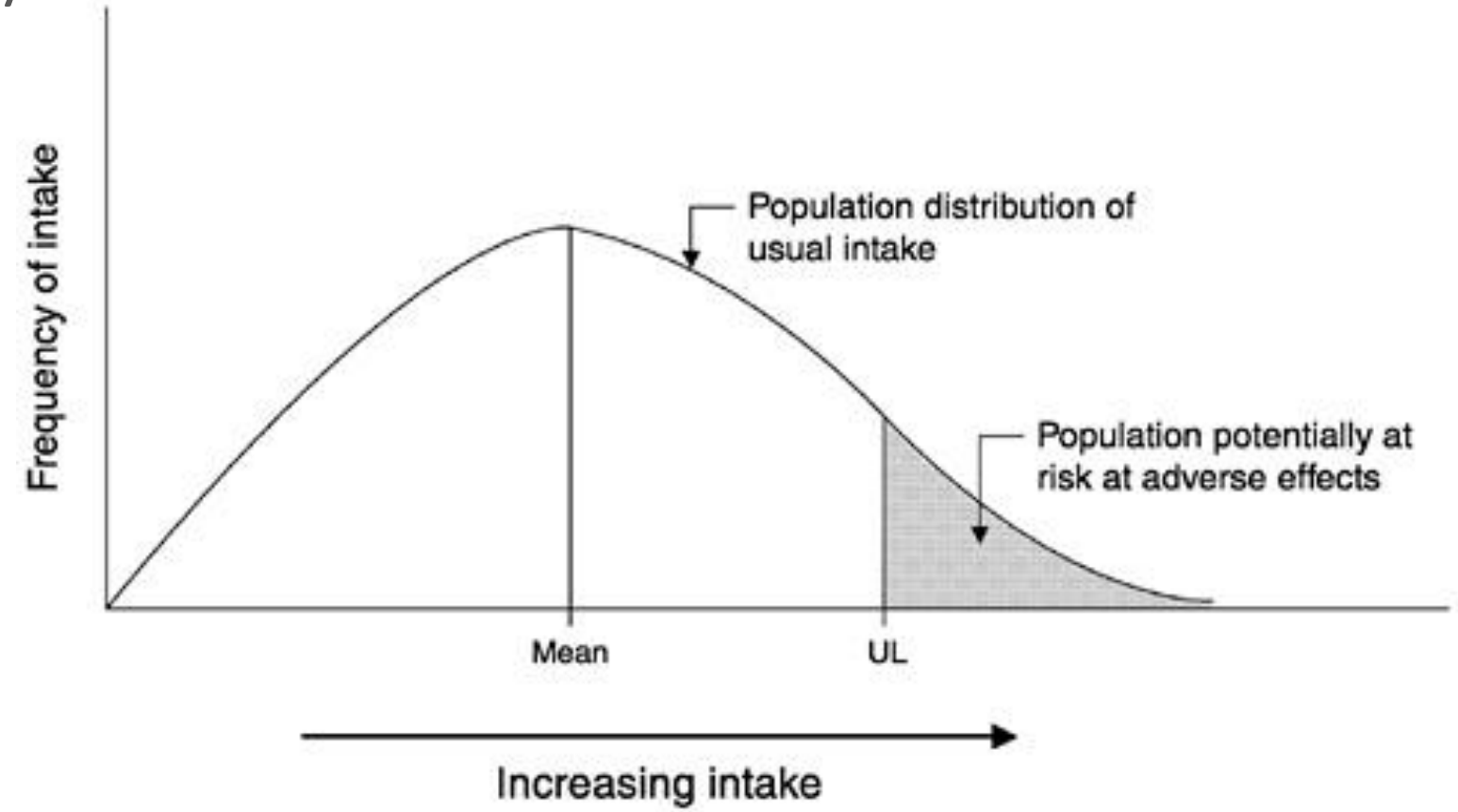
Two general methods

1. Assessing the proportion of individuals in a group who are potentially at risk of adverse health effects from excess nutrient intake
    - Similar to Cut-Point EAR method

2. Using probability-Risk function to assess individual risk of toxicity
    - Similar to Probability Approach

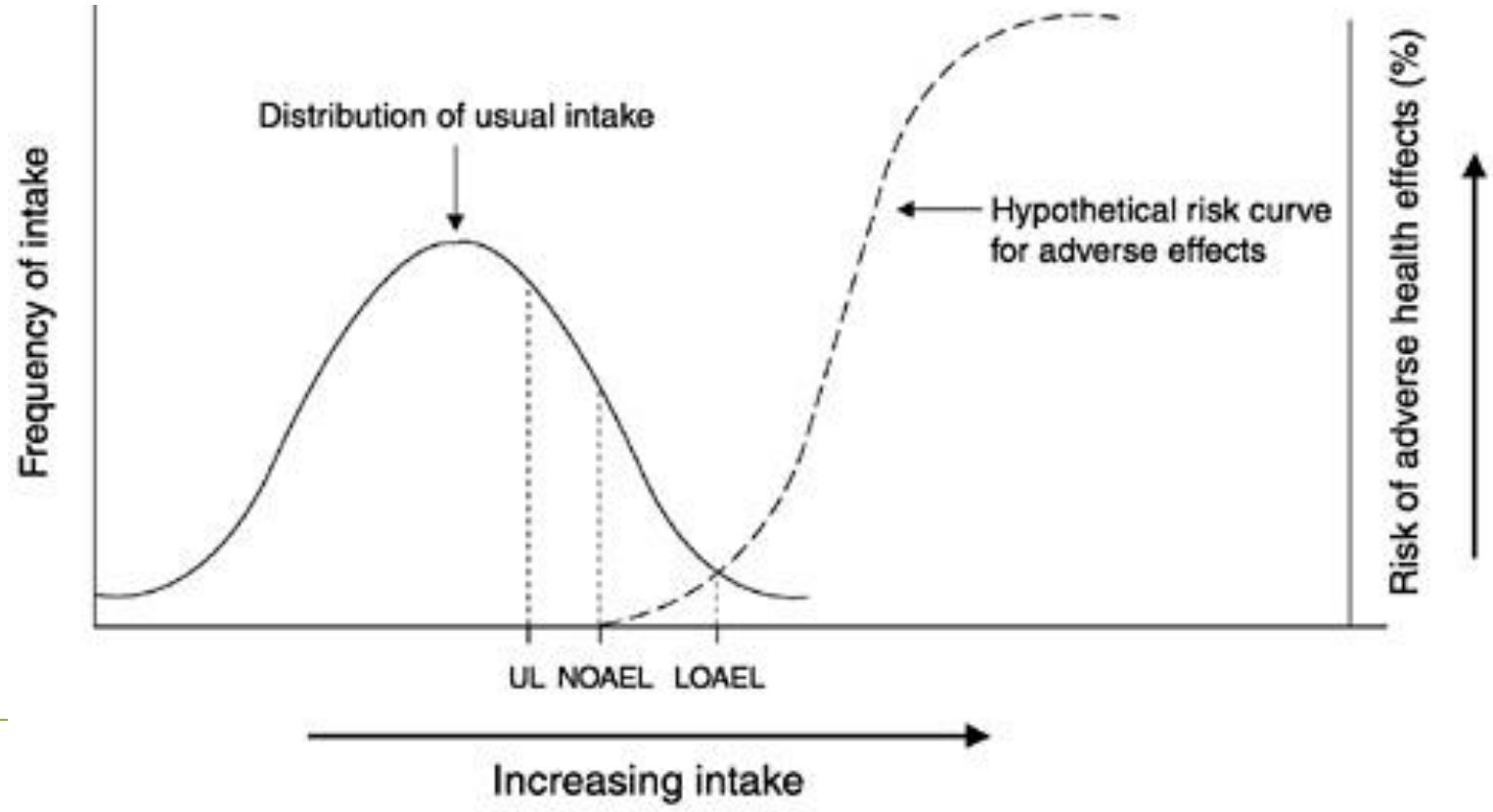
Assessing Toxicity

The fraction of the population consistently consuming a nutrient at intake levels in excess of the Tolerable Upper Intake Level (UL) is potentially at risk of adverse health effects



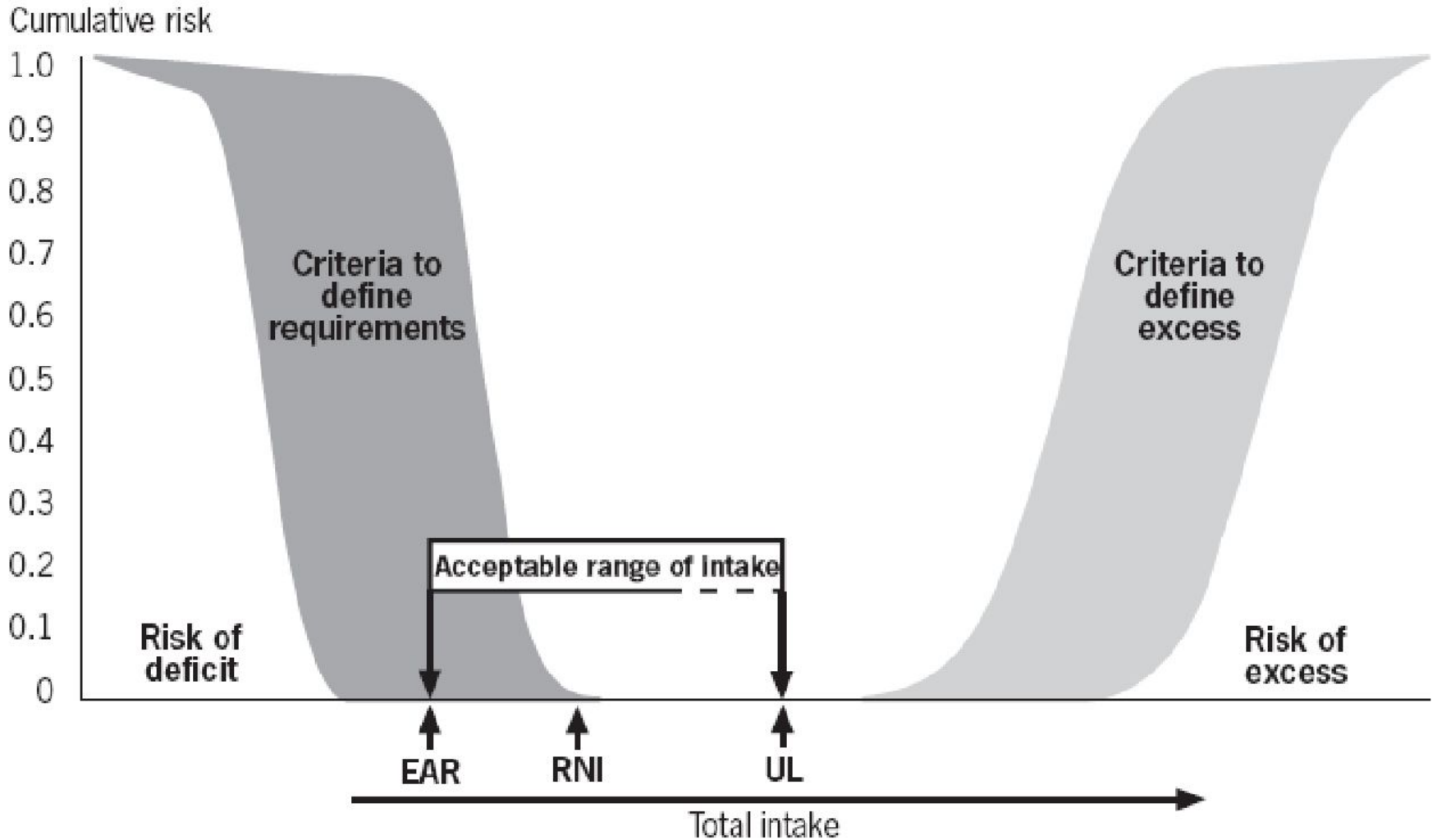
The fraction of the population having usual nutrient intakes above the Tolerable Upper Intake Level (UL) is potentially at risk

The probability of adverse effects increases as nutrient intakes increase above the UL, although the true risk function is not known for most nutrients



Relationship Between Requirements, EAR and RNI (RDA)

From FAO/WHO

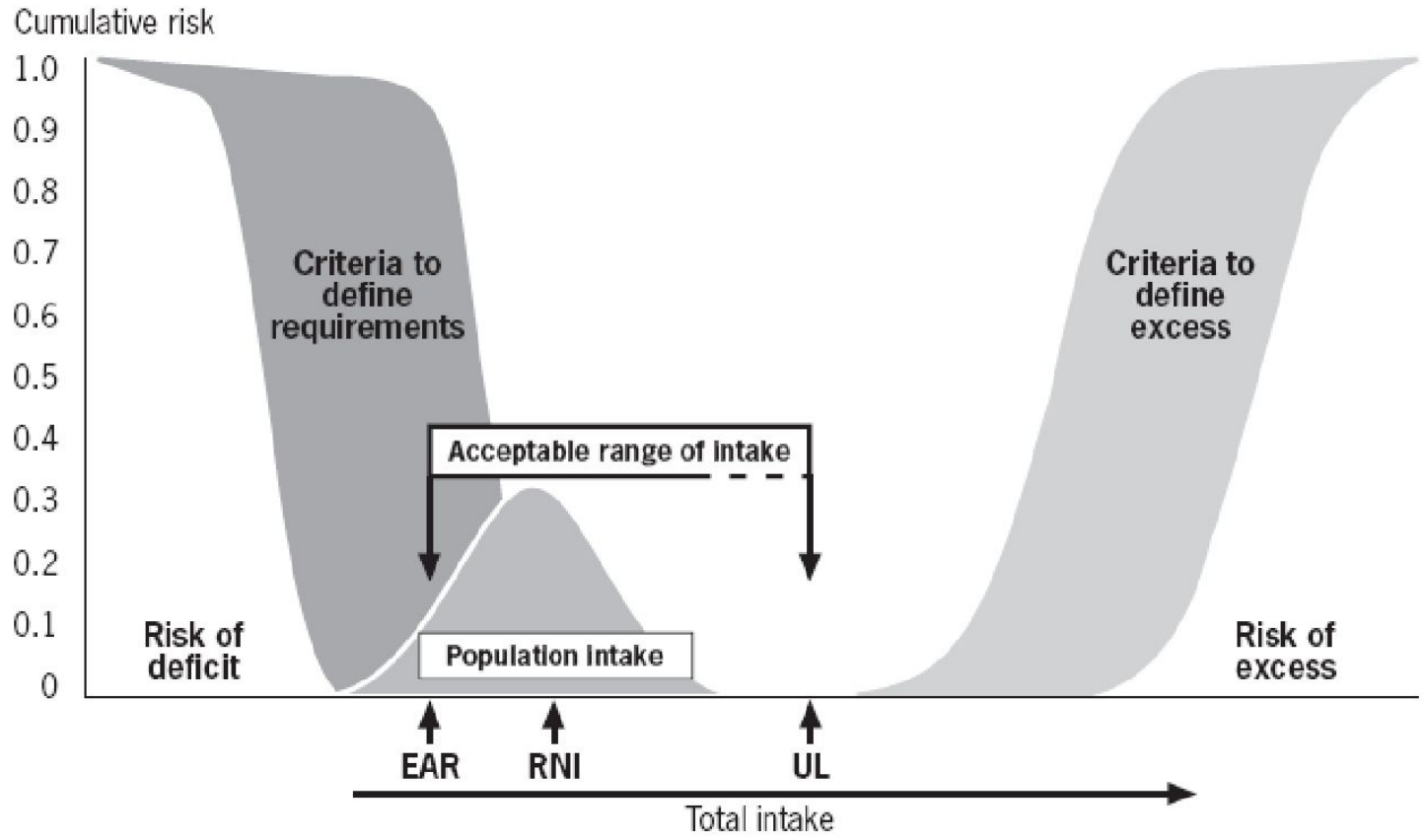


Population Intake and the U-shaped Curve

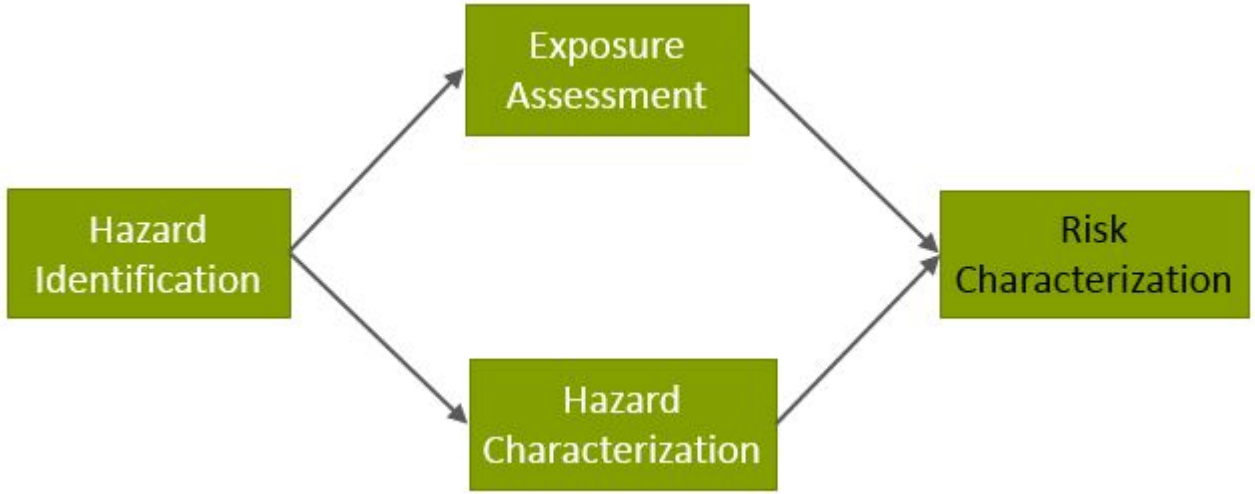
Overlay population intake distribution

Proportion of individuals having intakes **below** the **EAR** are at risk of **deficiency**

Proportion of individuals having intakes **above** the **UL** are at risk of **toxicity**



5. Risk Characterization



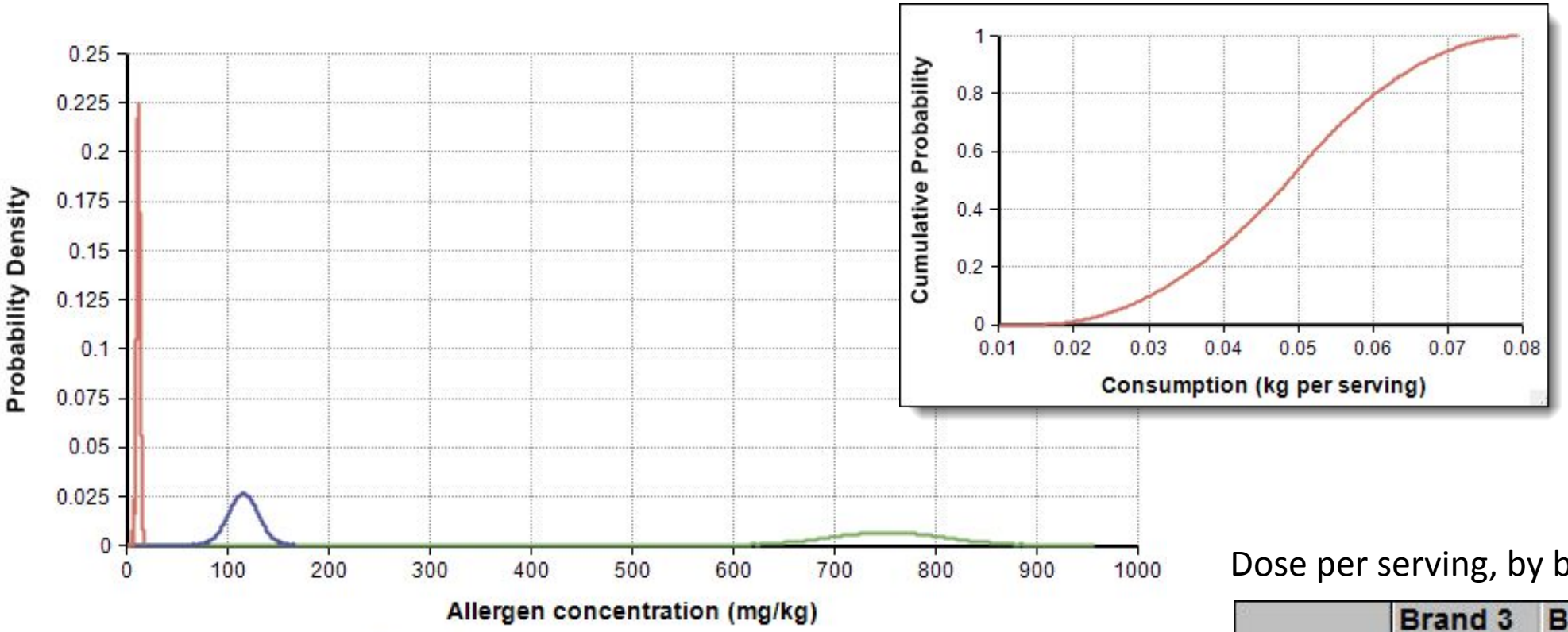
The Final Step: Risk Characterization

- The qualitative (?) and/or quantitative estimation of the probability of occurrence and severity of known or potential adverse health effects in a given population
  - Including attendant uncertainties
  - Uses hazard identification, hazard characterization and exposure assessment
  - Contains computational and narrative components
- The analytical task is to appropriately combine estimates of the frequency and extent of exposure (resulting from the exposure assessment stage) with the relationship between exposure and consequences to yield estimates of the magnitude of consequences with corresponding estimates of their probability.

5a. Risk Characterization of Acute Exposure

Risk of Allergic Response to Hazelnut Protein in Chocolate Spread, per serving, in sensitive population

Combining Concentration and Consumption Gives Dose



Concentration of allergen (mean)
Brand 1: 0.752 ± 0.059 mg/g
Brand 2: 0.115 ± 0.015 mg/g
Brand 3: 0.011 ± 0.002 mg/g

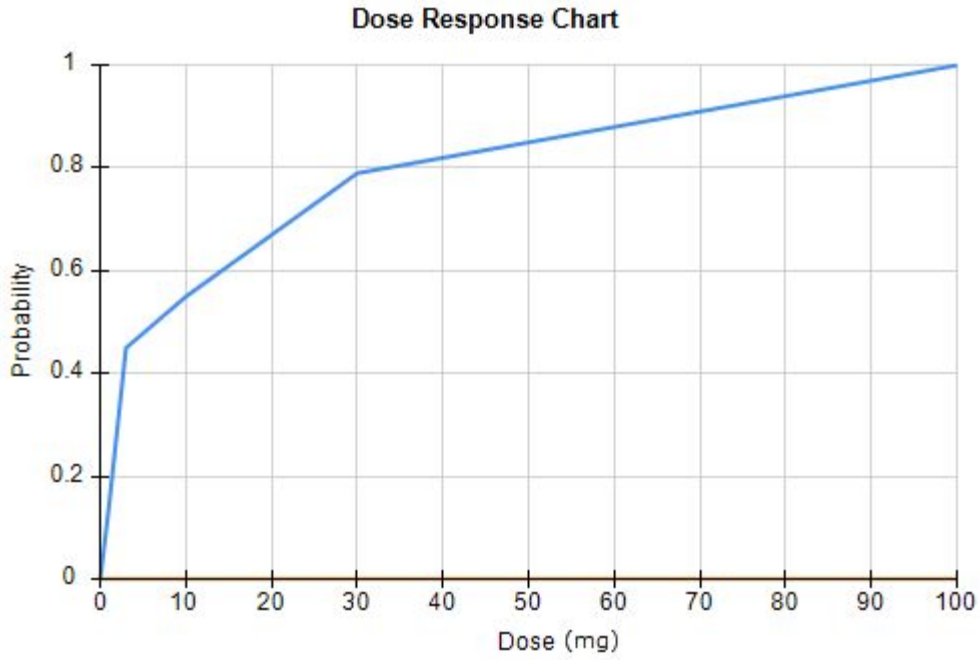
Dose per serving, by brand (mg allergen)

	Brand 3	Brand 2	Brand 1
Min	0.1602	1.441	12.49
Median	0.5238	5.539	36.31
Mean	0.5309	5.571	36.35
Max	1.237	11.81	64.83
Std. Dev	0.1705	1.737	10.46

Dose-Response for Allergen: Acute Exposure, Local Response

Spanjersberg et al. (2007) reported the threshold of sensitivity for 29 patients as follows:

- four patients responded to 1 mg,
- nine to 3 mg,
- three to 10 mg,
- seven to 30 mg and
- six to 100 mg of hazelnut protein



From this an empirical distribution can be constructed based on the cumulative fraction of subjects responding at each intake (above right).

Risk Characterization for Allergen in Chocolate Spread

Dose per serving, by brand (mg allergen)

	Brand 3	Brand 2	Brand 1
Min	0.1602	1.441	12.49
Median	0.5238	5.539	36.31
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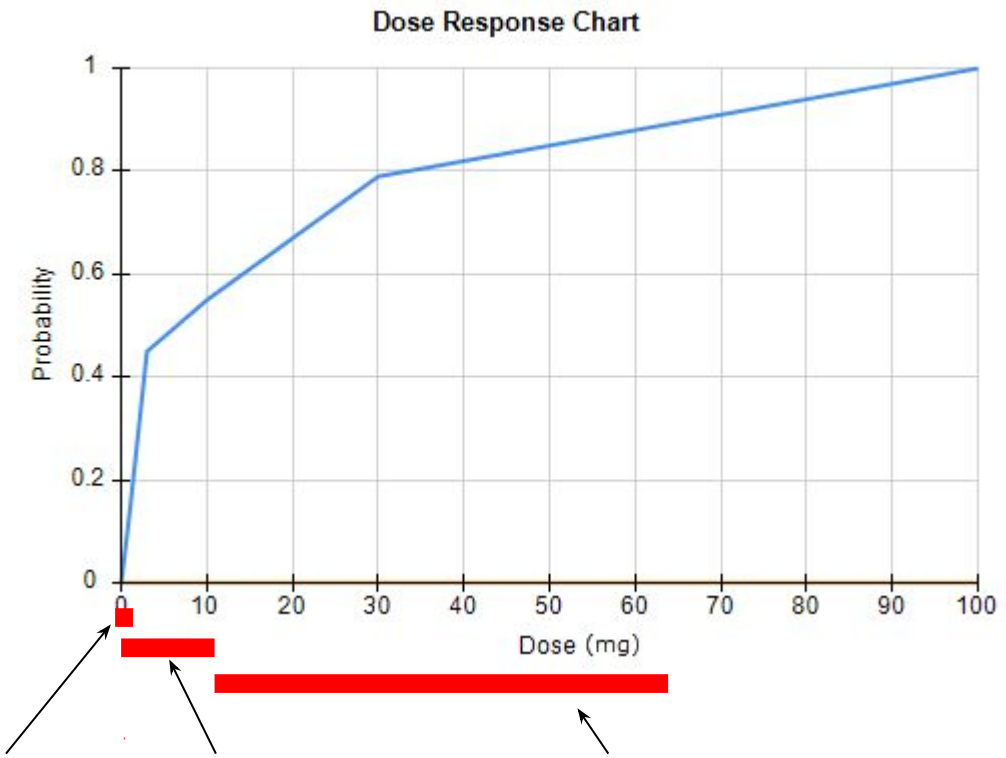

Dose range for Brand 3 (P <0.1)

Dose range for Brand 2 (P < 0.6)

Dose range for Brand 1 (P ~ 0.55 to 0.9)

5b. Risk Characterization of Chronic Exposure to a Carcinogen

Excess Risk of Cancer from Lifetime Exposure to Arsenic in Rice

Estimating Average Lifetime Dose (LADD) at 50th Percentile

Lifetime Average Daily Dose (LADD) Calculation	Rice intake (g/kg-day)	Lifestage duration (years)	"weights"	Weighted daily rice intake	
persons 3 to 5 years (50th %ile)	2.837	3	0.04	0.11	
persons 6 to 11 years (50th %ile)	2.354	6	0.08	0.18	
persons 12 to 19 years (50th %ile)	1.639	8	0.10	0.17	
persons 20 to 39 years (50th %ile)	1.54	20	0.25	0.39	
persons 40 to 69 years (50th %ile)	1.161	30	0.38	0.44	
persons 70+ years (50th %ile)	1.123	12	0.15	0.17	
		79		1.45	Lifetime average rice (cooked) intake (g/kg-day)

Divide by 3.4 to get the weight of dry rice consumed: 0.43 g/kg-day

$$0.43\ \frac{g\ dry\ rice}{kg\ body\ weight\ per\ day} \times 96\ \frac{\mu g\ arsenic}{kg\ dry\ rice} \times 0.001\ \frac{kg}{g} = 0.04\ \frac{\mu g\ arsenic}{kg\ body\ weight\ per\ day}$$

Estimating Average Lifetime Dose (LADD) at 99th Percentile

Lifetime Average Daily Dose (LADD) Calculation	Rice intake (g/kg-day)	Lifestage duration (years)	"weights"	Weighted daily rice intake
persons 3 to 5 years (99th %ile)	30.713	3	0.04	1.17
persons 6 to 11 years (99th %ile)	11.875	6	0.08	0.90
persons 12 to 19 years (99th %ile)	19.351	8	0.10	1.96
persons 20 to 39 years (99th %ile)	11.551	20	0.25	2.92
persons 40 to 69 years (99th %ile)	12.116	30	0.38	4.60
persons 70+ years (99th %ile)	14.76	12	0.15	2.24
		79		13.80 Lifetime average rice (cooked) intake (g/kg-day)

Divide by 3.4 to get the weight of dry rice consumed: 4.06 g/kg-day

$$4.06 \frac{g\ dry\ rice}{kg\ body\ weight\ per\ day} \times 96 \frac{\mu g\ arsenic}{kg\ dry\ rice} \times 0.001 \frac{kg}{g} = 0.39 \frac{\mu g\ arsenic}{kg\ body\ weight\ per\ day}$$

Cancer Slope Factors (oral) for Inorganic Arsenic

Table 3.4 Linear Slope Estimates and ED01 from Morales *et al.* (2000) Model 1

Endpoint	Sex	ED01 (µg/L)[a]	SEM[b]	Linear Slope[c] (cases per mg/kg bw/day)
Bladder cancer	M	395 (326)	35	0.89 (0.76, 1.02)
Bladder cancer	F	252 (211)	21	1.39 (1.20, 1.58)
Bladder cancer	M+F	324 (267)	29	1.08 (0.92, 1.24)
Lung cancer	M	364 (294)	36	0.96 (0.81, 1.12)
Lung cancer	F	258 (213)	23	1.36 (1.16, 1.56)
Lung cancer	M+F	311 (252)	30	1.13 (0.95, 1.30)

[a] Effective Dose for 1% (ED01) is equivalent to a BMD1 for a quantal endpoint. The lower bound, equivalent to a $BMDL_1$, is given in parentheses. The values reported in Morales *et al.* (2000) were converted to dietary equivalents using the standard values used by the authors; a water consumption value of 2 liters and a body weight of 70 kg.

[b] The standard error of the mean (SEM) was calculated for the lower bound, assuming a normal distribution of the ED01.

[c] The values provided are the median and in parentheses are the 5^{th} and 95^{th} percentiles of the uncertainty distribution (CI90%).

Excess Risk of Cancer from Inorganic Arsenic in Rice

Endpoint	Sex	ED01 (µg/L)[a]	SEM[b]	Linear Slope[c] (cases per mg/kg bw/day)
Bladder cancer	M+F	324 (267)	29	1.08 (0.92, 1.24)
Lung cancer	M+F	311 (252)	30	1.13 (0.95, 1.30)

Risk from Rice Consumption at the 50th percentile:

0.04 µg arsenic/kg body weight per day * 0.001 mg/µg * 1.08 risk bladder cancer /mg/kg bw/day
= 4.3E-5 lifetime risk of bladder cancer in each person exposed at the median intake

and 4.5E-5 lifetime risk of lung cancer in each person exposed at the median intake

Risk from rice consumption at the 99th percentile:

0.39 µg arsenic/kg body weight per day * 0.001 mg/µg * 1.08 risk bladder cancer /mg/kg bw/day
= 4.2E-4 lifetime risk of bladder cancer in each person exposed at the 99th percentile of intake

and 4.4E-4 lifetime risk of lung cancer in each person exposed at the 99th percentile of intake

5c. Risk (Safety) Characterization of Chronic Exposure to a Non-Carcinogen

Risk of Renal Toxicity due to Dietary Cadmium Exposure

Risk Characterization

Based on point(s) of departure

- Ratio of NOAEL (or BMD) to estimate of exposure

Comparison with toxicity benchmarks

- ARfD – dose to which individual can be exposed for one day and expect no adverse health effects
- ADI – dose to which an individual can be exposed over the course of a lifetime and expect no adverse health effects

Non-cancer Risk (Safety) Characterization

Margin of Exposure (MoE) = POD vs Dose

Margin of Safety (MoS) = Dose vs TDI

Hazard Quotient (HQ) = Dose/TDI

Non-cancer Risk Characterization

$$\text{Margin of Exposure (MoE)} = \text{POD/ADD}$$

$$\text{Average Daily Dose (ADD)} = \frac{\text{C x IR}}{\text{BW}}$$

C = Contaminant concentration

IR = Ingestion rate

BW = Body weight

Comparison of TRVs for Dietary Cadmium

What is the overall influence of all of the differences that have been identified on the EFSA, JECFA and ATSDR values?

	EFSA	JECFA	ATSDR
PoD µg/g creatinine	**4**	**5.24**	**0.5**
Adjustment Factor (applied to biomarker)	3.9		
PoD after adjustment	1	5.24	0.5
Dietary to urinary ratio (median)	0.36	0.23	0.66
Equivalent Intake ug/kg bw/day	0.36	1.2	0.33
Choice of 5th percentile		0.8	
"Diabetic" factor (applied to dietary)			3
Daily TI or MRL µg/kg bw/day	**0.36**	**0.8**	**0.1**

- ATSDR: most conservative urinary PoD (European populations, and pHC)
- JECFA: most conservative overall adjustment to urinary PoD. Dietary to urinary adjustment includes TD and TK within a simulation model and choice of 5th %ile.
- ATSDR: least conservative dietary to urinary ratio despite choosing only females.
- ATSDR: additional uncertainty factor of 3.

Example of Toxicity Reference Values, for Ochratoxin A

Table 2. Uncertainty factors used in the derivation of risk metrics for OTA from the 90-day pig study.

	EFSA (2006)[a] Lowest dose tested: 8 µg kg bw^{-1} day^{-1}	Health Canada[a] Derived benchmark dose: BD_{10} = 1.56 µg kg bw^{-1} day^{-1}
Source of uncertainty:		
Intraspecies	10	10
Interspecies	15[b]	25[c]
LOAEL to NOAEL	3	
90-Day subchronic to chronic		2
Overall uncertainty	450	500
Resulting TDI (ng kg bw^{-1} day^{-1})	17	3.0

Notes: [a]Uncertainty factors applied to lowest dose tested (8 µg OTA kg bw^{-1} day^{-1}) or BD_{10} (data from Krogh et al. 1974).
[b]Toxicodynamics (2.5×); toxicokinetics related to OTA half-life (6×) as estimated by EFSA.
[c]Toxicodynamics (2.5×); toxicokinetics related to OTA half-life (10×) (see Table 3).

Source: Kuiper-Goodman et al., 2010

Margin of Exposure Risk Characterization for Ochratoxin A

Table 9a. Margin of exposure (MoE[a]) for regular specific commodity eaters ($tRCE_{com}$) for select age–sex strata and various exposure scenarios.

		No ML					ML				
PD exposure[b]	Age (years): Sex:	1 M + F	7–11 M + F	12–18 M	19–30 M	31–50 F	1 M + F	7–11 M + F	12–18 M	19–30 M	31–50 F
$\Sigma AP_{all\ com}$	Mean:	**4426**	7552	10856	11358	14836	6026	9778	13626	13859	18223
	p90:	**2446**	**4360**	6306	6399	8230	**3289**	5723	7854	7462	10228
$tRCE_{com}$	Means										
Durum wheat[b]		**3867**	6108	8528	9076	12013	**4205**	6682	9304	9910	13062
Durum[b] PF = 0.64 & pasta data		**4735**	7790	10892	11355	14841	**4741**	7800	10905	11368	14858
Rice		**3972**	6588	8767	9611	12384	[c]	[c]	[c]	[c]	[c]
Hot oatmeal		**2188**	**3918**	5633	5821	8563	**3464**	5815	8231	8570	11935
Breakfast cereal		**4298**	7344	10292	10762	13857	**4314**	7369	10332	10791	13903
Raisins		**3658**	7152	10286	10558	13578	**3887**	7284	10468	10792	13961
Beer					9043	11817				[d]	[d]
Coffee				10349	10464	13729			[c]	[c]	[c]
Wine					10860	13486				10927	13668

Notes: [a]MoE = TD_{05} (19.6 µg OTA kg bw^{-1} per day adjusted for 5–7-day gavage) divided by total RCE mean exposure to ochratoxin A (ng OTA kg bw^{-1} per day). MoE < 5000 (in bold) points to need for risk reduction.
[b]Using a processing factor of 0.82 or 0.64 plus pasta occurrence data where indicated.
[c]All occurrence values were below the EC ML for rice and coffee.
[d]There is presently no EC ML for beer.

Source: Kuiper-Goodman et al., 2010

5d. Risk Characterization of Sub-Chronic Exposure (Non-Cancer Exception)

Risk of Decreased IQ due to Dietary Lead Exposure in Children

The Canadian Total Diet Study

Dietary Exposure to Lead

Age Category	Median (µg/kg bw/day)	90th Percentile (µg/kg bw/day)	95th Percentile (µg/kg bw/day)
0-6 months	0.076	0.343	0.435
0.5-4 years	0.195	0.363	0.431
5-11 years	0.124	0.253	0.314
+12 years	0.069	0.148	0.180

Calculation of average daily dose (dietary) over 0 to 7 years:

0.5/7 * Dose at 0-6 months
+ 4.5/7 * Dose at 0.5-4 years
+ 2.0/7 * Dose at 5-11 years

Median = 0.166 µg/kg bw/day
90th %ile = 0.330 µg/kg bw/day
95th %ile = 0.398 µg/kg bw/day

Dose-Response Model for Lead in Children

"The respective BMDLs derived from blood lead levels in µg/L (corresponding dietary intake values in µg/kg b.w. per day) were:

- developmental neurotoxicity BMDL01, 12 (0.50);
- effects on systolic blood pressure BMDL01, 36 (1.50);
- effects on prevalence of chronic kidney disease BMDL10, 15 (0.63)."

At an intake of 0.50 µg/kg-day, expect decrease of 1 IQ point

Dose-Response Model for Lead in Children

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- developmental neurotoxicity BMDL01, 12 (0.50);
- effects on systolic blood pressure BMDL01, 36 (1.50);
- effects on prevalence of chronic kidney disease BMDL10, 15 (0.63)."

At an intake of 0.50 µg/kg-day, expect decrease of 1 IQ point

Estimated dose:

Median = 0.166 µg/kg bw/day

90th %ile = 0.330 µg/kg bw/day

95th %ile = 0.398 µg/kg bw/day

Lead exposure at the 95th %ile in Canadian children can reduce IQ by nearly 1 pt

Source Apportionment in Risk Characterization

Apportionment of TDI

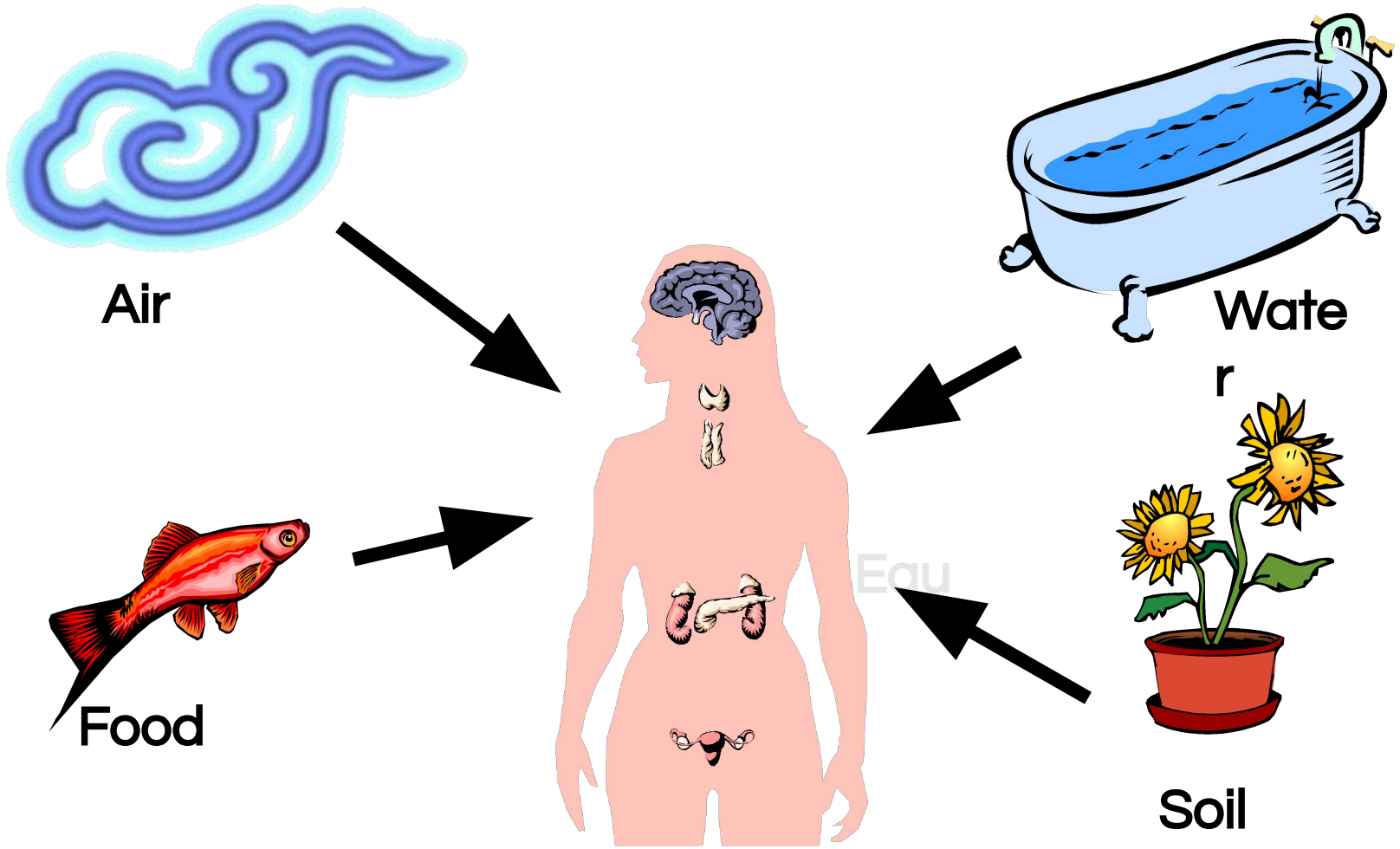
- Allocate 100% TDI to drinking water if it's the sole source of exposure
- But…not all chemical is found in water
- Air, water, food, soil & consumer products
- Relative contributions of exposure media

Relative Source Contribution

- Calculate using data on dose received via each exposure medium or source
- Predict using exposure models (emission sources, usage patterns, physicochemical properties, dimensions)
- Use default value of 0.2 in the absence of measured or predicted data

Exposure

Route-specific dose depends upon concentration & contact



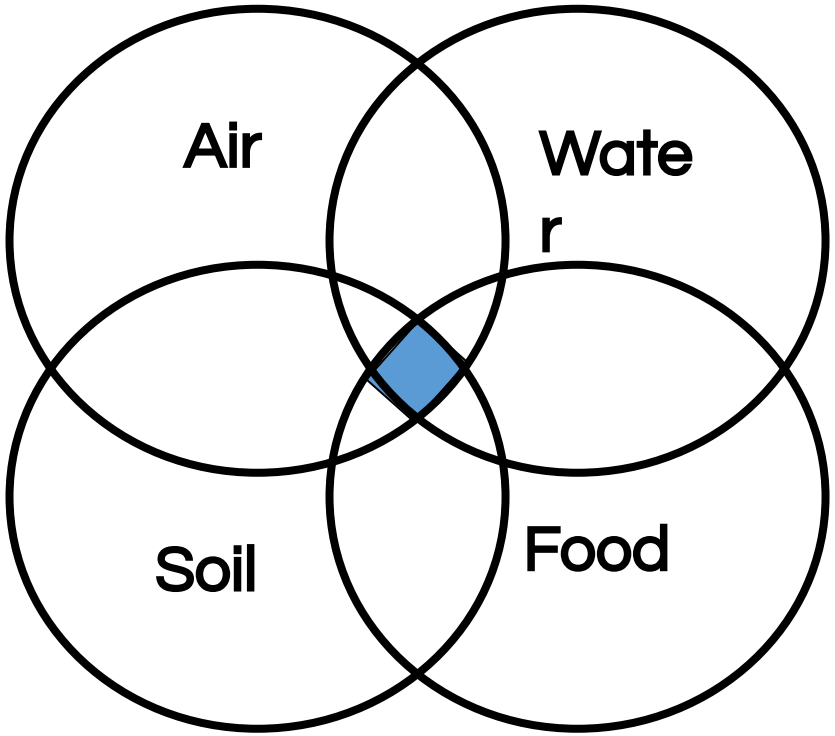
Estimates of Exposure

Ambient air	1.15 µg/kg/d
Drinking water	3.65 µg/kg/d
Food	0.20 µg/kg/d
Soil	-ND-
Total intake	5 µg/kg/d

Relative Source Contribution (RSC) to DOSE

Source	Fraction	RSC
Ambient air	1.15/5	0.23
Drinking water	3.65/5	0.73
Food	0.20/5	0.04
Soil	0/5	0.00
Total intake	5 µg/kg/d	1.00

Multimedia Exposure to Pollutants



Implementing RSCs

Situation: 50% of the total intake comes from food, 20% from water and 30% from air. The effects are similar for all routes.

Solution:

- TDI x 0.5 to derive guidance value for food

6. Burden of Disease Measures in Chemical Risk

Including Severity in Risk Characterization: Use of Burden of Disease Measures

Two Options to Value Illness

The risk arising from different food-hazard combinations needs to be in a common metric in order to compare them

Two common options are:

- Monetary (dollars, euros, etc.)
- Health-based: Disability-adjusted Life Years (DALYs)

The number of cases can be multiplied by the “per case” figure for either of these values to estimate and compare overall burden.

Option 1: Cost of Illness

A monetary value of societal cost per case of illness

E.g. for Salmonellosis

- estimated annual economic cost* of illness and death caused by Salmonella is $2.7 billion
- Estimated annual cases just over 1 million
  - Cost per illness ca. $2000

* In this case, cost includes medical costs, value of time lost from work, and value of premature death

Option 2: a Health-Based Metric

Imagine two different hazards:

- Hazard “A” caused 2 fatalities
- Hazard “B” caused 100,000 cases of gastroenteritis with 10% long-term disability

Which incurred the larger burden of disease?

How can we compare morbidity with mortality?

The DALY Metric

The Global Burden of Disease Study

- Murray and Lopez, 1996; since updated
- http://www.who.int/healthinfo/global_burden_disease/en/
- https://www.who.int/healthinfo/global_burden_disease/GlobalDALYmethods_2000_2015.pdf?ua=1

The Australian Burden of Disease Study

- http://www.aihw.gov.au/bod/
- https://www.aihw.gov.au/reports-data/health-conditions-disability-deaths/burden-of-disease/overview

A DALY Combines Morbidity and Mortality Outcomes in One Measure

Fatal outcomes and less severe outcomes can be combined in a single value called the Disability Adjusted Life Year (DALY)

- 1 DALY is incurred when one person dies a year short of his life expectancy, or 2 people die 6 months early
- 1 DALY is incurred when 5 people suffer a 20% loss of function lasting 1 year
- 1 DALY is incurred when 1 person dies 6 months early and 1 person suffers a 50% loss of function lasting 1 year

Definition of a DALY

For *each case* of illness, the DALY value is

- Severity Weight x Duration
- E.g. 50% loss of function x 10 years = 5 DALYs
- 0.5 x 10 = 5 DALYs

Death is given a severity weight of 1

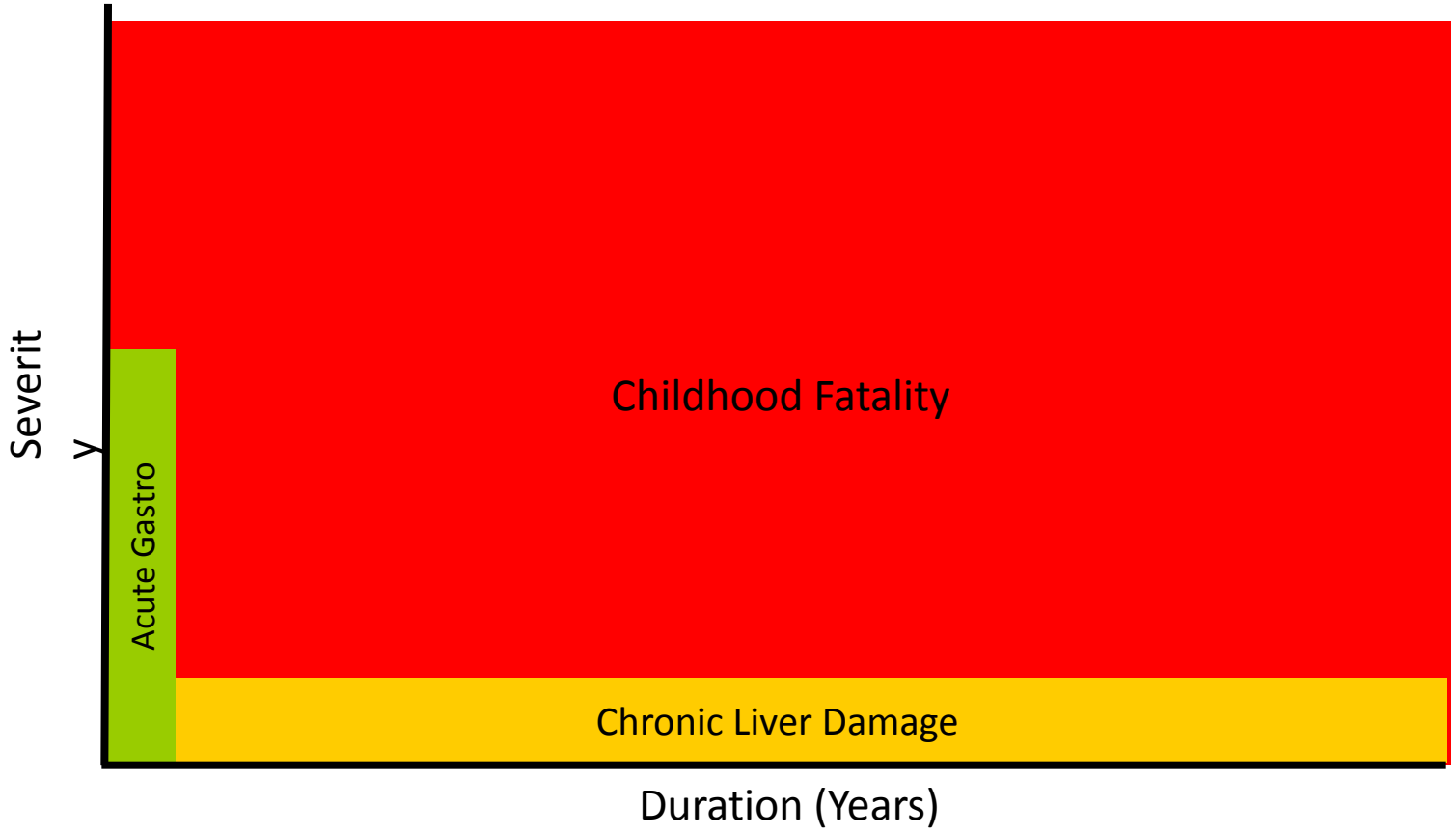
Population burden is DALY/case x Number of Cases

Sampling of Health Issues and their Severity Weights

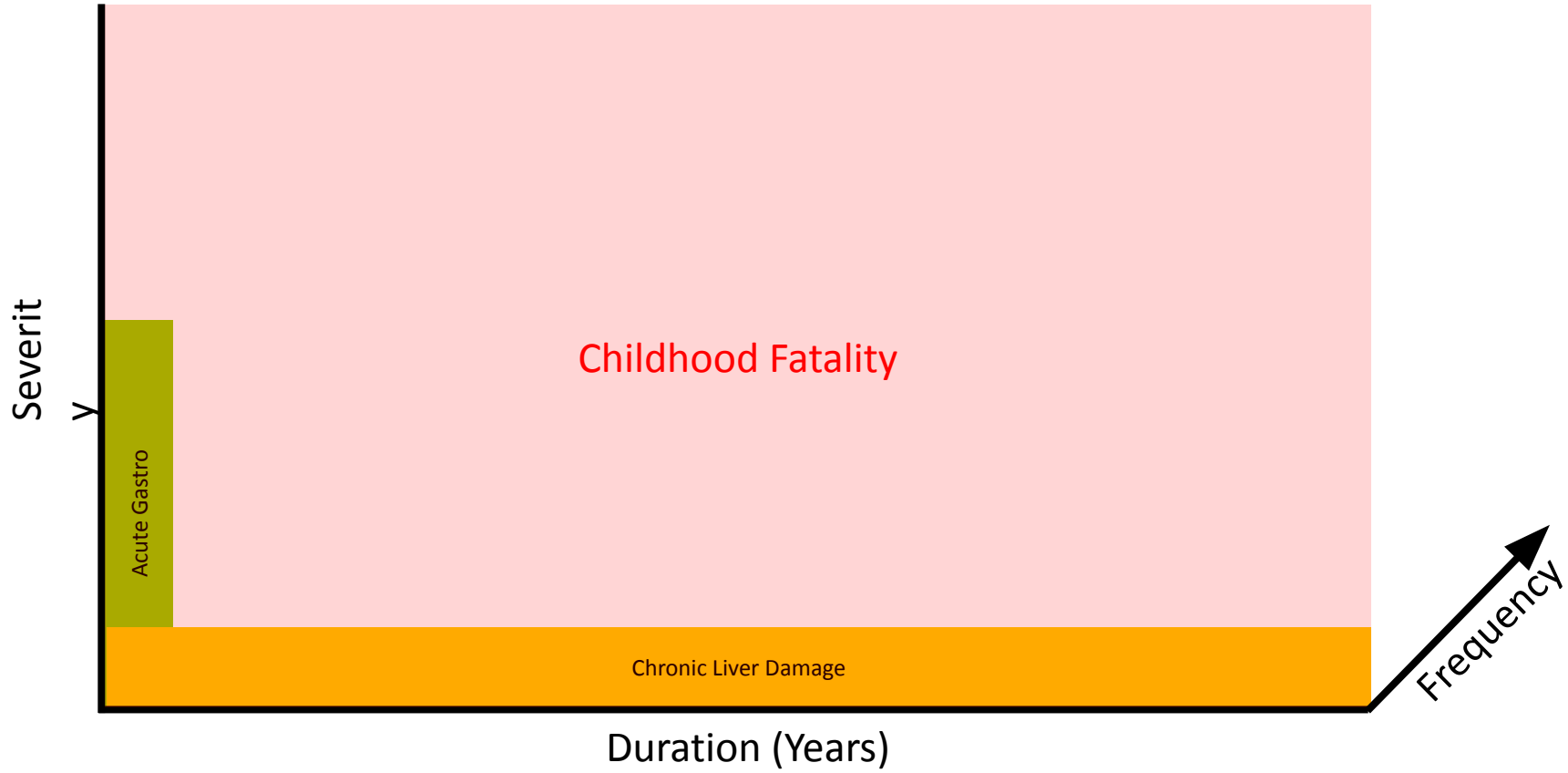
Mild Asthma	0.03
Severe Asthma	0.23
Uncomplicated gastroenteritis	0.09
Complicated gastroenteritis	0.42
Amputation, toe	0.06
Obsessive Compulsive Disorder	0.6
Death	1.0

(*Severity weights are also called disability weights*)

Disability Adjusted Life-Years (DALY)



Incorporating Frequency



The Weighted DALY per case Assigns a Value to Each Case of Illness

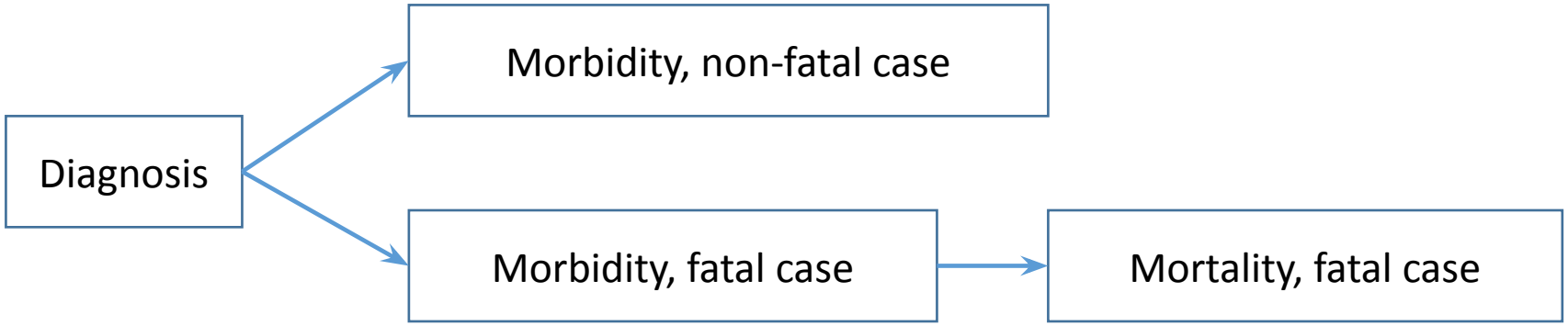
Need to know the *average* burden per case, taking into account the various health outcomes possible

- Step 1: Identify the outcomes
- Step 2: Assign a value to each
- Step 3: Weight according to proportion of cases experiencing each outcome

Note that this is equivalent to obtaining a monetary value by dividing total cost by number of cases

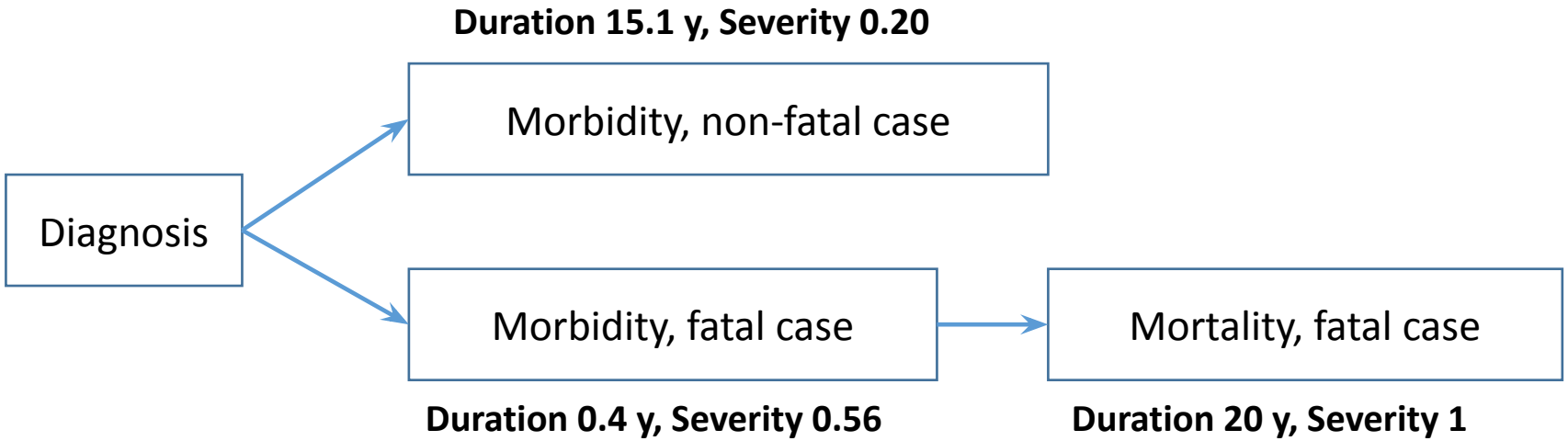
Health Burden Example: Liver Cancer DALY per Case

Step 1: Identify outcomes



Health Burden Example: Liver Cancer DALY per Case

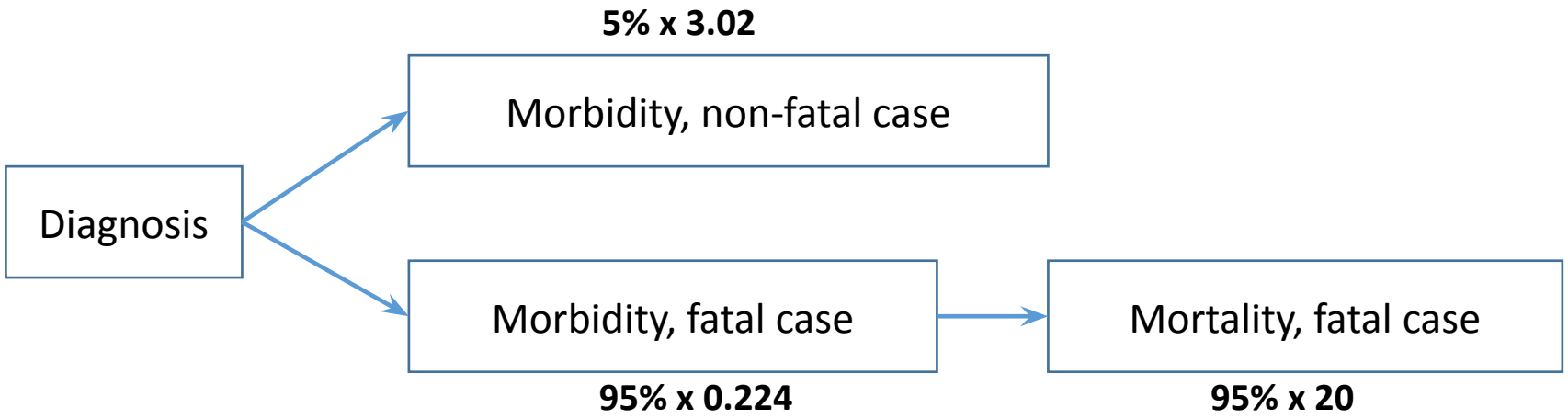
Step 2: Assign a DALY to each outcome



Note that the duration for 'Mortality' is usually the remaining life expectancy at age of death.

Health Burden Example: Liver Cancer DALY per Case

Step 3: Weight according to the proportion of each outcome and sum to find the weighted average



Average DALYs per Case = 5% x 3.02 + 95% x 0.224 + 95% x 20 = **19.4**

Health Metric Example: Gastrointestinal Pathogen STEC O157

DALYs = Number*Severity weight*Duration

Outcomes	Disease burden (DALY) per 1000 symptomatic cases of (gastroenteritis)
Watery diarrhoea	1000 x 53% (watery diarrhoea) x 0.067 x 0.009 = 0.3
Bloody diarrhoea	1000 x 47% (bloody diarrhoea) x 0.39 x 0.015 = 2.8
Death from diarrhoea	1000 x 2.7 x 10^{-4} (mortality) x 13.2 = 3.5
HUS	1000 x 10^{-2} (HUS) x 0.93 x 0.057 = 0.5
Death from HUS	1000 x 10^{-2} x 1.04 x 10^{-1} (mortality) x 26.2 = 27.3
ESRD	1000 x 10^{-2} x 1.18 x 10^{-1} x (ESRD) x 8.7 = 10.2
Death from ESRD	1000 x 10^{-2} x 1.18 x 10^{-1} x 2.52 x 10^{-2} (mortality) x 34 = 10.1
Total	54.7

Data based on estimates for the Netherlands, 1990-2000

Per case this is 0.0547 DALY

HUS is haemolytic uremic syndrome; ESRD is end-stage renal disease

Source: Havelaar & Melse, 2003

8. Deterministic versus Probabilistic Risk Assessment

What is a deterministic model?

- In a deterministic model, the outcomes are precisely determined through known relationships among model parameters
- A given input will always produce the same output
- There is no consideration of any random variation in the system
- Model can be built using expected values, worst case estimates, etc.

Example: Building a deterministic model

Scenario:

1. Potatoes are sold having a certain concentration (distribution) of glycoalkaloids
2. Consumers store them for a varying amount of time, during which the levels can increase (especially in light)
3. Peeling the potatoes removes a portion of the glycoalkaloids
4. Consumption of the potatoes varies over a wide range

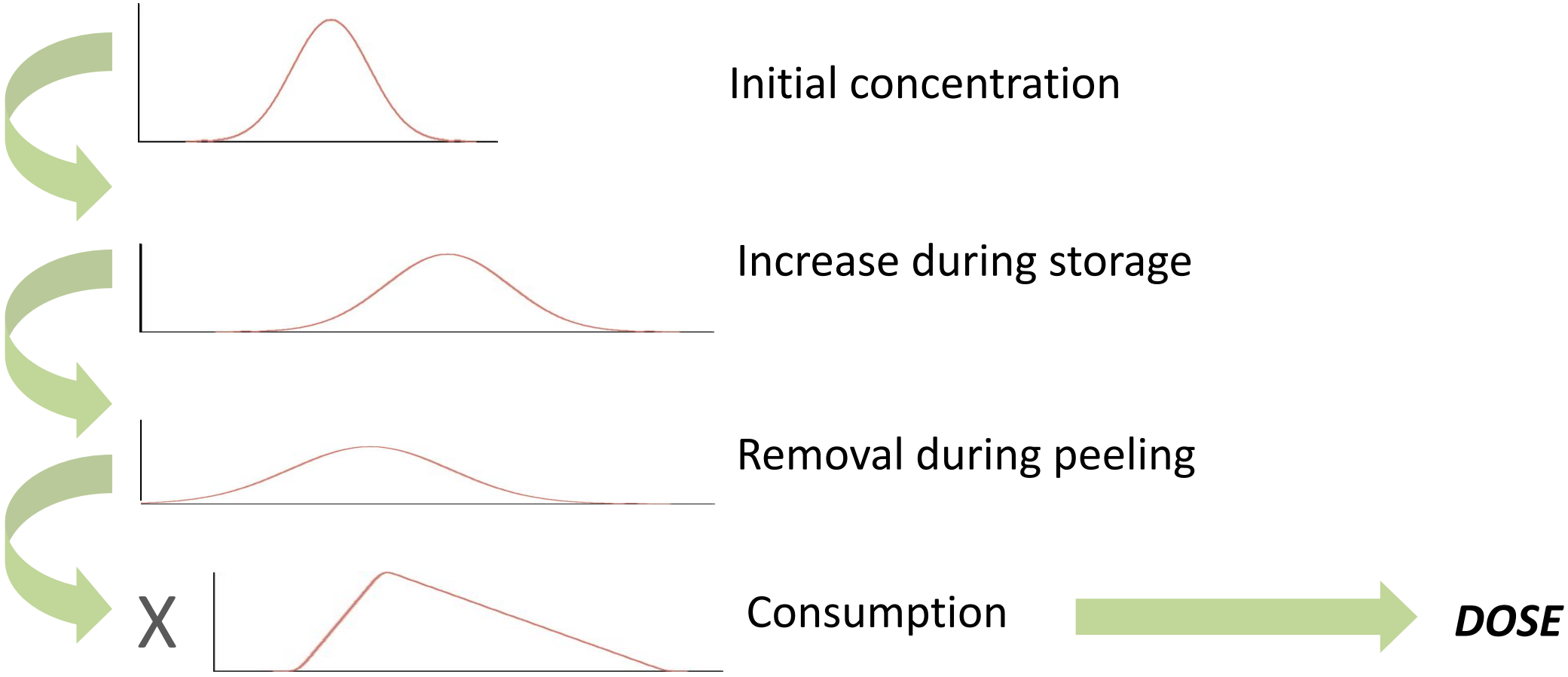
Glycoalkaloids are relatively heat resistant

Intake above ca. 1 mg/kg can result in nausea and vomiting

- a dose of 3-6 mg/kg is thought to be lethal

Image: Encyclopedia of New Zealand

Example Scenario: Glycoalkaloids in Potatoes



Example Scenario: Glycoalkaloids in Potatoes

First Approach

- Estimate dose using central values

Second Approach

- Estimate dose using worst case

Example Scenario: “Mean” Estimate

	Distributions	Nominal Values
Initial Concentration	= normal(90,15) mg/kg	90 mg/kg
Increase during Storage	= uniform(10,200) mg/kg	105 mg/kg
Fraction after Peeling	= triangular(0.4,0.6,0.8)	0.6
		117 mg/kg
Serving Size	= triangular(1.5,3.0,9.0) g/kg bw	3.0 g/kg bw

Dose per kg bw = 3.0 g * 0.001 kg/g * 117 mg/kg = 0.35 mg

Example Scenario: Worst Case Estimate

	Distributions	Worst Case Values
Initial Concentration	= normal(90,15) mg/kg	135 mg/kg
Increase during Storage	= uniform(10,200) mg/kg	200 mg/kg
Fraction after Peeling	= triangular(0.4,0.6,0.8)	0.8
		268 mg/kg
Serving Size	= triangular(1.5,3.0,9.0) g/kg bw	9.0 g/kg bw

Dose per kg bw = 9.0 g * 0.001 kg/g * 268 mg/kg = 2.41 mg

What is a conservative estimate?

- In estimating risk, there can be a desire to “err on the safe side” such that in the presence of uncertainty, the choice is made in the direction of increasing the estimate of risk.
- Sometimes this is done systematically to create a “worst case” scenario.
  - For example, the concept of a “maximally exposed individual” is typical in site-specific chemical risk assessment.
- The individual assumptions and the resulting estimates are sometimes called “conservative.”

Interpreting Point Estimates

If conservative point estimate falls below maximum acceptable risk, then we know that the risk is truly acceptable

- … but the extent of overprotection is unknown

If conservative point estimate falls above maximum acceptable risk, then we do not know if the risk is truly unacceptable or is the result of propagated conservatism.

Burmaster 1995

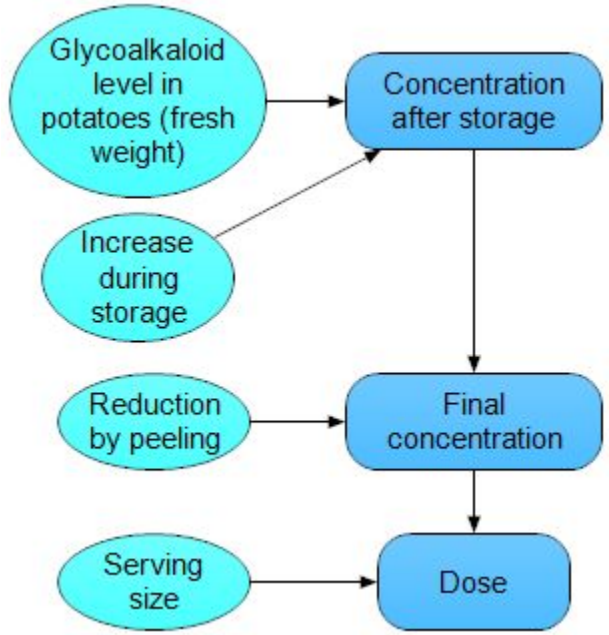
Probabilistic Analysis

- Evaluates almost all the possibilities
- Recognizes the variation that exists in the real world
- Allows the uncertainty associated with our knowledge of the real world to be accounted for.

Probabilistic Analysis

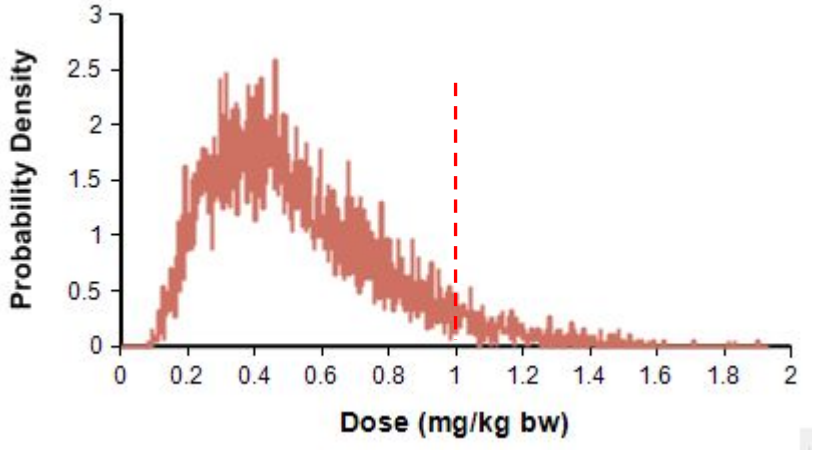
Distributions

Initial Concentration = normal(90,15) mg/kg
Increase during Storage = uniform(10,200) mg/kg
Fraction after Peeling = triangular(0.4,0.6,0.8)
Serving Size = triangular(1.5,3.0,9.0) g/kg bw



Dose =

Intake above ca. 1 mg/kg can result in nausea and vomiting - a dose of 3-6 mg/kg is thought to be lethal



Recall that for point estimates…

If conservative point estimate falls below maximum acceptable risk, then we know that the risk is truly acceptable (Amount of overprotection is unknown)

If conservative point estimate falls above maximum acceptable risk, then we do not know if the risk is truly unacceptable or result of propagated conservatism.

Burmaster 1995

Probabilistic vs. Point Estimate

Using the mean value:

- quite likely to occur - realistic
- doses higher than this frequently occur - not conservative

Using the conservative estimates

- not very likely to occur - not realistic
- doses higher than this rarely occur – “conservative”
- Still, may not be conservative enough
  - Should 95% confidence be a surrogate for ‘safe’

Probabilistic vs. Point Estimate

Point Estimates

- Probability of an event occurring is not considered
- Represents a significant loss of information.
- Risk Management decisions made with very little information.
- Assessments can be overly conservative, or inadequately protective, depending on the application.

Probabilistic vs. Point Estimate

Selection of conservative estimate is a contentious issue:

How conservative should it be?

- Worst Case Scenarios (creativity may the only limit to this)
- Default regulatory guidelines

Propagating conservative estimates through assessment results in estimates of risk with no probability context

- Reduces credibility of assessment
- Risk Management decisions not “based on science“

Conservatism as a Specific Challenge in Comparative Risk Assessment

Deliberately conservative estimates are particularly problematic (and may be worse than useless) when trying to compare risks (and other downstream decisions like resource allocation).

Comparing apples to oranges is hard enough. It is even harder when you add trying to compare ultra-high-risk applies to super-huge-risk oranges.

It can be difficult to convince career scientists who have always focused on safety to “take their thumb off the scale.”