An Introduction to FDA-iRISK®: a Comparative Risk Assessment Tool

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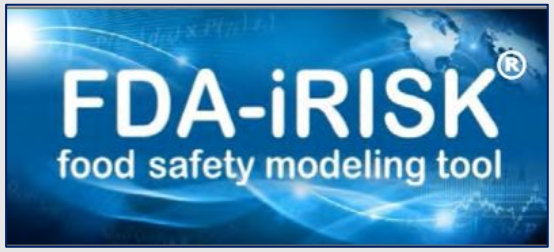
Risk Sciences International



Aim

- Provide overview of FDA-iRISK tool
- Explain the components of the tool
- Provide guided hands-on experience using the tool to build scenarios

Introduction to FDA-iRISK

What is FDA-iRISK?

- A fully quantitative tool that can estimate, using predictive models, the public health outcome or economic burden of hazards (including microbial and chemical hazards) in foods
- The tool provides a step-wise data-entry, documentation, computing, and reporting environment.
- The option of using probability distributions to describe factors affecting prevalence and concentration of a hazard in a food, along the farm-to-table food chain
- Storage of data and assumptions in databases

What is FDA-iRISK?

- An interactive, web-based system that enables users to relatively rapidly conduct fully quantitative, fully probabilistic risk assessments of food safety hazards

  - underwent two external peer reviews of the underlying structure and mathematical equations:

  - the first focused on microbial hazards; the second on chemical hazards.

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Who will use FDA-iRISK?

- FDA-iRISK is intended to be used by risk assessors and food safety professionals who are *knowledgeable about the hazards, foods and processes that they are describing*.
- Users may or may not be familiar with risk assessment methodology, particularly as it pertains to developing quantitative estimates of risk

<u>Important note</u>:

FDA-iRISK itself does not contain or provide scientific data other than what has been entered explicitly by the user

- *Users of FDA-iRISK provide all of the data, assumptions, and knowledge about hazards and foods*

What is FDA-iRISK?

- Provides an appropriate database and computational infrastructure to support a majority of the types of calculations typically required in food-safety risk assessments
- User's technical knowledge combined with the reliability associated with the computational infrastructure should…
  - …ensure higher quality and more productive risk assessment activity
  - …avoid some common conceptual and mathematical challenges that can make quantitative risk assessment either too difficult or too error-prone for some potential users

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FDA-iRISK Applications

- **Allow risk comparisons across many dimensions**
  - Hazards, foods, processing/handling practices, population groups
- **Predict risks / compare burdens of illnesses for microbial and chemical hazards**
  - Ranks them, e.g. 50 food-hazard pairs, based on a common metric
- **Quantify / compare effectiveness of interventions**
  - Predict reductions in risks and burdens

Faster, user-friendly information for timely decisions

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FDA-iRISK Version 4.0 Enhancements

- Version 4.0 available since July 2017
- Multi-food chronic chemical scenarios
- Multi-hazard chronic chemical scenarios
- Dietary shifts
- Improved sensitivity analysis
- Custom dose response models (empirical)
- Monotonically decreasing dose response models
- 2D Monte Carlo (variability and uncertainty)

What FDA-iRISK can do – Example: Rank Risks from Food-Hazard Pairs

Scenario	Lifecourse Duration	Eating Occasions or Consumers	Total Illnesses	Mean Risk of Illness	Total DALYs per Year	DALYs Per EO or Consumer
L. monocytogenes in Cantaloupe	N/A	5.98E+8	40.0	6.70E-8	103	1.73E-7
Salmonella in Peanut Butter	N/A	1.70E+10	3340	1.96E-7	63.4	3.73E-9
L. monocytogenes in soft ripened cheese	N/A	1.89E+9	3.36	1.77E-9	19.2	1.02E-8
Aflatoxin B1 in Tortilla Chips	77	2.50E+7	0.811	3.24E-8	15.7	6.30E-7
Inorganic Arsenic in Apple Juice	50	1.00E+6	0.105	1.05E-7	1.24	1.24E-6

Note: Risk estimates based on data and assumptions made; apple juice scenario based on draft FDA risk assessment (2013).

Generate a full report, including a summary of risk estimates, ranking results, data, and rationale

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Target Users and Audiences

Risk managers and decision makers

- need risk assessments to inform their decisions

Risk assessors and food safety professionals

- need to quantitatively assess risk, determine public-health impact of preventive controls & interventions

Academia

- Students, professors, researchers

… and others who need a platform on which to collaborate and share risk scenarios

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FDA-iRISK:
A Collaboration of Experts

Peer Review I
5 Experts from

- Univ. Florida
- Technical Univ. Denmark
- Univ. Maryland
- Coleman Sci. Consulting
- George Washington Univ. Med. Center

v2.0 Beta-testing
9 Experts from

- Rutgers Univ.
- Univ. Florida
- Technical Univ. Denmark
- Health Canada
- ANSES/EFSA work group
- BfR
- Swedish National Food Agency
- Canadian Food Inspection Agency (CFIA)
- Unilever

Peer Review II
5 Experts from

- Technical Univ. Denmark
- Johns Hopkins Bloomberg Sch. Public Health
- Rutgers Robert Wood Johnson Med. School
- CFIA
- Exponent, Inc.

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How does FDA-iRISK work?

RISK:

Probability x Consequence

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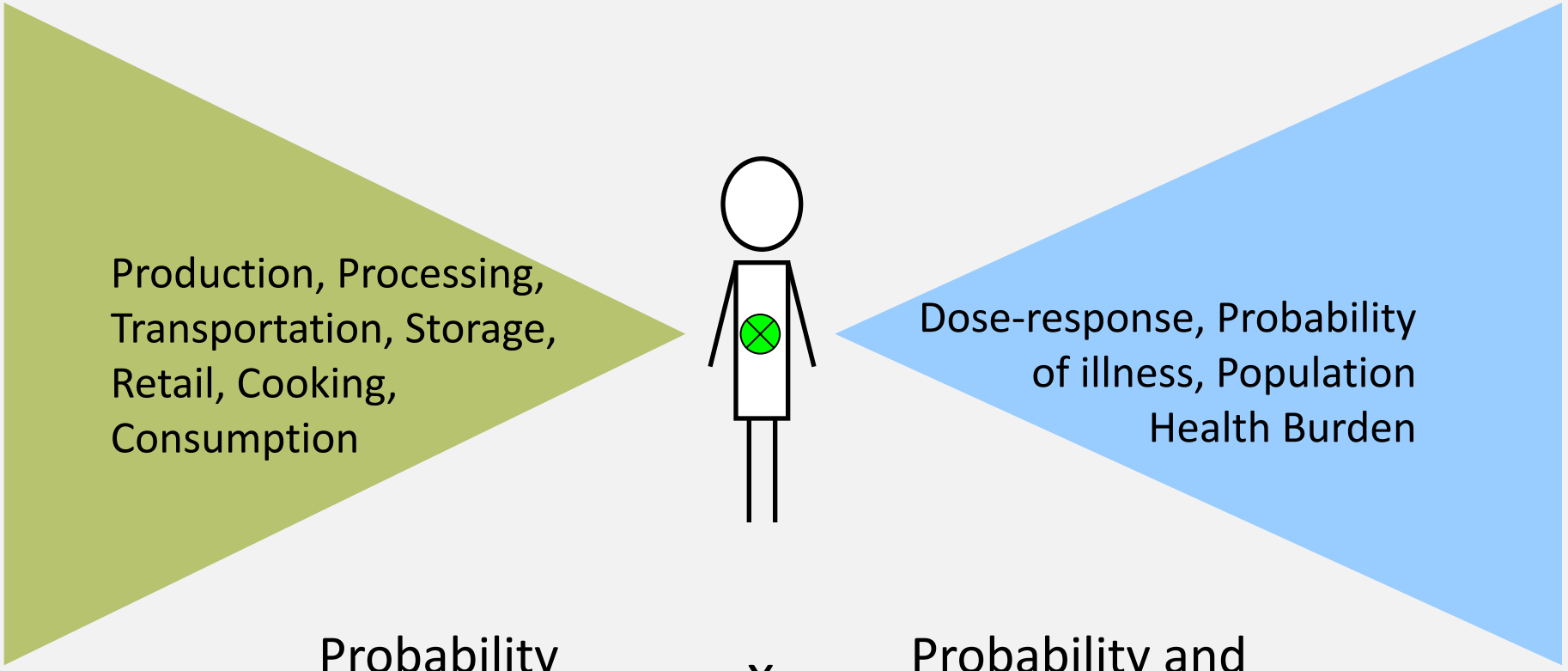
Probability x Consequence



Probability and Extent of Exposure

x

Probability and Severity of Consequences

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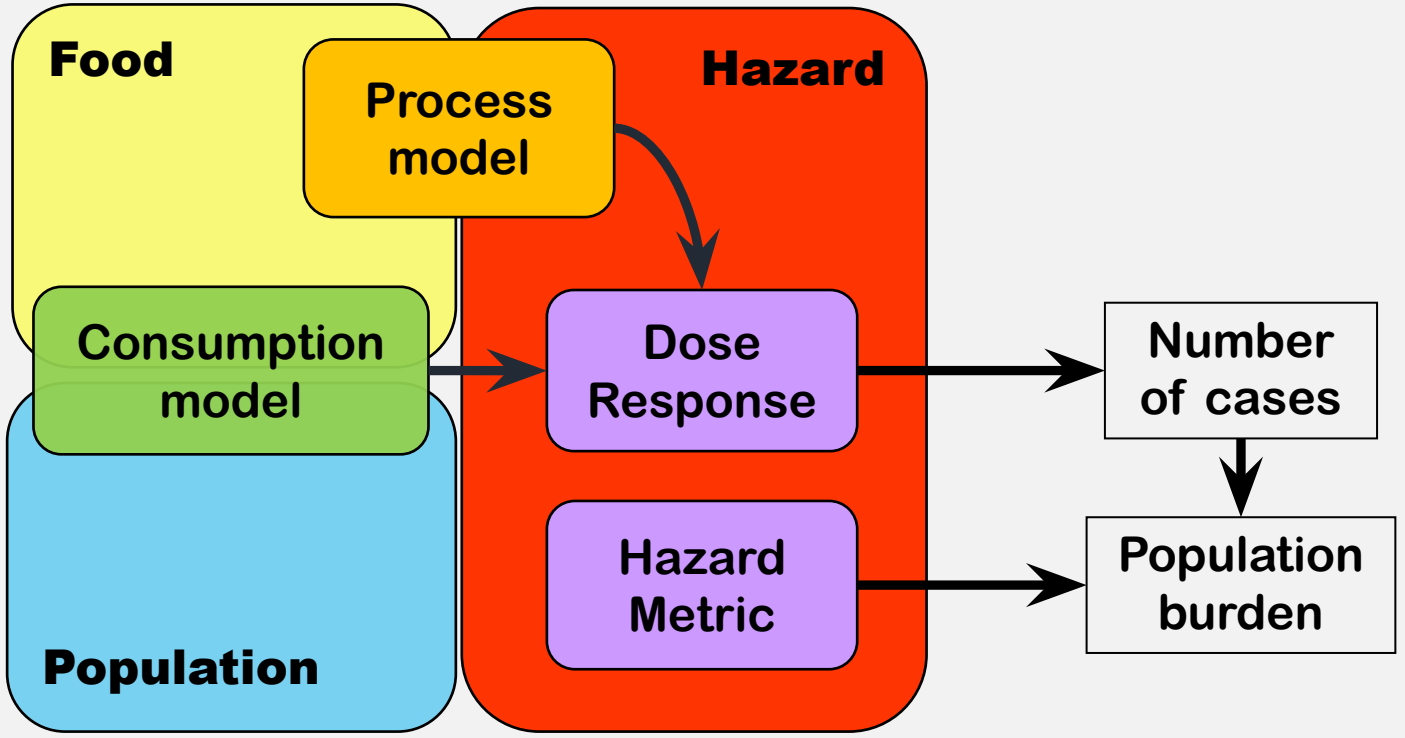
FDA-iRISK Scenarios

- FDA-iRISK directly connects probability and consequence through specification of a Risk Scenario (a risk assessment model)
  - Specific to each food-hazard combination
  - Describing various key aspects of the hazard, the food, and the processing of the food as it relates to the fate of the hazard within the food.

The 7 Elements of a Risk Scenario



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Estimating Exposure and Risk

- Once the user has described these key elements, the tool is capable of combining the user's input into a quantitative risk assessment model (i.e., a risk scenario)
  - estimates the exposure and risk of illness or health burden to the consumer
- Multiple scenarios can be developed in parallel
  - Rank individual risk scenarios (across different food-hazard pairs)
  - Group risk scenarios together and rank as a group
    - Burden summed across the group
    - Scenarios in a group can be weighted by contribution to the group

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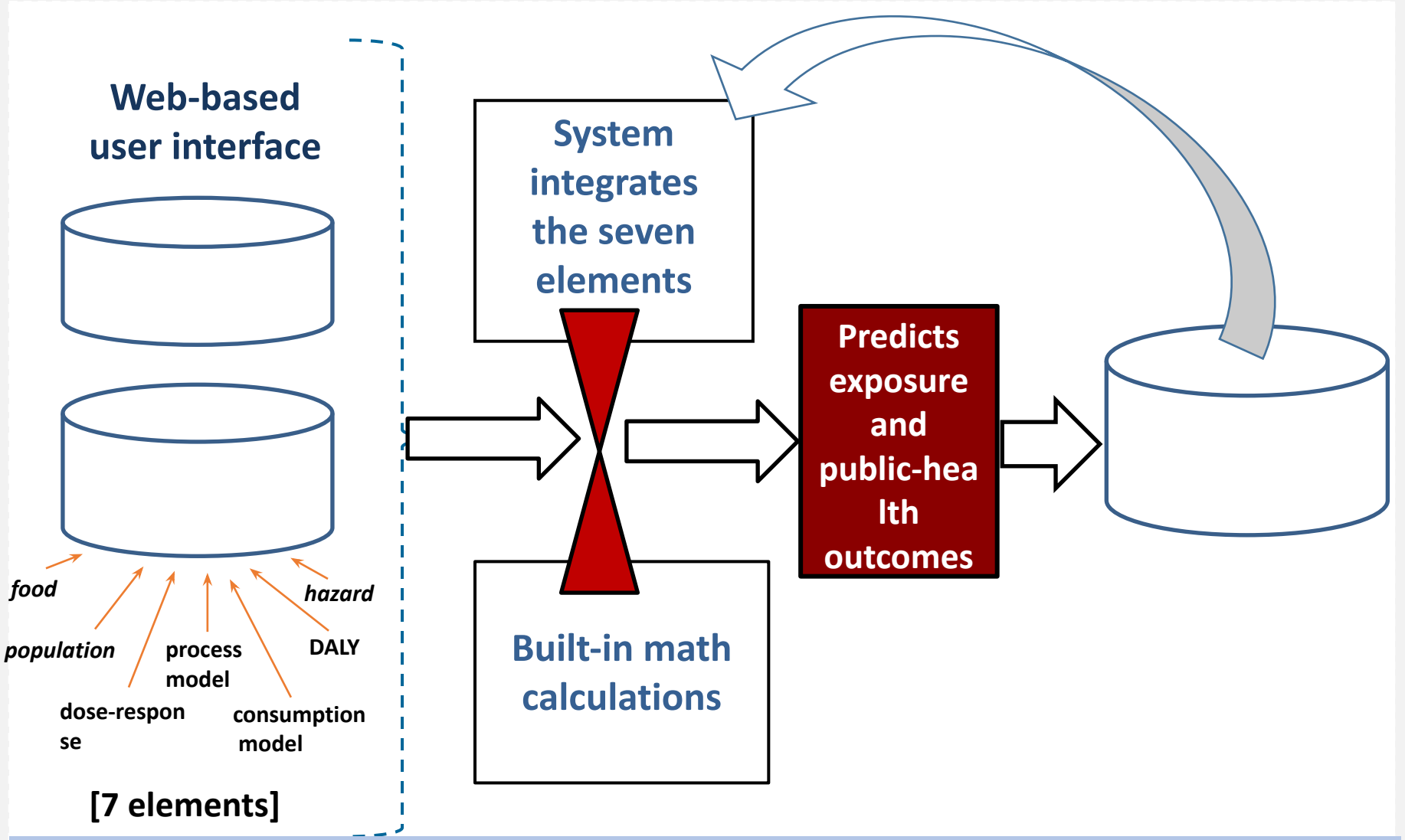
How FDA-iRISK works



FDA-iRISK captures data from scenarios & outcomes to build a global picture of risks & interventions.

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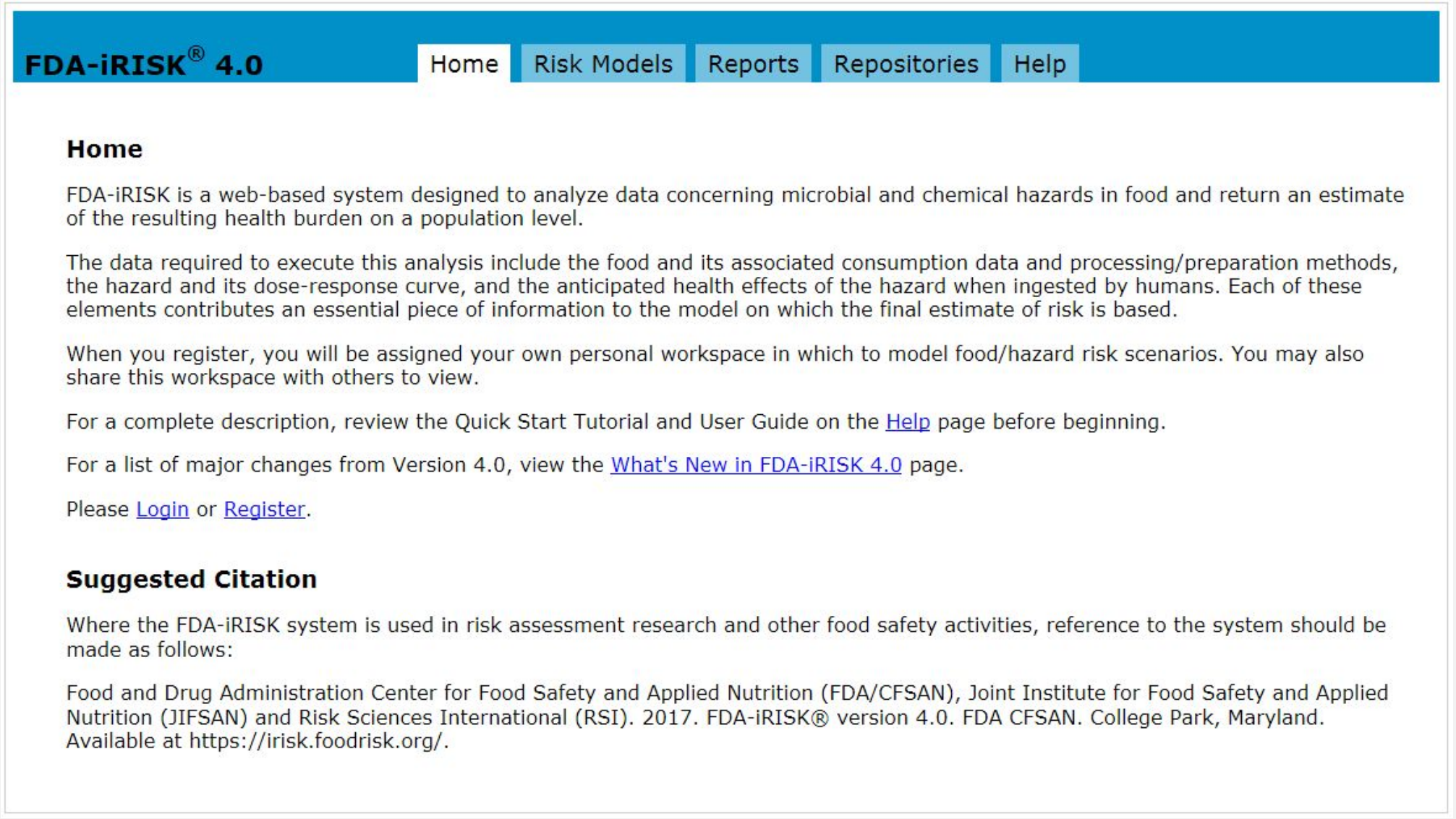
Web Interface: Users Access, Create, Save and Share Scenarios



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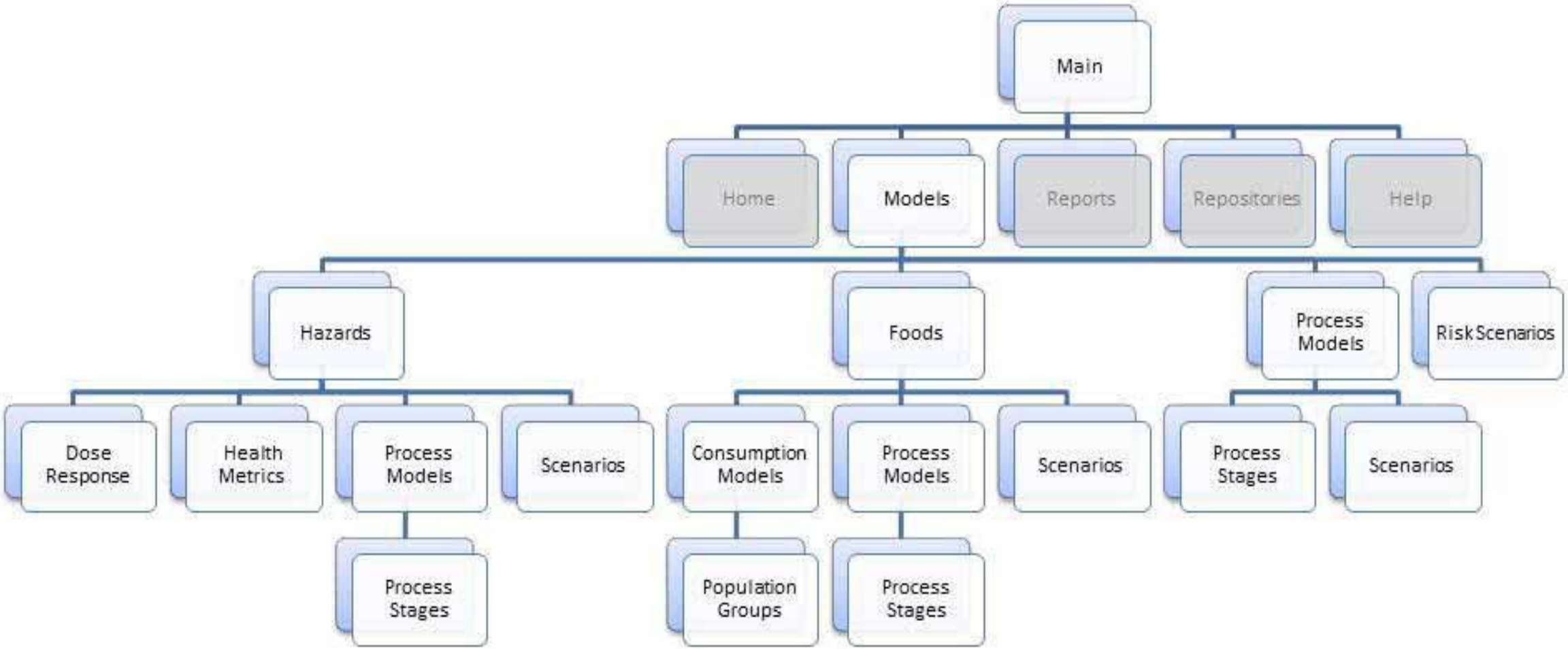
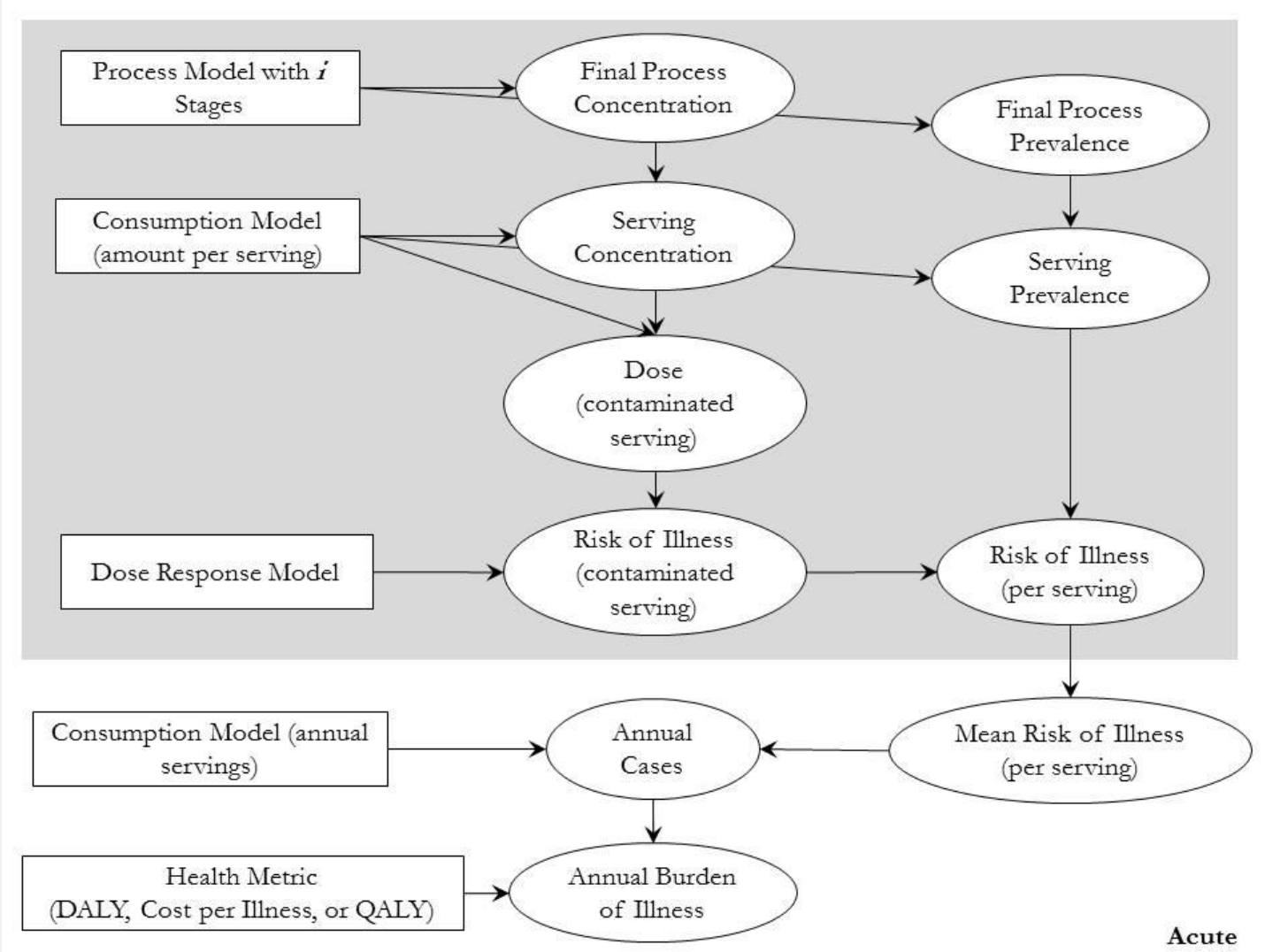
FDA-iRISK Map



FDA-iRISK Model Structure: Scenario Types

- Microbial or Acute Chemical Hazard (Single Food, Single Hazard)
- Chronic Chemical Hazard (Single Food, Single Hazard)
- Chronic Chemical Hazards (Multiple Foods, Single Hazard)
- Chronic Chemical Hazards (Multiple Foods, Multiple Hazards)

FDA-iRISK Model Structure (Microbial & Acute Chemical Hazards – Single Food)



User inputs (data required)

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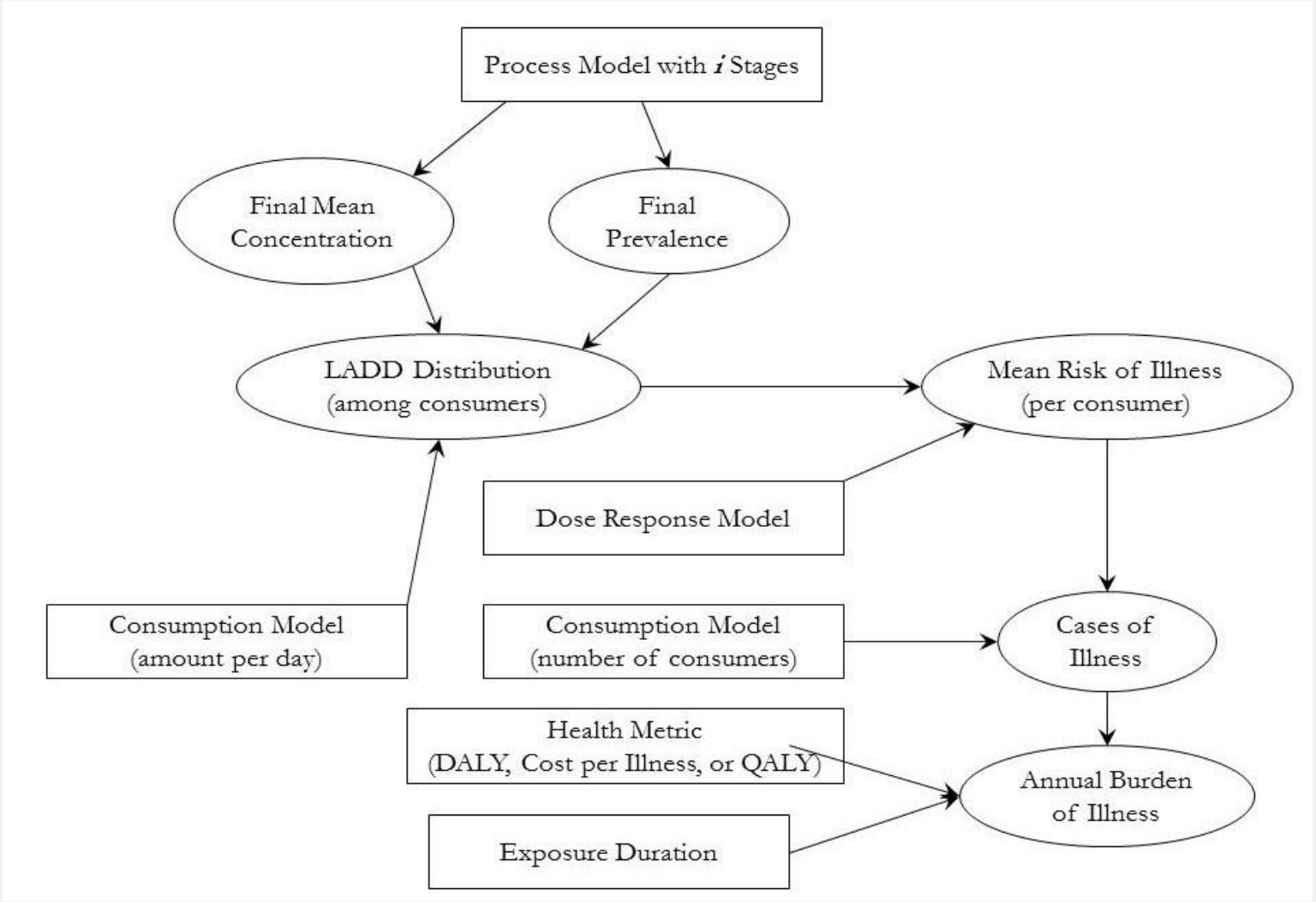
FDA-iRISK Model Structure (Chronic Chemical Hazards – Single Food)



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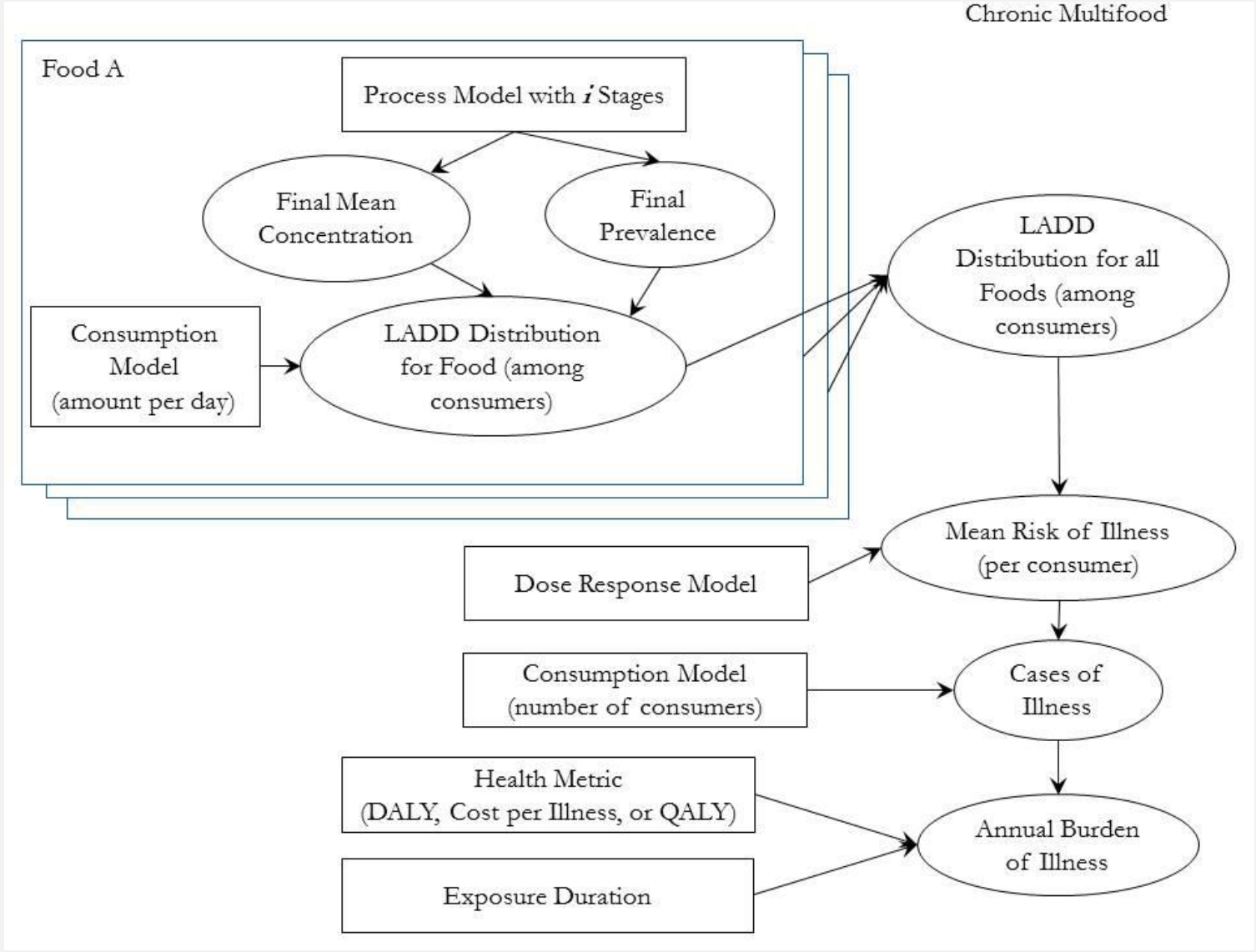
FDA-iRISK Model Structure (Multi-Food Chemical Hazards)



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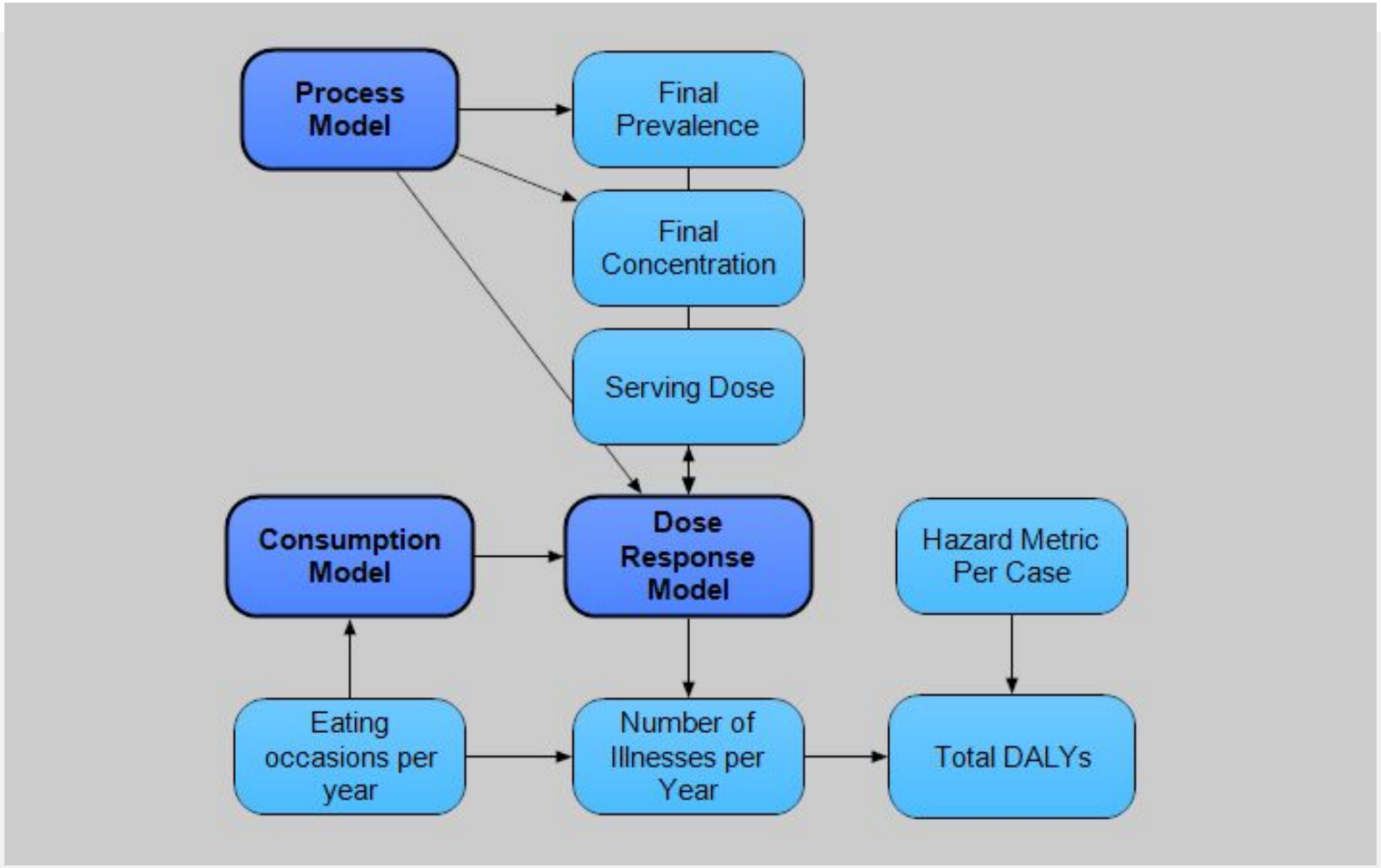
The Engine Behind FDA-iRISK

Simulation & Software

Behind the Scenes

- Fully probabilistic
- Uses Analytica™ (Lumina Decision Systems) as the simulation engine
- Simulation models are custom built on the fly from a component library using the required pieces as defined by the user's scenario

Sample Scenario in Analytica



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Scope of Models

- Scope is controlled by the user
- Only condition is model links to consumption

Simulation

- If distributions are used for inputs then Monte-Carlo simulation is implemented
- System has a built-in monitor of the stability of the simulation results
- Simulation is stopped when stability (convergence) is achieved
  - (

Scenario Details for: Process Model Initial Concentration: Fixed Value (Value:2)

Type:	Results Computed	Scenario Weight:	N/A
Hazard:	Inorganic Arsenic Imported (Chemical)	Metric Type:	DALY
Food:	Apple Juice Imported	Exposure Type:	Chronic
Process Model:	Inorganic Arsenic in Apple Juice Imported	Converged:	Yes (by 9000 samples)
Consumption Model:	Consumption of Apple Juice (0-50 yrs)		

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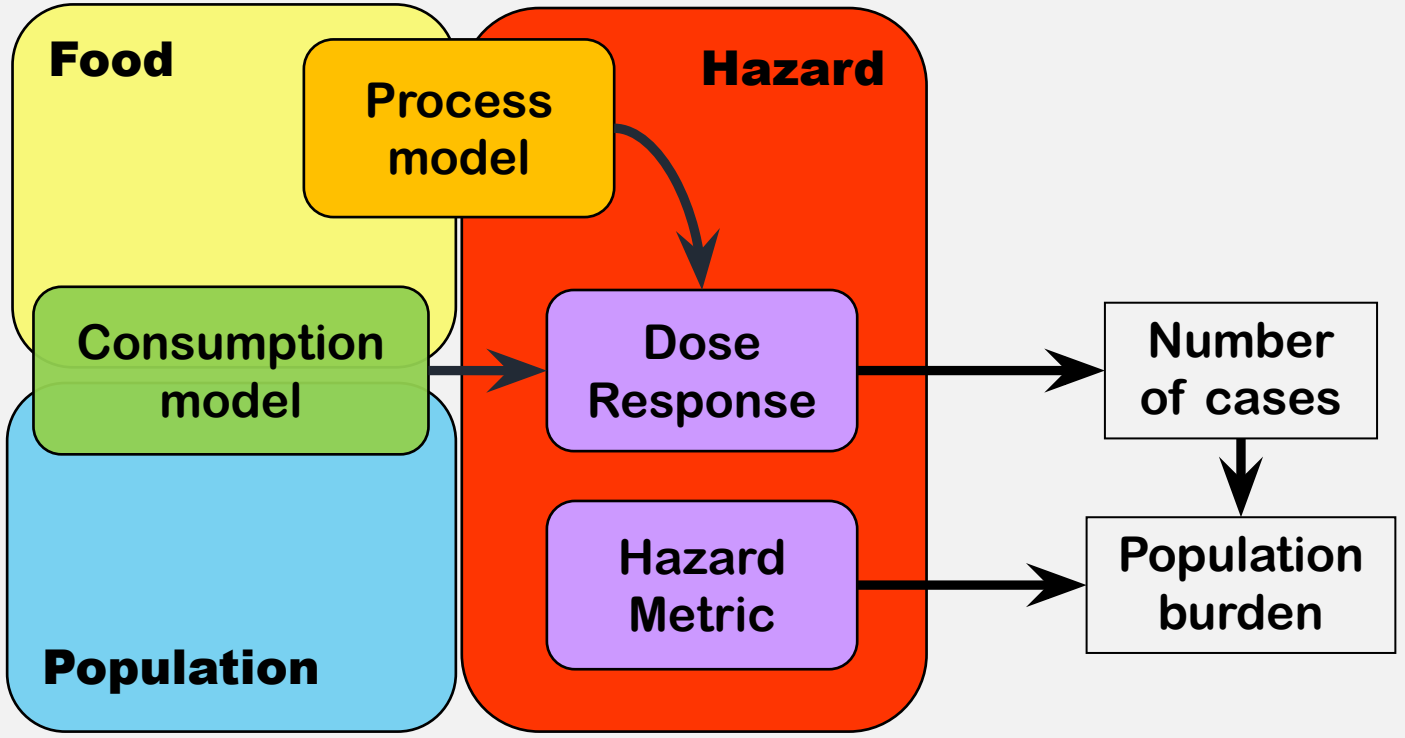
Building Scenarios in FDA-iRISK

The 7 Elements of a Risk Scenario



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Foods

- Each food can have one or more consumption models
- Consumption models can vary by age, sub-populations of interest, and other factors
- Required consumption model type depends on scenario type
  - Acute
  - Chronic
    - Chronic Multi-food

Consumption Model - Acute

- Risk scenarios for acute exposure assume that illness results from a single exposure to a certain amount of microbial pathogen or chemical
- The effect of this dosage can depend on the individual consuming the food, both in terms of the probability of becoming ill, and in terms of the severity or type of illness
  - user can define various mutually exclusive **population groups** for consideration in a risk scenario for a single acute exposure

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Consumption Model - Chronic

- For chronic exposure, the consumption model is used to generate a value for the average amount of the food consumed per day (on a per unit body weight basis) over a lifetime of exposure
- Takes into account:
  - the different daily amounts that may be eaten at different life stages,
  - the body weight during those stages and
  - the duration of those life stages relative to the entire lifespan.

Consumption Model - Chronic

- The average amount of the food consumed per day is then multiplied by the average concentration of hazard in the food
  - represents all servings consumed in a lifetime
  - determined by both the average concentration of the hazard and the prevalence of contamination
- Result is the Lifetime Average Daily Dose (LADD)

Dose-response

Consumption Models Summary

- Acute exposure
  - Assume illness can follow any single eating occasion
  - Dose depends on amount of food eaten per person per eating occasion
  - Eating occasions per year used to scale individual risk to population risk
  - Microbial pathogens and chemicals
- Chronic exposure
  - Assume long-term exposure precedes illness
  - Dose depends on average amount of food eaten per person per day
  - Number of consumers used to scale individual risk to population risk
  - Most chemicals

Calculation of Dose

- Per eating occasion (for acute exposures)

  concentration of hazard in food (from process model)

  X amount of food per eating occasion (from consumption model)

- Per consumer (for chronic exposures)

  mean (concentration X prevalence) of hazard in food

  X average amount of food per day per kg body weight (from consumption model)

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Sample Chronic LADD Calculation

Age Range	2 to 10	11 to 17	18 to 64	65 to 85
1) Body weight (kg)	26	57	80	80
2) Consumption (g/day)	53	20	10	15
3) Cons. by wt. (g/kg-d)	2.04	0.35	0.13	0.19
4) Time Span (years)	9	7	47	21
5) Fraction of total span	0.107	0.083	0.560	0.25
6) ADC (g/kg-day)	0.218	0.029	0.070	0.047
7) LADC (g/kg-day)	0.364			
8) Hazard Concentration (ng/g)	4.43			
8) LADD (ng/kg-day)	1.61			

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Hazard

- Available Hazard Types:
  - Microbial (always acute)
  - Acute Chemical
  - Chronic Chemical
- Can also be applied to:
  - Allergens (using acute chemical structure)
  - Nutrients (using chronic chemical structure)
  - Others – with imagination and care! (e.g. physical, …)

The Dose-Response Model

Connecting Exposure to Probability of Illness

Microbial Dose-Response Models

- Always considered to be acute exposure
- Dose is expressed as $\log_{10}$ cfu, pfu, or user-defined
- May be based on feeding studies or outbreak data
- Non-linear
  - Beta-Poisson
  - Exponential
  - Weibull
- Linear
  - Non-threshold Linear
  - Threshold linear
- Custom

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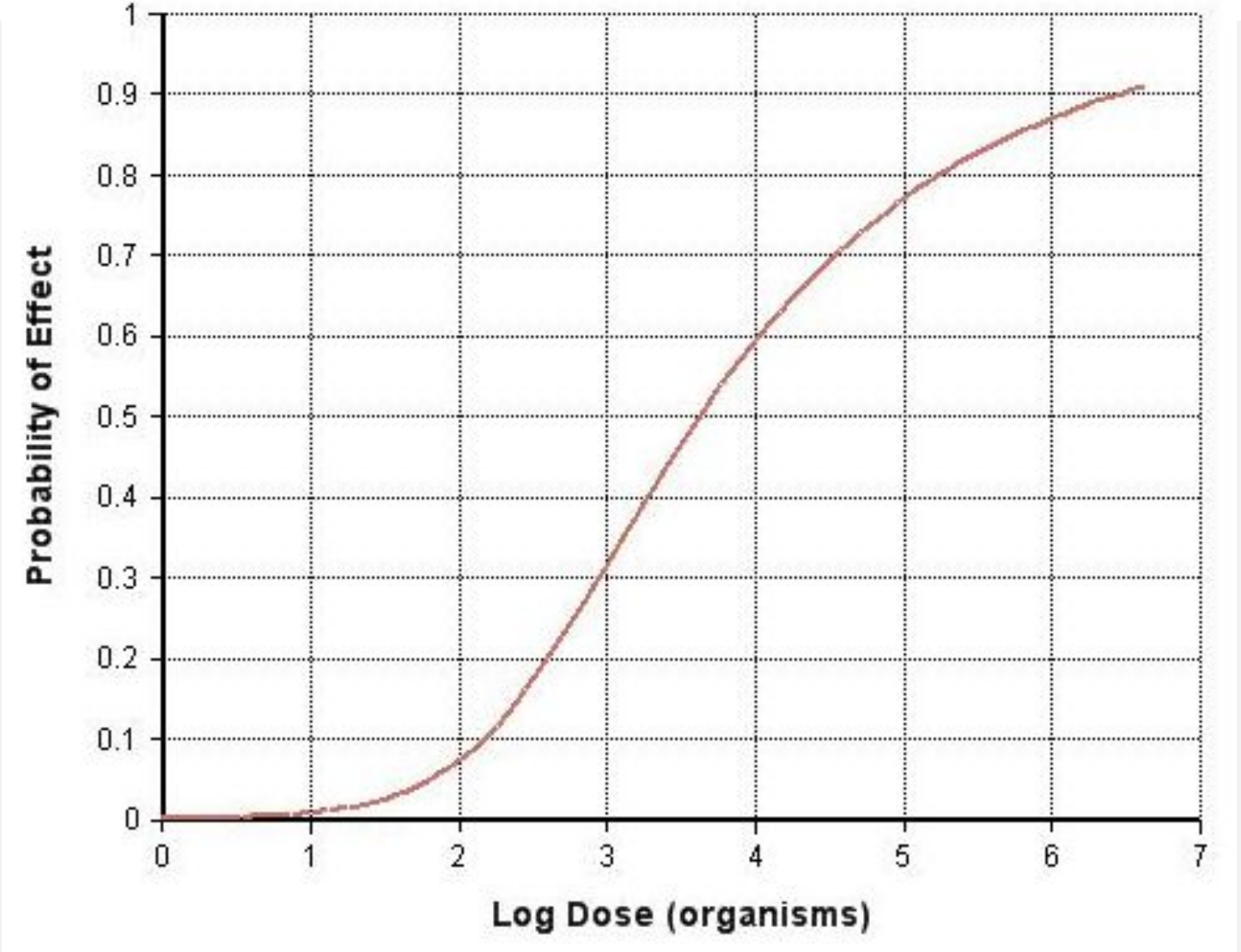
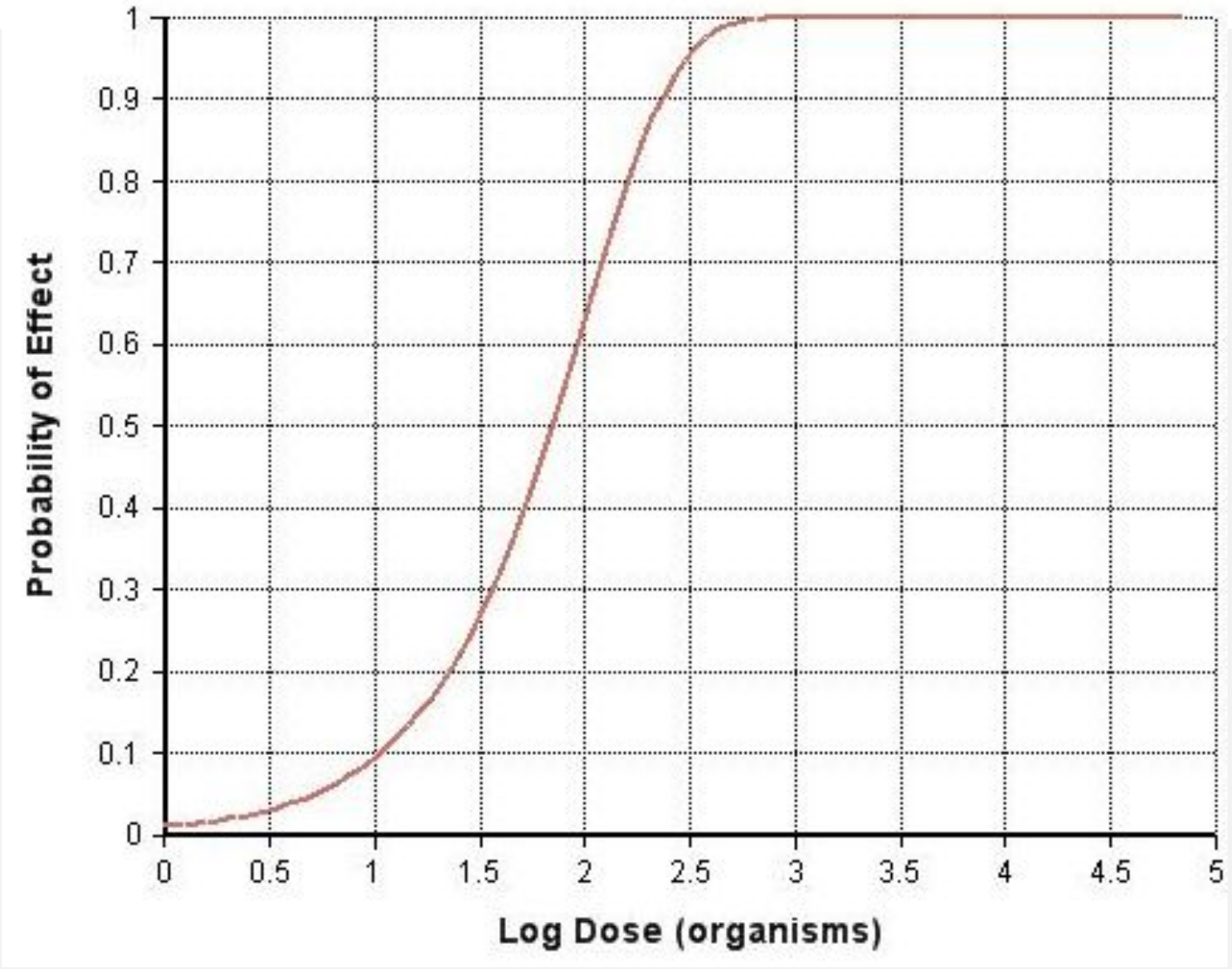
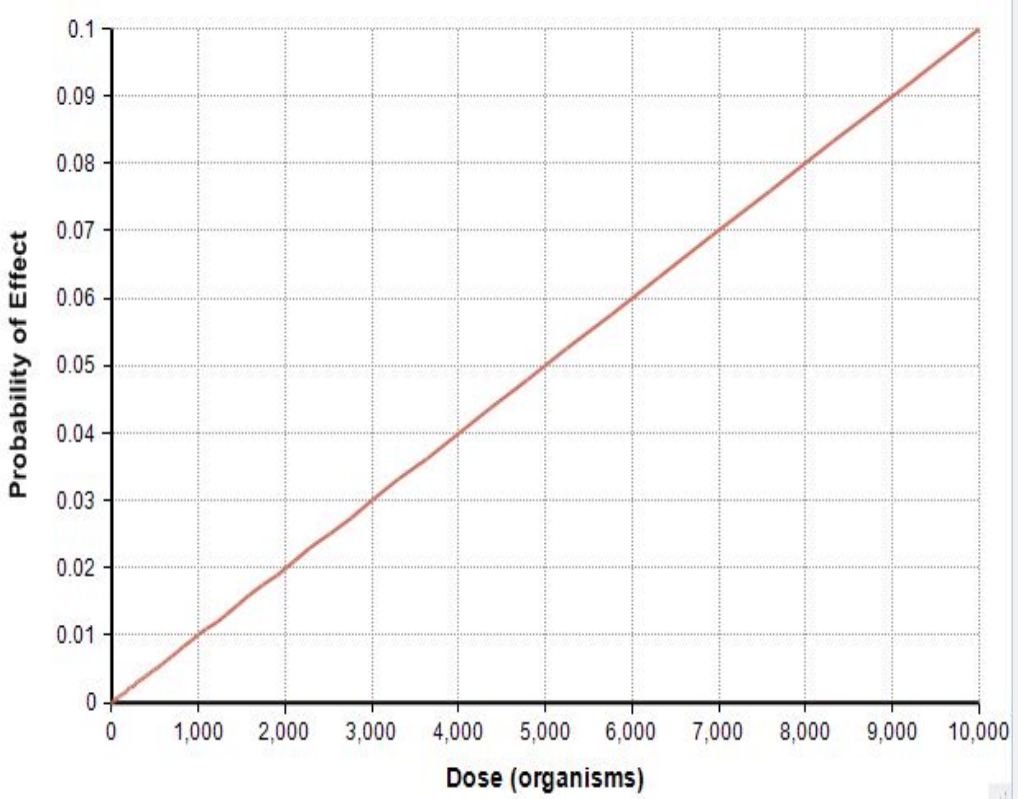
The Beta-Poisson (Acute Microbial)

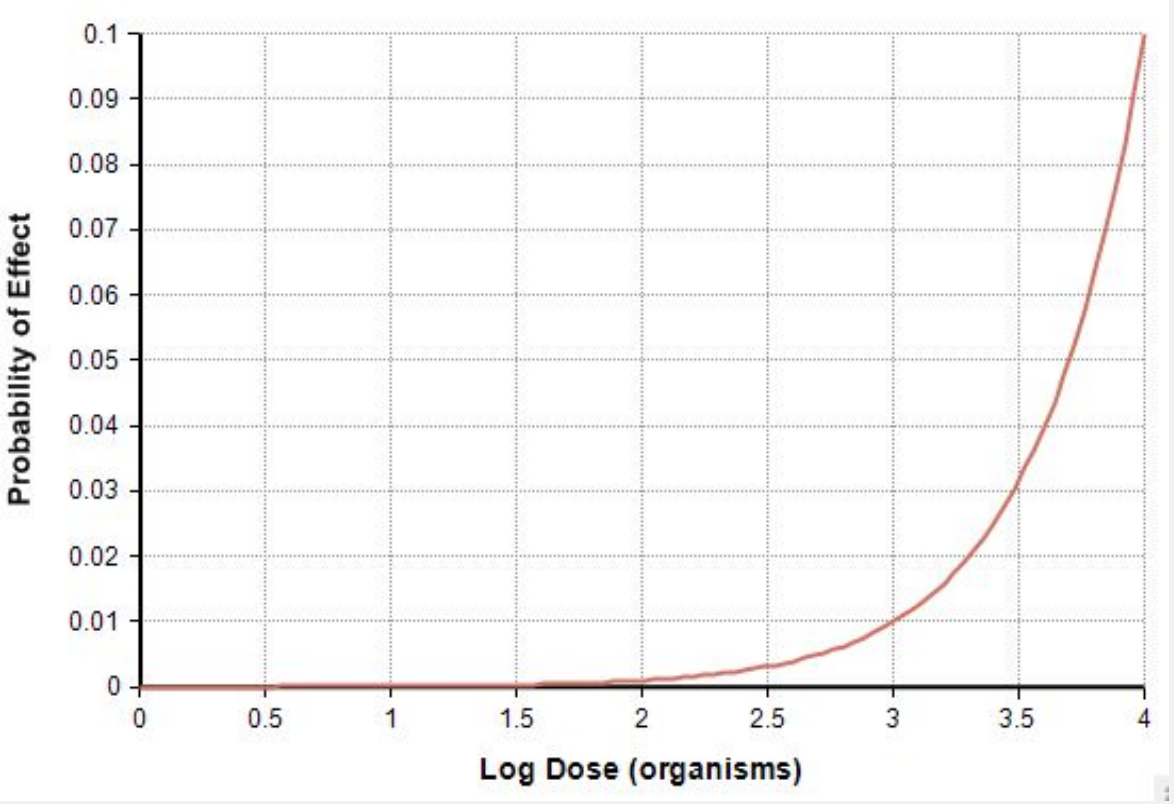


The Exponential (Acute Microbial)



The Non-Threshold Linear





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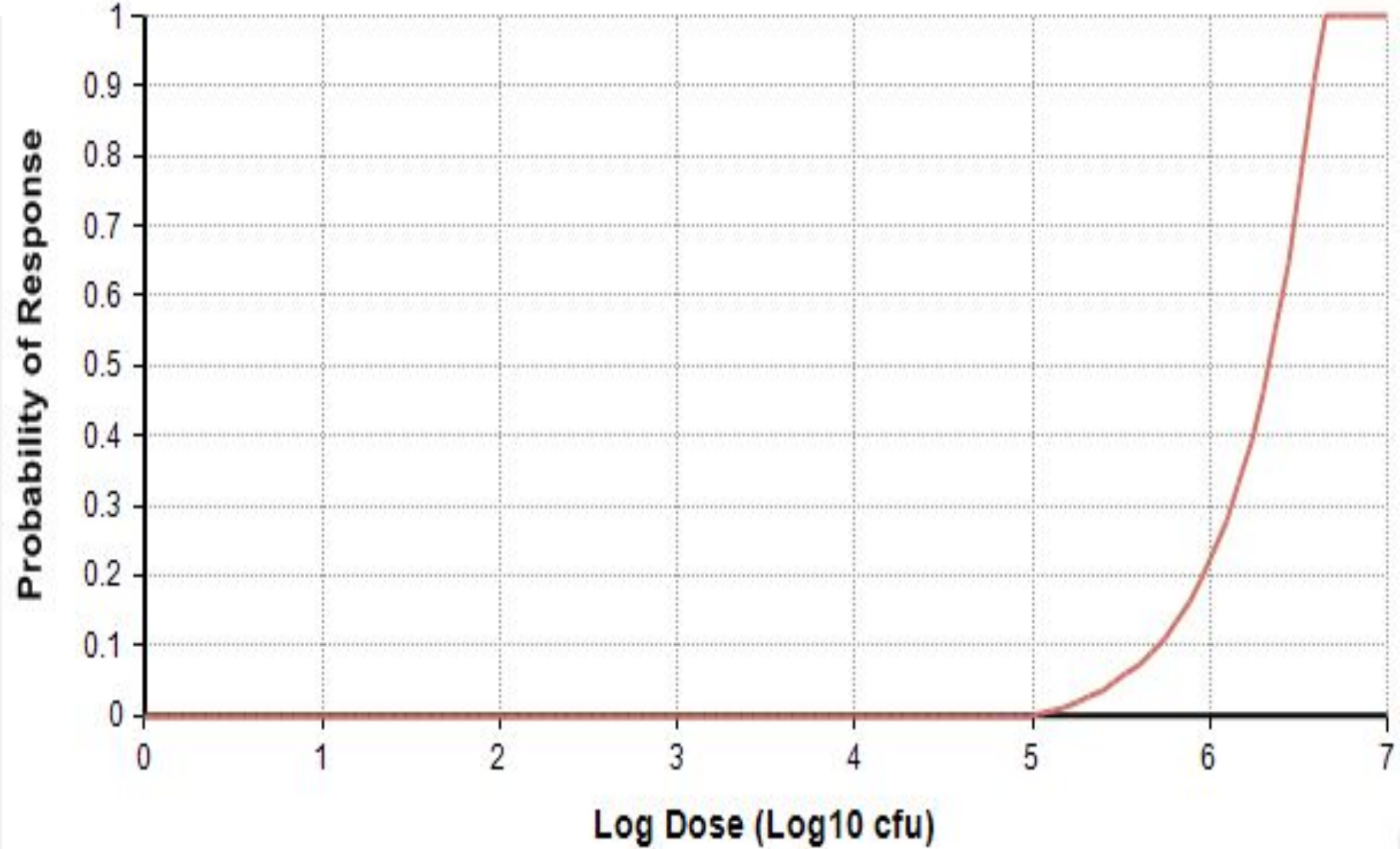
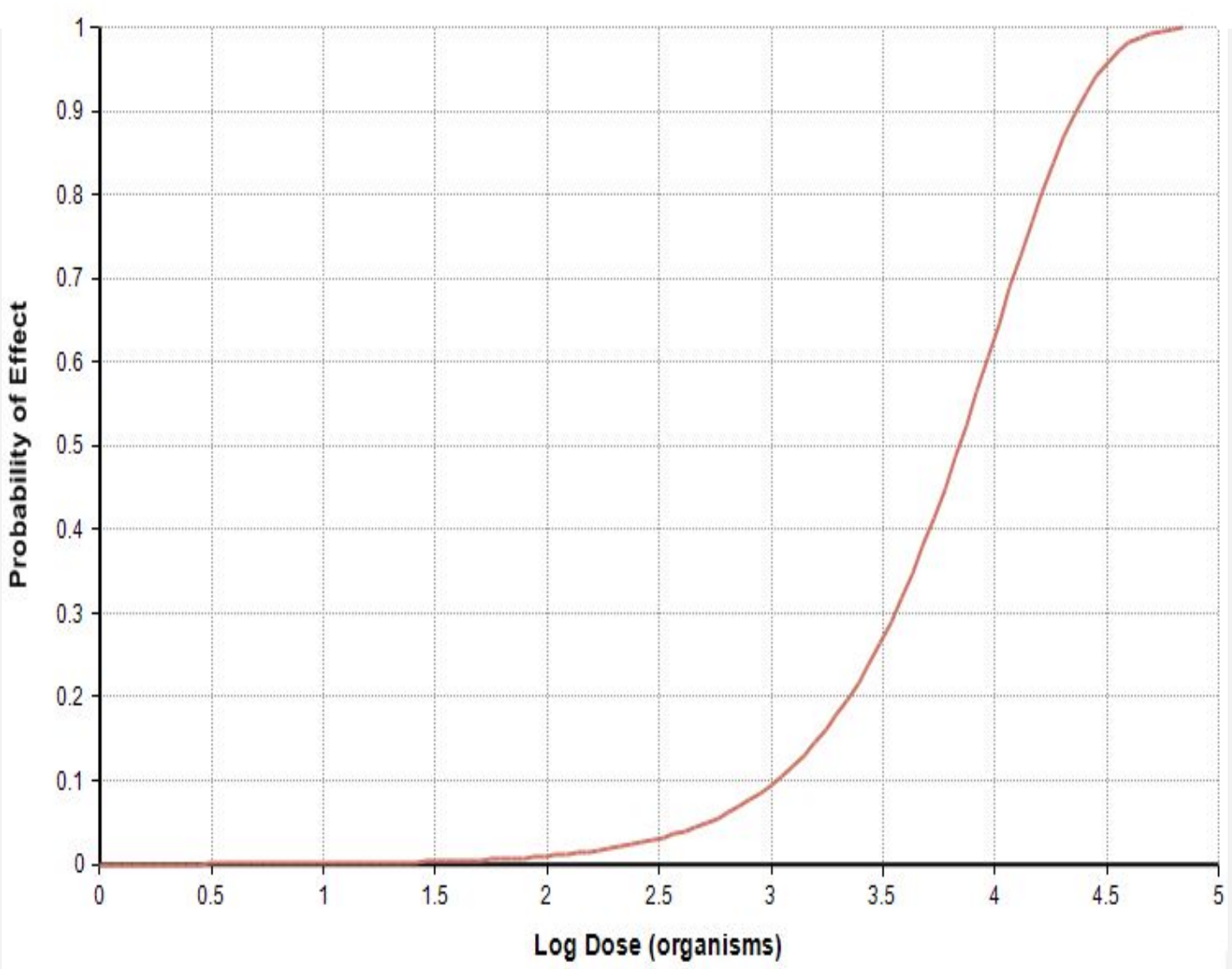
Threshold Linear



Weibull

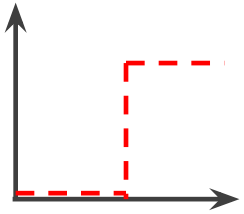

Probability of Effect
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Log Dose (organisms)

Chemical Dose Response Models

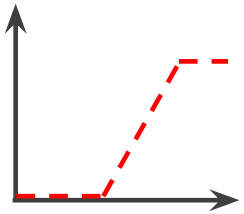
- May be for acute or chronic exposure
- Dose is expressed as mg or mg/kg for acute, mg/kg body weight per day for chronic
- Human data (occupational exposures, or highly exposed populations) or animal data with appropriate adjustments incorporated
- Both linear and non-linear forms, with and without thresholds

Dose-Response models: Chemical (Acute)

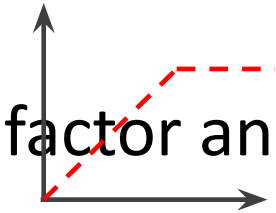
- Doses in mass or in mass/kg body weight
- Step Threshold



- Threshold linear



- Linear by slope factor and Non-threshold linear



Evaluating Chemical Exposures

- A reference dose can be used in a “safety assessment”
  - most of the people, most of the time will suffer no adverse effects at exposures below RfD
- A reference dose provides little information about the effects of exceeding it
- A dose-response model, on the other hand, provides an estimate of the probability of adverse effect at varying doses

Example of a Reference Dose

"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 Opinion on Ochratoxin A)

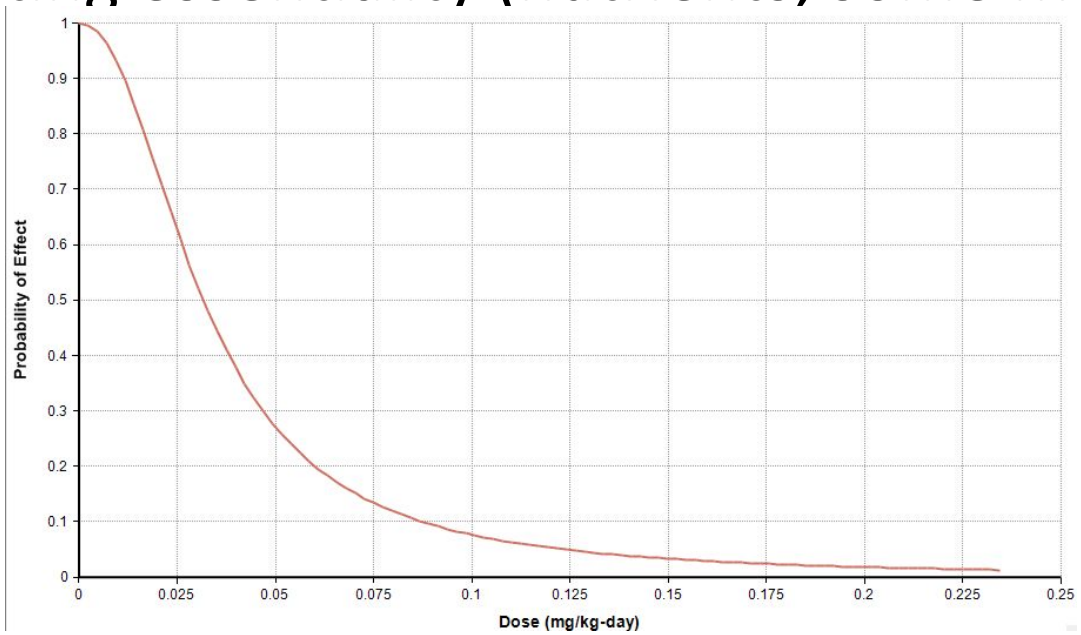
Dose-Response models: Chemical (Chronic)

- Acute models plus other non-linear models
- Replicates
  - FDA published models
  - Options in EPA's Benchmark Dose Software (BMDS)
- Doses in mass/kg-bw per day

- Cumulative Lognormal
- Empirical
- Gamma
- Linear by Slope Factor
- Logistic
- Log-Logistic
- Log-Logistic with Background
- Multistage
- Non-Threshold Linear
- Probit
- Restricted Log-Probit (LogNormal)

Dose-Response models: Nutrients

- FDA-iRISK offers several monotonically-decreasing dose-response models for use in evaluating essentiality (nutrients, some metals)
- Models include:
  - Decreasing Logistic
  - Decreasing Log-Logistic
  - Decreasing Probit
  - Empirical



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Health Metrics

Cost of Illness, DALYs and QALYs

Options to Value Burden of Illness

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

  (Note: FDA-iRISK also provides #illnesses as a metric for risk ranking, e.g., same hazard in different foods)

- FDA-iRISK provides 2 main options
  - Monetary (dollars, euros, etc.)
  - Health-based: Disability-Adjusted Life Years (DALYs) or Quality-Adjusted Life Years (QALYs) lost

- The number of cases (predicted by the tool), can be multiplied by either of these values to estimate overall burden.

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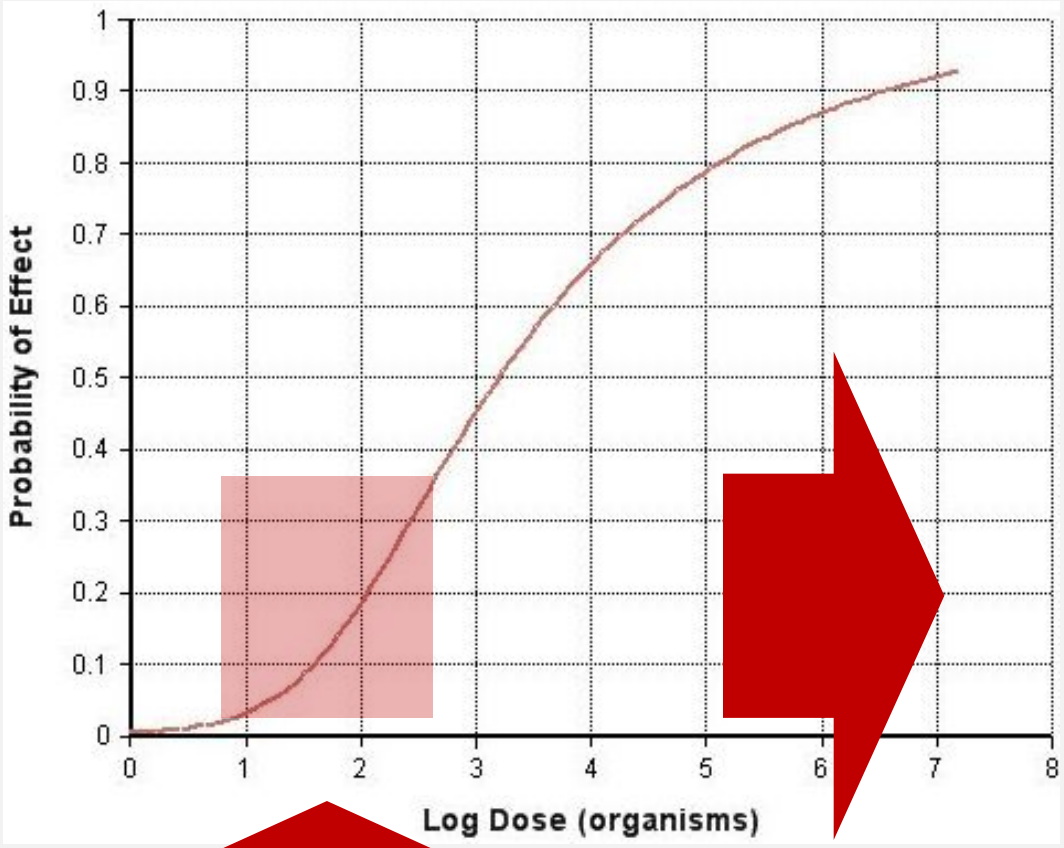
Number of Cases (Illnesses) Estimated from Dose Response Model Output



Dose distribution

Mean Risk of Illness

(per serving for acute or per consumer for chronic)

Number of servings (acute) or consumers (chronic)

Number of cases

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Option 1: Cost of Illness

- A monetary value of societal cost per case of illness

Example 1: for Salmonellosis

Based on estimated annual economic cost* of illness and death caused by *Salmonella* of $2.7 billion in the US, and estimated annual cases just over 1 million

- Average cost per illness ca. $2000

Example 2: for Salmonellosis, cost estimate by Minor et al., Risk Analysis 35(6), 2015

- Average cost per illness $5,337

* 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
  - Kemmeren et al., 2006 (RIVM report)
  - WHO Global Health Estimates

  http://www.who.int/healthinfo/global_burden_disease/en/

- The Australian Burden of Disease Study
  - http://www.aihw.gov.au/bod/

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 disability weight of 1

- Population burden is DALY/case x Cases

Selected Health Outcomes and their Severity Weights

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

(Severity weights are also called disability weights)

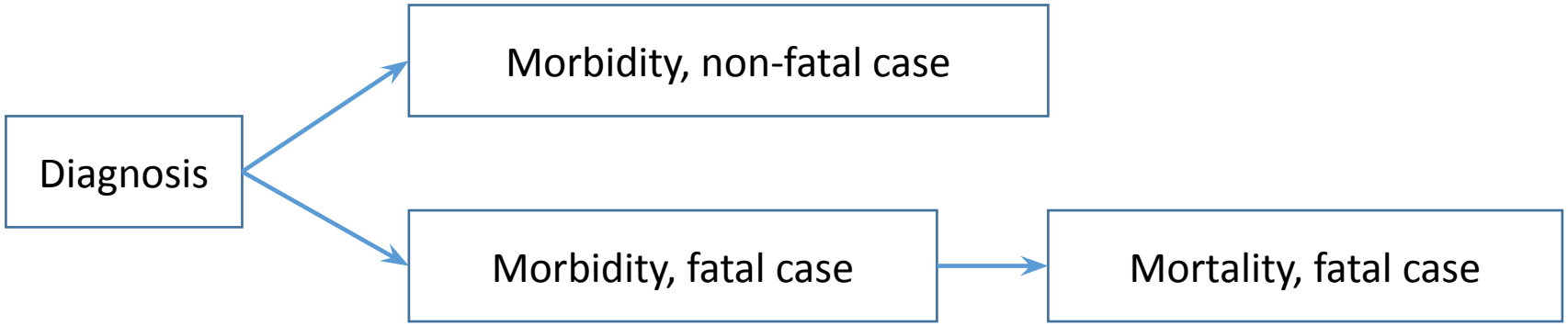
The Health Metric Assigns a Value to Each Case of Illness

- 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

Note that this is equivalent to obtaining a monetary value (average cost per case) by dividing total cost by number of cases

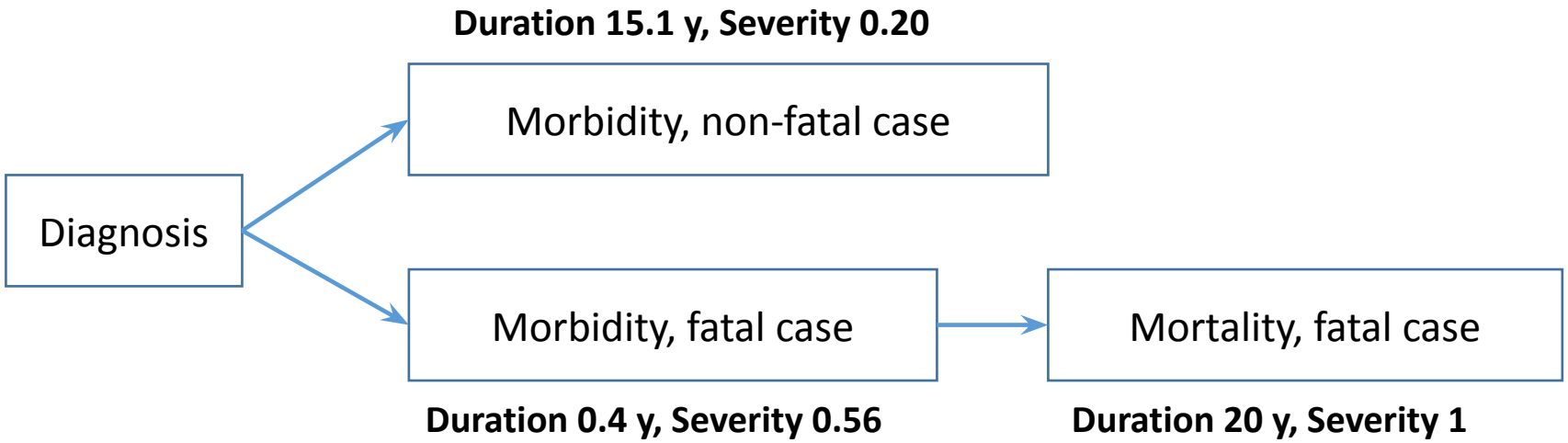
Health Metric Example: Liver Cancer DALY per Case

- Step 1: Identify outcomes



Health Metric Example: Liver Cancer DALY per Case

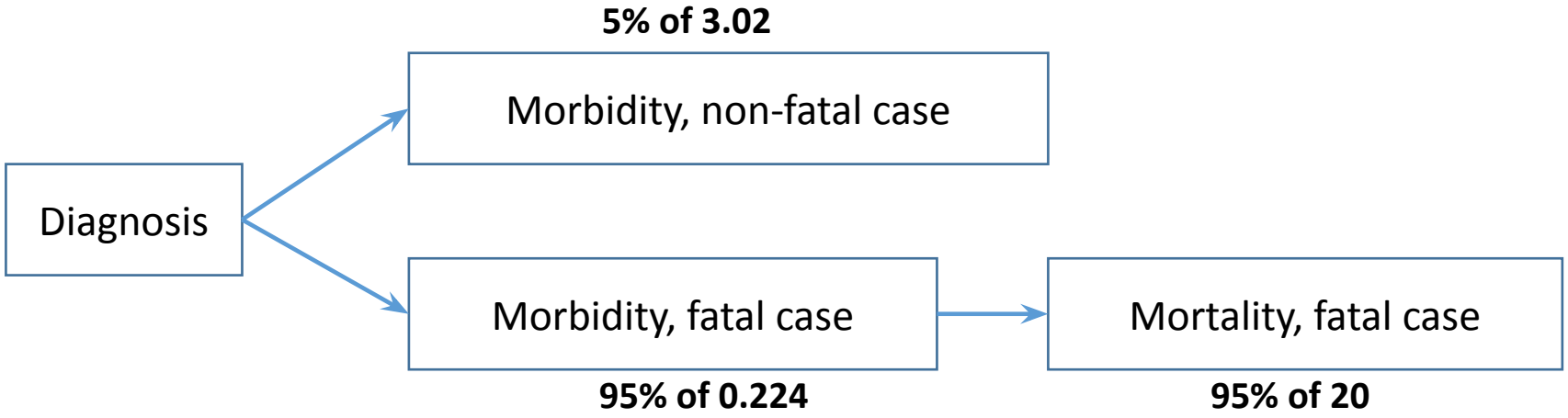
- Step 2: Assign a DALY to each outcome



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

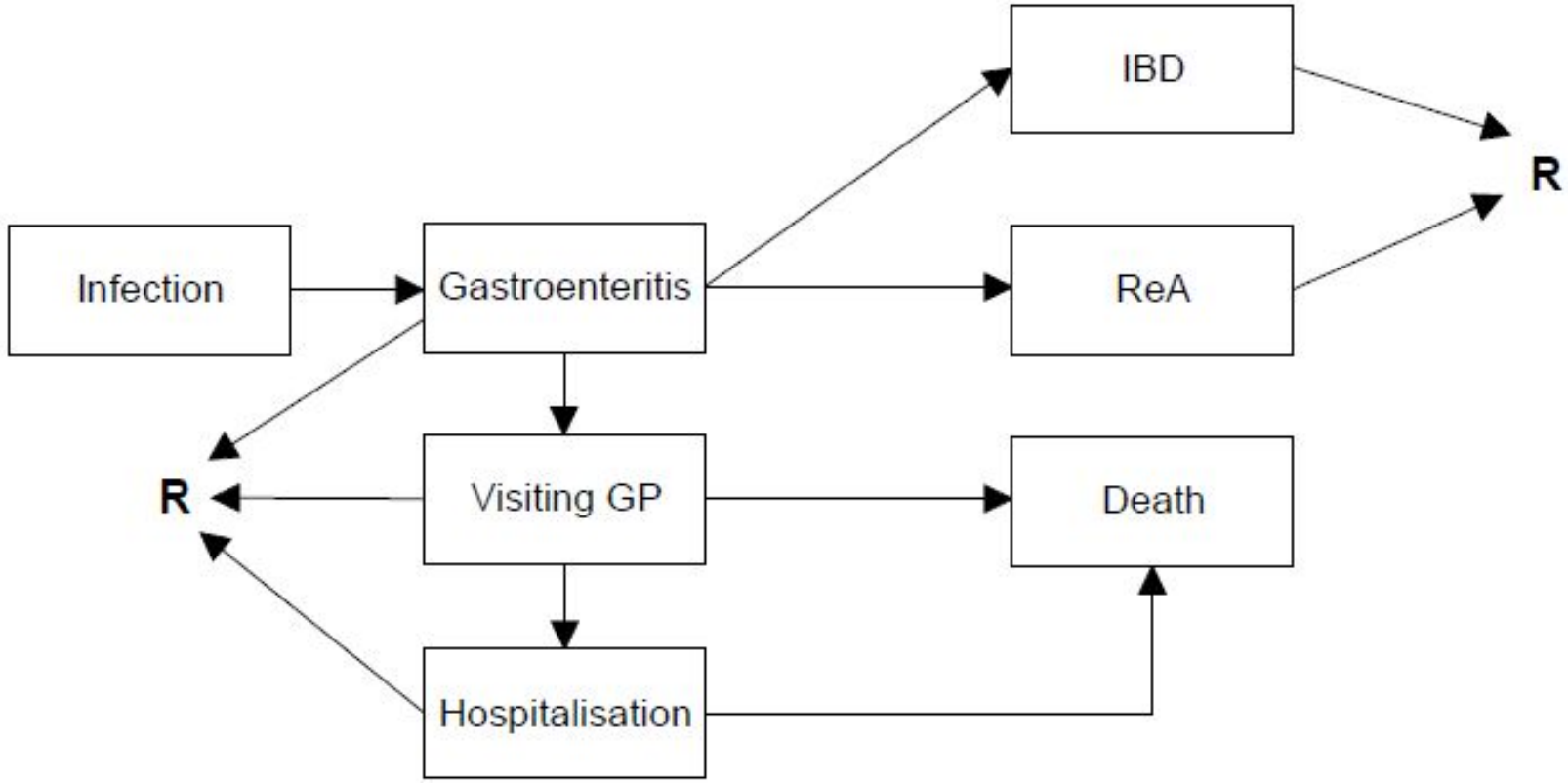
Health Metric Example: Liver Cancer DALY per Case

- Step 3: Weight according to the proportion of each outcome and sum to find the weighted average (19.4)



Health Metric Example: Salmonellosis DALY per Case

- Step 1: Identify outcomes



Health Metric Example: Salmonellosis DALY per case

- Step 2: Assign a DALY to each outcome

Possible Outcomes	Severity Weight	Duration	DALY per case
GE, no GP	0.001	0.015	0.000015
GE, GP only	0.011	0.029	0.00032
GE, hospitalized	0.017	0.044	0.00075
GE, fatal	1	40	40
Reactive Arthritis, no GP	0.127	0.608	0.077
Reactive Arthritis, GP only	0.21	0.608	0.128
Reactive Arthritis, hospitalized	0.37	0.608	0.225
Inflammatory Bowel Disease	0.26	40	10.4

Source of raw data: Kemmeren et al., 2006 (RIVM report)

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Health Metric Example: Salmonellosis DALY per case

- Step 3: Weight according to the proportion of cases

Possible Outcomes	Severity Weight	Duration	DALY per case	Fraction of all cases	DALY weighted by fraction
GE, no GP	0.001	0.015	0.000015	0.86	0.00001
GE, GP only	0.011	0.029	0.00032	0.15	0.00005
GE, hospitalized	0.017	0.044	0.00075	0.02	0.00001
GE, fatal	1	40	40	0.0011	0.045
Reactive Arthritis, no GP	0.127	0.608	0.077	0.01	0.0008
Reactive Arthritis, GP only	0.21	0.608	0.128	0.0023	0.0003
Reactive Arthritis, hospitalized	0.37	0.608	0.225	0.0002	0.00005
Inflammatory Bowel Disease	0.26	40	10.4	0.0002	0.002
SALMONELLOSIS					**0.048**

Source of raw data: Kemmeren et al., 2006 (RIVM report)

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Two Health Metrics for Salmonellosis

- Cost per illness

  e.g., $5,337 per case

- DALY value

  e.g., 0.048 DALY per case

The number of cases (predicted by the FDA-iRISK taking into account contamination in food, consumption and dose-response), can be multiplied by either of these values to estimate overall burden.

Process Models

Process Model (to estimate contamination in food)

- Links the food to the hazard
- Is specific to each food-hazard combination, and is defined for each combination
  - 1 food may have multiple process models if multiple hazards are of interest
- Describes the behavior of the hazard in response to the processes imposed on the food prior to consumption

Scope of Process Models

- Scope is controlled by the user
- Only condition is that the process model links to consumption
- Starting point will depend upon the purpose of assessment, data availability, and desired level of complexity

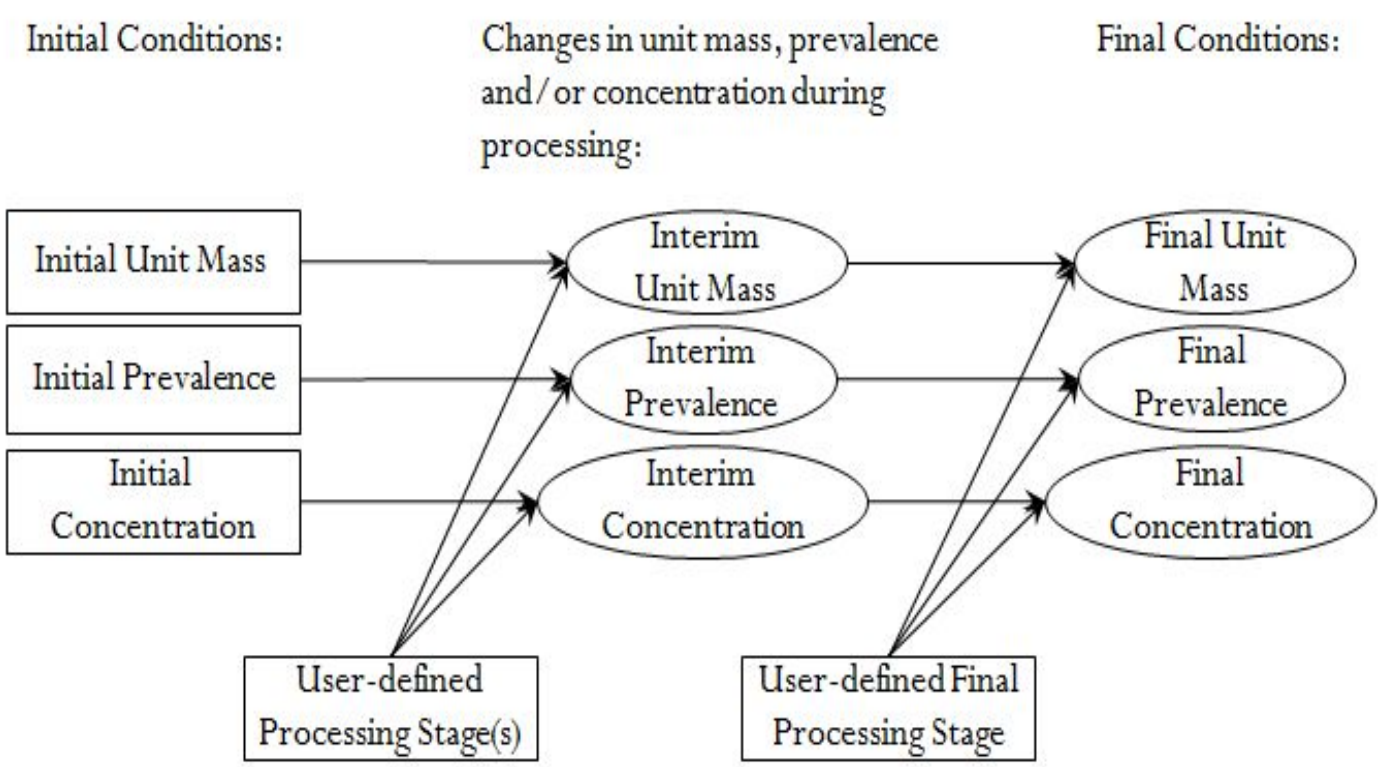
The Process Model

- The user describes how the prevalence or level (or mass) of the hazard is affected at each stage of processing and preparation of the food

- FDA-iRISK creates a process model which combines all these effects and predicts the final prevalence and level of hazard in the food at consumption

Mathematical structure of a process model

- User inputs initial conditions and defines sequential process stages
  - defines effect of processing on unit mass, prevalence, and/or concentration
- FDA-iRISK calculates these values after every stage until the final values are obtained



FDA-iRISK Process Model

- Provides a template for users to develop a process model with multiple steps, choose a process type, and populate the model with data

- Lists process types through which the hazard concentration and prevalence can change at various steps in food chains, such as:
  - environmental contamination (increase by addition)
  - decrease/inactivation
  - increase/growth (microbial only)

FDA-iRISK Process Model: "Process Types"

- **Describes a typical process step where contamination occurs, increases, or decreases**

  (built-in choices for users to select, as part of process model)

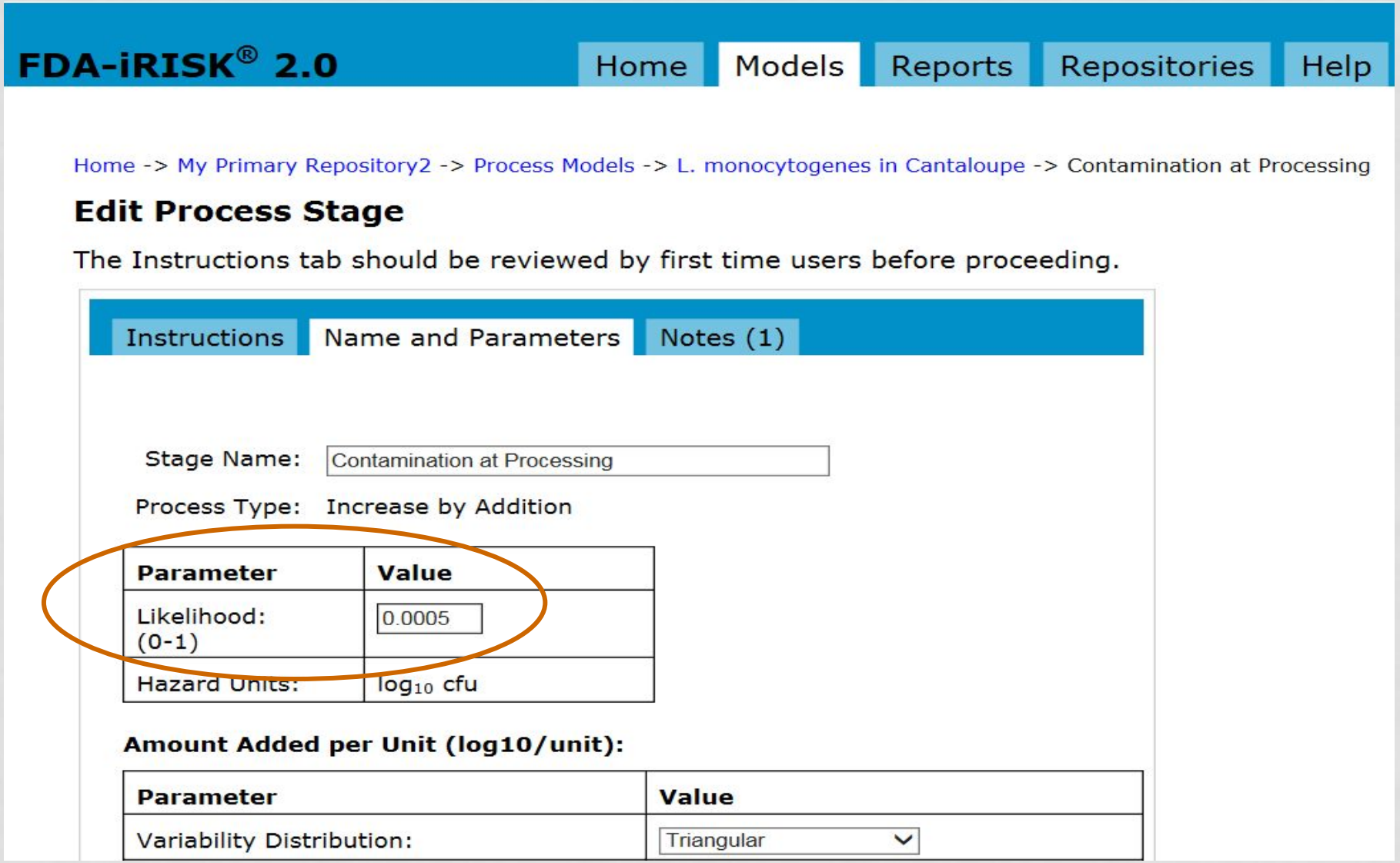
1. Increase by addition	5. Pooling	9. Redistribution (partial)
2. Increase by growth	6. Partitioning	10. Redistribution (total)
3. Increase by cross-contamination	7. Evaporation or Dilution	11. No change
4. Decrease	8. Sampling	

12. Set Maximum Population Density

Increase by Addition

- Represents a contamination event
- Defined by amount added per unit, and likelihood of addition
  - Prevalence may increase
  - Average concentration may increase or decrease (concentration describes contaminated units only)
  - Unit mass is unchanged

Process Model Example: Treatment of Rare Events



Enable modeling likelihood <0.001

Increase by Growth (Microbial Hazards Only)

- During storage or breakdown in cold chain etc.
- Defined by log increase in concentration
  - Prevalence is unchanged
  - Concentration increases by user-supplied factor
  - Unit mass is unchanged
- Version 4.0 also includes predictive growth models

Increase by Cross-contamination (Microbial Hazards Only)

- This process type adds contamination to a unit using a defined pool of organisms and transfer rate.
- Similar to the addition process type
- User can specify a likelihood of the event
- Defined by log increase in concentration
  - Prevalence may increase
  - Average concentration may increase or decrease (concentration describes contaminated units only)
  - Unit mass is unchanged

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Decrease

- Inactivation (thermal processing, antimicrobial treatments, etc.) of microbes, or depletion (denaturation, volatilization etc.) of chemical hazards
- Defined as proportion of hazard lost
  - Prevalence may decrease for microbes only (if concentration falls below 1 cfu/unit mass)
  - Concentration decreases
  - Unit mass is unchanged
- Version 4.0 increase decrease by inactivation model for microbial hazards

Pooling

- Combination of units into larger unit mass
- Defined by new unit mass
  - Prevalence is determined by probability that all combined units are “clean” – this value is subtracted from 1
  - Concentration is determined by the number of positive units in each new unit
    - Determined by the previous prevalence and the difference in size between old and new mass
  - Mass is new unit mass (defined by user)

Partitioning: Chemical

- Dividing mass of food into smaller units
- Defined by new unit mass
  - Prevalence is unchanged
  - Concentration is unchanged
  - Mass is new unit mass (defined by user)

Partitioning: Microbial

- Dividing mass of food into smaller units
- Defined by new unit mass
  - Prevalence is ≤ previous prevalence
  - Concentration is ≥ previous concentration
  - Mass is new unit mass (defined by user)

Evaporation and Dilution

- Drying of food or adding water or other (uncontaminated) diluent
- Defined by multiplier of concentration
  - Prevalence is unchanged
  - Concentration changes by user-supplied factor
  - Unit mass changes according to same factor

Partial Redistribution

- Cross-contamination among individual units of food (not environmental contamination)
- User specifies multiplier for prevalence
  - Prevalence increases while concentration decreases by the same factor

Important to note for microbial pathogens

  - The increase in prevalence may be constrained by the number of "bugs" available in the system
  - Unit mass is unchanged

Total Redistribution

- Total cross-contamination among individual units of food; no user input required
  - For chemical hazards, prevalence becomes 1
  - For microbial hazards, prevalence becomes 1 if the total microbial load will support at least 1 cfu per unit
  - Concentration decreases by the same factor as prevalence is increased
  - Unit mass is unchanged

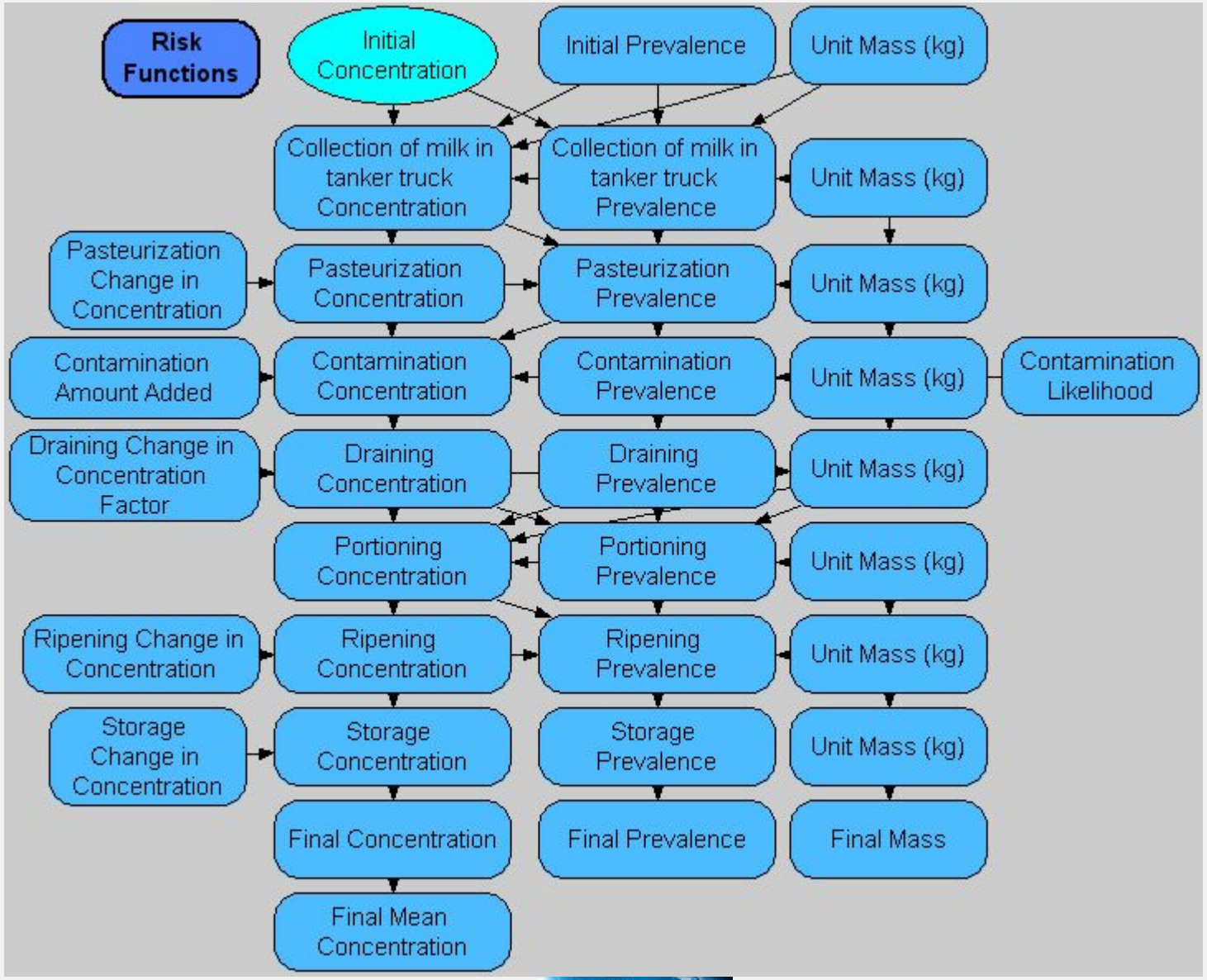
Chemical Process Models

- Chemical concentration is mass/mass and assumed to be homogeneous
- Process types available include:
  - Addition
  - Decrease
  - Pooling and Partitioning (i.e. separation into smaller units)
  - Evaporation and Dilution
  - Partial and Total Redistribution
  - Sampling

Microbial Process Models

- Follows the concentration in cfu/g or pfu/g (input can be on $\log_{10}$ scale)
- Concentration is defined only for contaminated units, therefore it will never equal zero
  - Can define initial units as uncontaminated
- If FDA-iRISK estimates fewer than 1 cell per unit of food, the prevalence will decrease
- All process types available including growth

Any number of Process Stages can be defined, in any order



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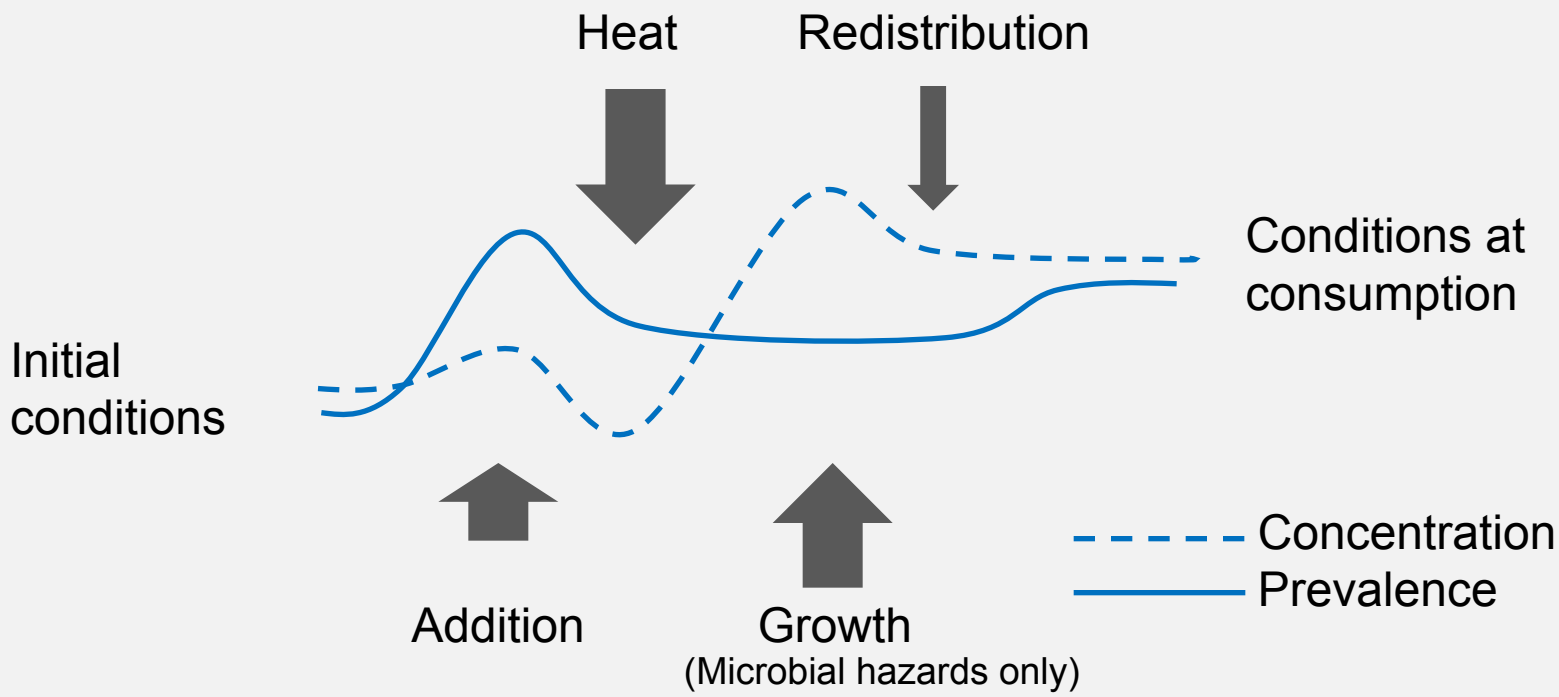
FDA-iRISK Simulates Level and Prevalence through Stages of Processing



The user inputs initial conditions and defines processes.
FDA-iRISK uses Monte Carlo simulation to estimate final prevalence, levels and unit size.

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Features of the Process Model

- Quantitative estimation is enhanced by:

Flexibility:

- Process model is open-ended, built of any combination of several process types:
  - addition, growth, decrease, partitioning, pooling, evaporation/dilution, partial or total cross-contamination

Probabilistic Approach:

- Inputs can be fixed values or distributions
- Monte Carlo simulation is used to obtain a concentration distribution, and a final prevalence at consumption

Results and Reports

Output Formats and Report Layout

- Report types
  - Full report (PDF, Word)
  - Summary report (Excel)
  - Convergence report (Excel)
  - Model summary report (data only, no results; PDF)
- Choices for risk ranking endpoint
  - Exposure (Dose)
  - Illnesses
  - Health Metric (DALYs, QALYs, COI)
  - Health Metric by Eating Occasion or Consumer

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Sensitivity Analysis in FDA-iRISK

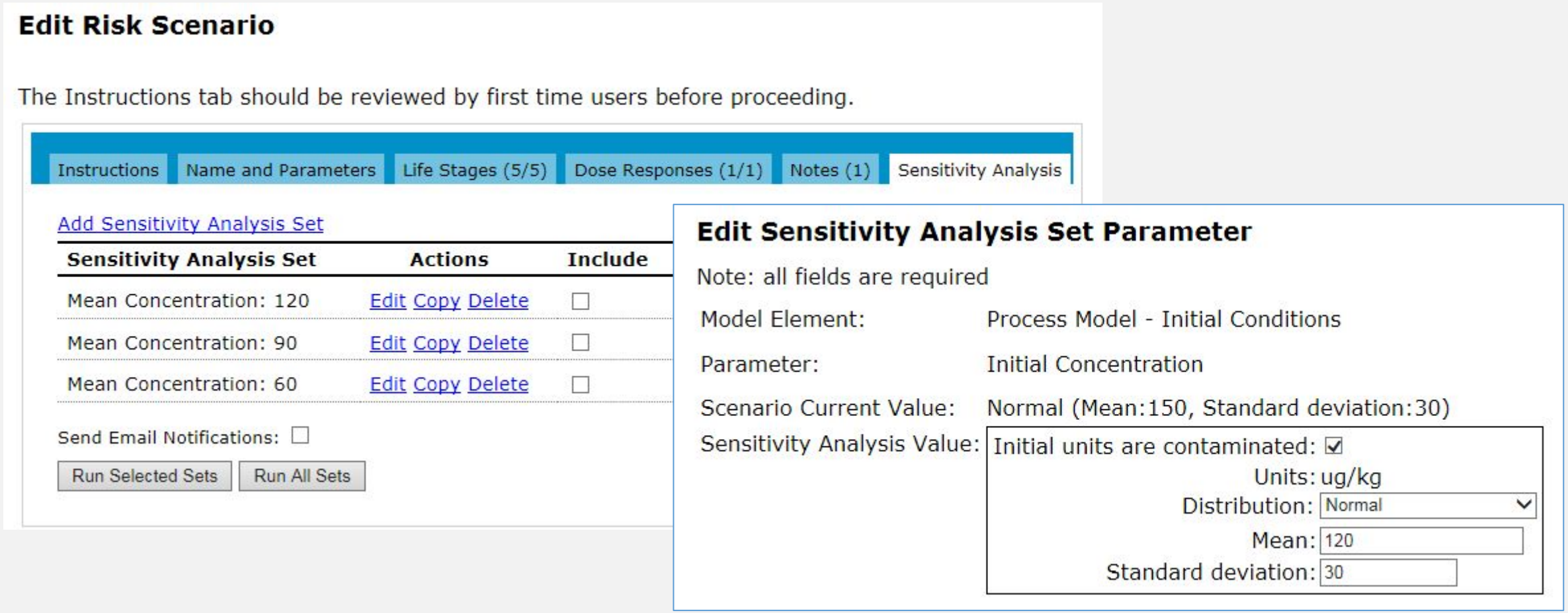
"what-if"

Ask FDA-iRISK – “what if”?

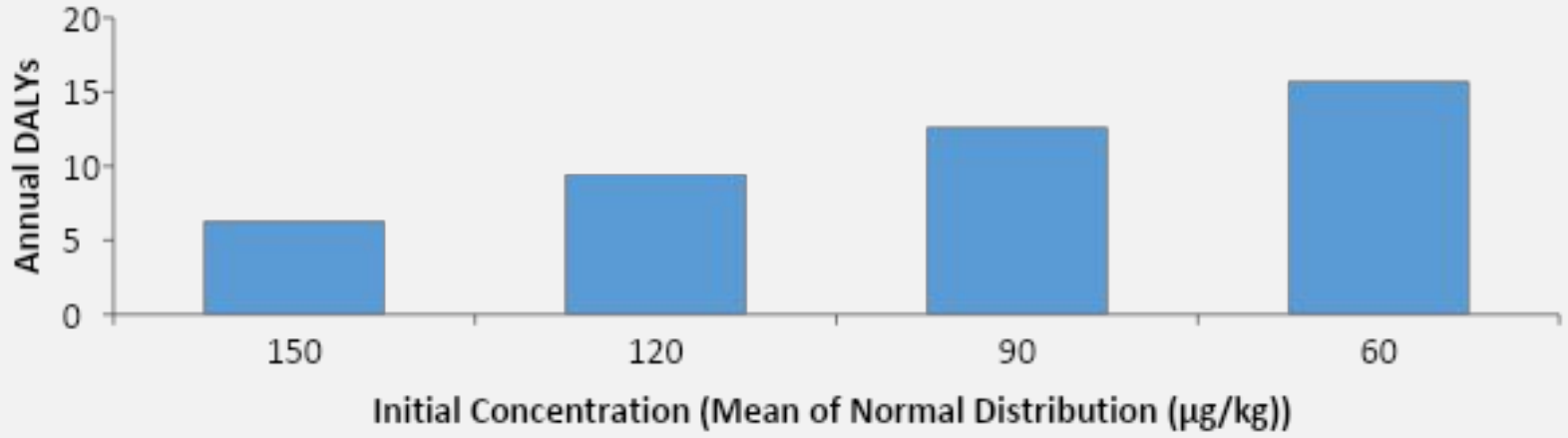
- FDA-iRISK allows evaluation of alternative scenarios and specific interventions
  - alternative scenarios for dose-response, consumption
  - interventions applied at any step(s) of food production / manufacturing / handling, from farm to table

… using a baseline risk scenario

Sensitivity Analysis



Sensitivity Analysis: Impact of Initial Concentration of Aflatoxin B1



Scenario or Scenario Group	Total DALYs per Year
Process Model Initial Concentration: Normal (Mean:150, Standard deviation:30)	15.7
Process Model Initial Concentration: Normal (Mean:120, Standard deviation:30)	12.6
Process Model Initial Concentration: Normal (Mean:90, Standard deviation:30)	9.44
Process Model Initial Concentration: Normal (Mean:60, Standard deviation:30)	6.30

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Working as a Team in FDA-iRISK

Sharing, Importing, Copying

Working with others

- Multiple repositories per user
- Invitations can be sent to other users to individual repositories
  - Can specify which scenarios in a given repository to share
  - must check the “Shared” box to enable sharing of scenarios **within** a repository

Working with others

- Import and copy :
  - entire repositories
  - individual model elements
- At this time individual scenarios cannot be imported, but process model import will bring all elements needed to reproduce a scenario

Guided walk-through of FDA-iRISK

Case Studies

Case study 1: Chemical Hazard

Case study 2: Microbial Hazard

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food safety modeling tool

Notes

- 2 case studies will be presented
  - 1 chronic chemical hazard, 1 microbial hazard
- Models are available in Sample Models repository in FDA-iRISK
- These scenarios are for illustration purposes only and results are not endorsed as estimates of risk.
  - The results and the risk estimates presented in the example are based on the data used and assumptions made. The predicted illnesses and DALYs will change if model inputs are different for contamination, consumption, dose-response and health metric.

Case Study 1:
Chronic Chemical Hazard

Aflatoxin B1 in Tortilla Chips

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Scenario description

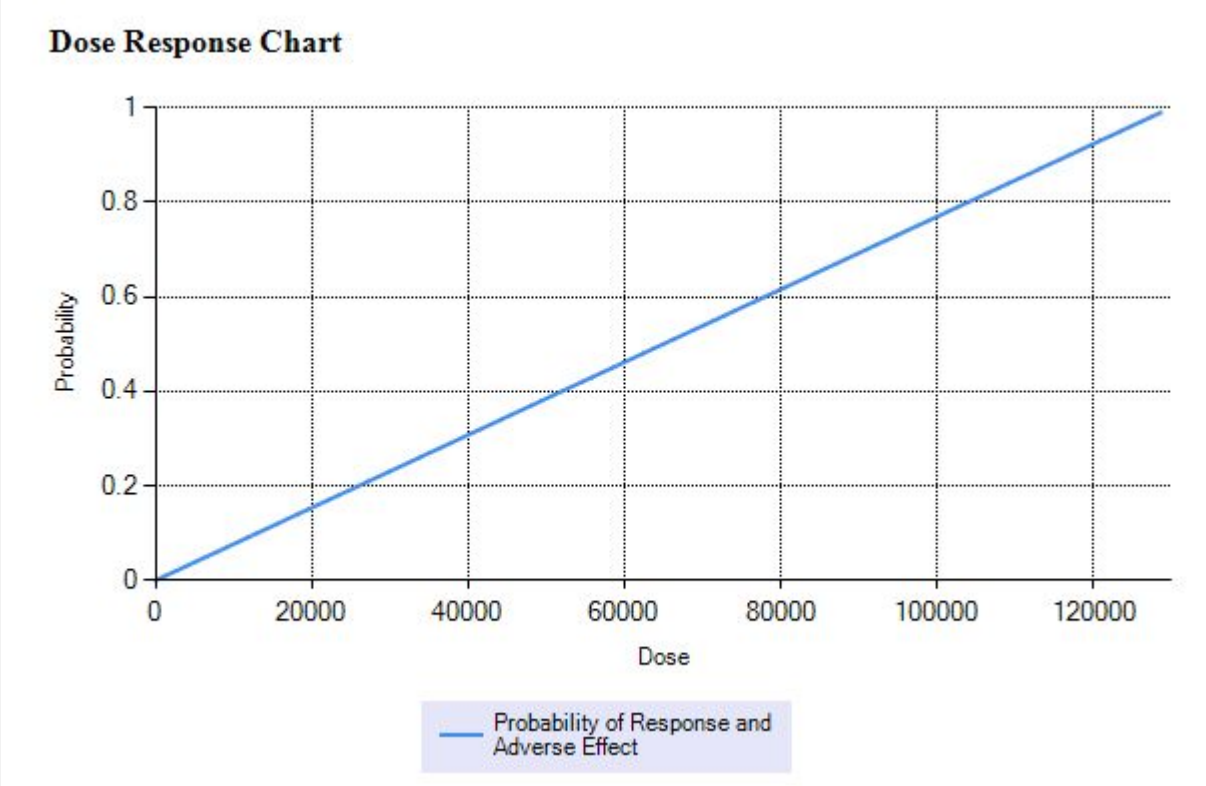
- Aflatoxin B1 is produced by the mold, *Aspergillus* (*flavus* and *parasiticus*)
- Aflatoxin B1 is a human carcinogen
- *Aspergillus* molds can grow in crops such as grains, nuts, and legumes, and as such there is a risk of contamination of tortilla chips
- Health endpoint considered is liver cancer
- Hazard metric of interest is DALY
- Interest in understanding how the contamination level affects the

Data: Consumption

- Estimated 25 million annual consumers of tortilla chips
- 5 population groups:
- Children 1 – 5
  - Consumption 6.0 g/day, Body weight = Uniform [10-30 kg], Span = 5 years
- Children 6 – 10
  - Consumption 9.0 g/day, Body weight = Uniform [20-60 kg], Span = 5 years
- Children 11 – 15
  - Consumption 13.0 g/day, Body weight = Uniform [30-70 kg], Span = 5 years
- Youth 16 – 20
  - Consumption 18.0 g/day, Body weight = Uniform [60-90 kg], Span = 5 years
- Adults 20+

Data: Dose Response

- Model and parameters were generated by replicating the dose-response models reported in the FDA draft quantitative assessment of Aflatoxin B1 in tortilla chips
- Linear by Slope Factor
  - Slope: 7.7E-6 (1/(ng/kg-day))
  - Probability of Adverse Effect Given Response: 100%



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Data: Health Metric – Liver Cancer

- The individual morbidity sequelae, the disability weight of each, and the duration of each are from the liver cancer tables of the Australian Burden of Disease study
- 95% of liver cancers expected to be fatal
- Estimated 4.8 months survival from time of fatal diagnosis
- Life expectancy in U.S. at time of death from liver cancer is about 20 years

Data: Health Metric – Liver Cancer

Health Endpoint	Duration	Unit	Severity	DALY	Fraction of Cases	Weighted DALY	
Morbidity: fatal liver cancer	0.4	Y	0.56	0.22400	0.95	0.21280	Delete
Morbidity: non-fatal liver cancer	15.1	Y	0.2	3.0200	0.05	0.15100	Delete
Mortality: fatal liver cancer	20	Y	1	20.000	0.95	19.000	Delete
		Y					Add
Totals:					1.950000 (> 1)	19.4	

FDA-iRISK® food safety modeling tool

Data: Process Model – Initial Conditions

- Assume 1% of tortilla chips are contaminated with Aflatoxin B1
- Initial concentration can be approximated by a normal distribution with: mean = 150 µg/kg; and standard deviation = 30 µg/kg

Contamination estimates based on data from literature
Castillo-Uruetaab et al. (2011)

Process model : process stages

- Contamination data was available at the point that can be assumed representative of contamination at consumption
- Purpose of the scenario is not to explore role of individual process stages in determining risk
- Therefore no process stages are required in this particular scenario

Scenario Construction

- Food = tortilla chips
- Population Group = 5 groups,
  - children 1-5, children 6-10, children 11-15, youth 16-20, and adults 20+
- Estimated 25 million consumers annually
- Hazard = Aflatoxin B1
- Dose response = Linear by Slope Factor
- Health metric = DALYs calculated from endpoints

Scenario

Instructions | Name and Parameters | Population Groups (5/5) | Dose Responses (1/1) | Notes (0) | Sensitivity Analysis

Annual Consumers: 25E6

Population Group	Consumption	Span In Years	Include
Adults 20+	Fixed Value (Value: 15) g/day	57	☑
Children 11-15	Fixed Value (Value: 13) g/day	5	☑
Children 1-5	Fixed Value (Value: 6) g/day	5	☑
Children 6-10	Fixed Value (Value: 9) g/day	5	☑
Youth 16-20	Fixed Value (Value: 18) g/day	5	☑
		Total Span Included:	77

Instructions | Name and Parameters | Population Groups (5/5) | Dose Responses (1/1) | Notes (0) | Sensitivity Analysis

Dose Response	Health Metric	Include
Aflatoxin B1 Linear by Slope Factor	Liver Cancer (19.4) ▾	☑

Save | Save and Close | Close

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Results from Illustrative Scenario

Scenario or Scenario Group	Total DALYs per Year
Aflatoxin B1 in Tortilla Chips	15.7

Scenario	Lifecourse Duration	Eating Occasions or Consumers	Total Illnesses	Mean Risk of Illness	Total DALYs per Year	DALYs Per EO or Consumer	Total DALYs per Year (Weighted)
Aflatoxin B1 in Tortilla Chips	77	2.50E+7	0.811	3.24E-8	15.7	6.30E-7	15.7

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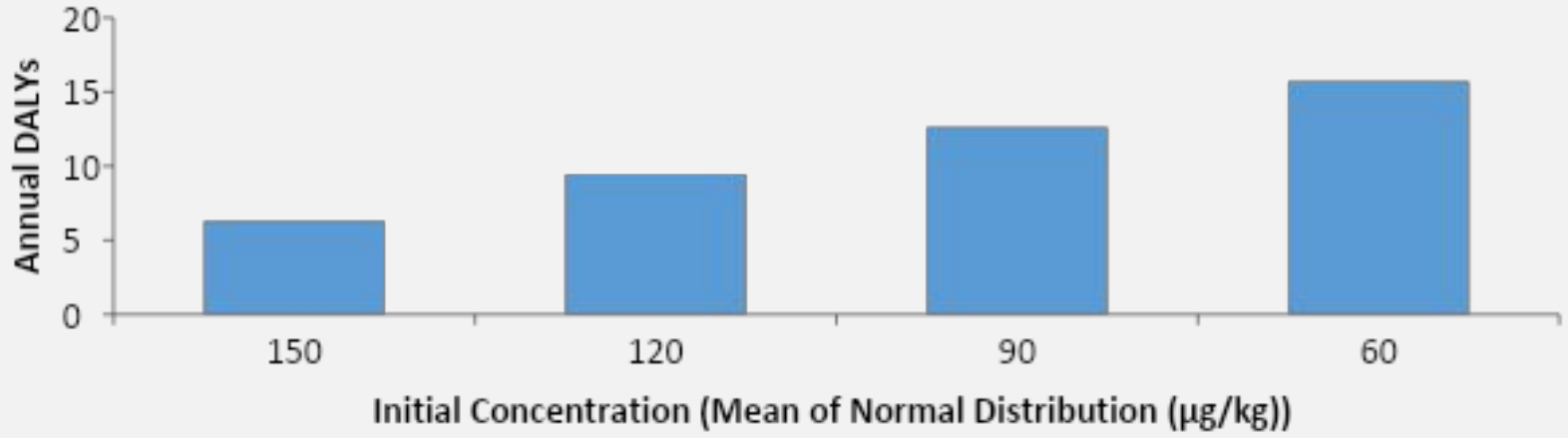
Sensitivity Analysis: Impact of Initial Concentration



Scenario or Scenario Group	Total DALYs per Year
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Process Model Initial Concentration: Normal (Mean:90, Standard deviation:30)	9.44
Process Model Initial Concentration: Normal (Mean:60, Standard deviation:30)	6.30

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Case Study 2: Microbial Hazard

L. monocytogenes in Fresh-Cut Cantaloupe

Scenario description

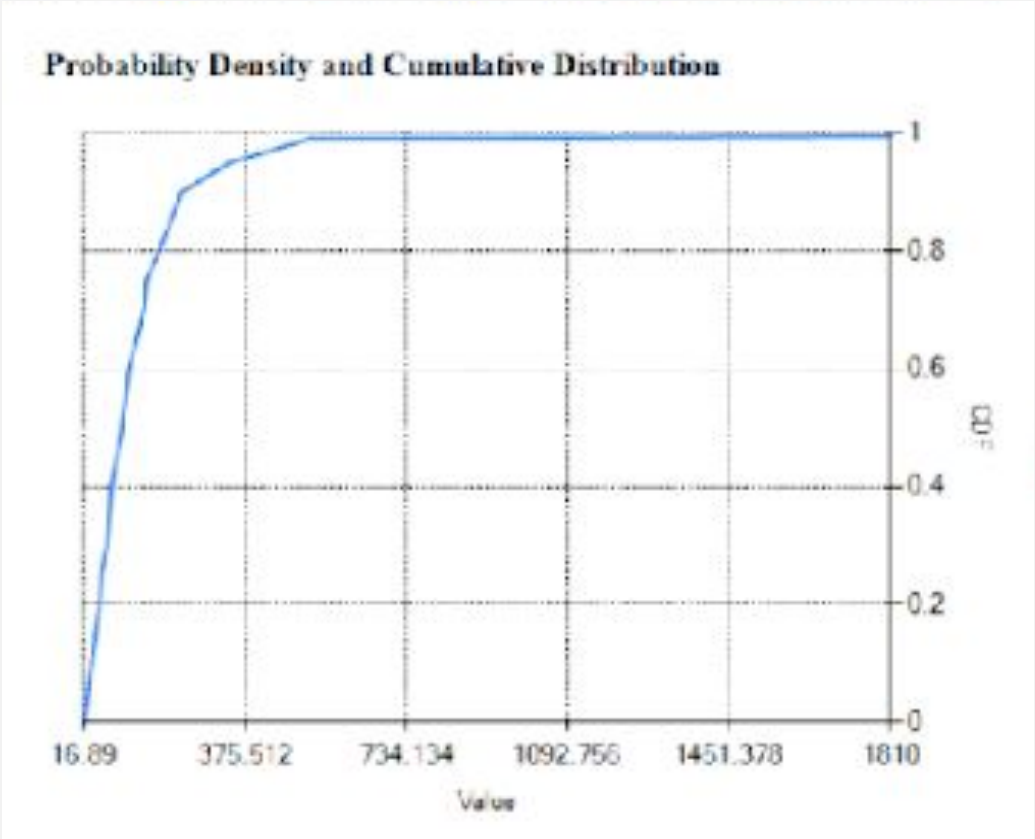
- Instances of the contamination of cut cantaloupe with *L. monocytogenes* available (prevalence and levels)
- There is additional concern about the cross-contamination of *L. monocytogenes* during the preparation (specifically the cutting) of cantaloupe from the cutting surface to the cantaloupe
- There is specific interest in the risk to the group of adults 65 years and over
- Hazard metric of interest is DALY
- Interest in understanding how the likelihood of the occurrence of cross-contamination during preparation affects the overall burden

Data: Consumption – serving size

- Specify serving size distribution

Based on NHANES 2007-2010 cantaloupe consumption by "seniors"

Able to use percentiles data directly in FDA-iRISK to specify the consumption distribution, as a cumulative empirical distribution

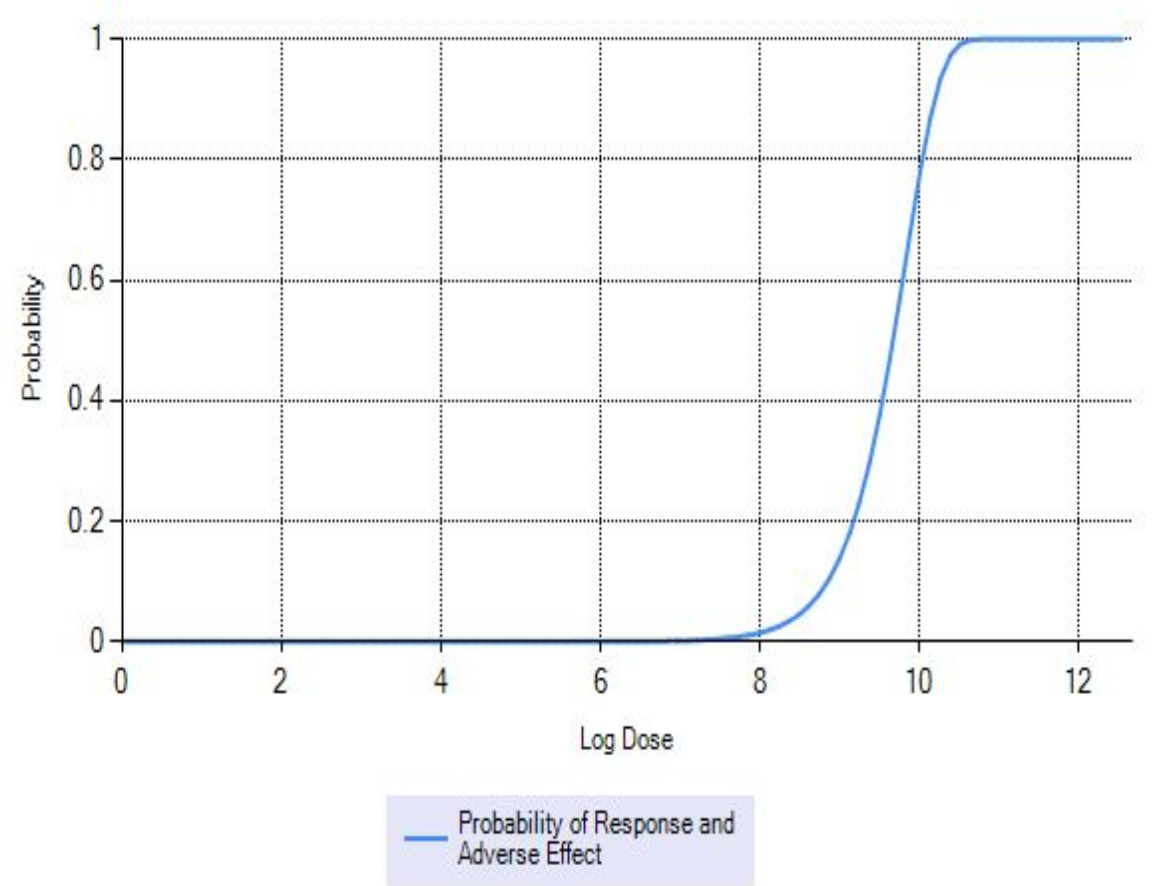


Data: Consumption – number of servings

- Analysis based on the NHANES data (2007-2010) shows that the number of eating occasions is 3,066,467 per day for the adults 55+ subpopulation.
- The total number of servings per year is
- 365 x 3,066,467 = 1,119,260,455 for 55+
- Based on the US census data (2013) 26.6 % of the population are 55+; of those, 14.2% are 65+
- Therefore number of eating occasions for 65+ is

Data: Dose Response

- Available in scientific literature, Pouillot et. al (2015)
  - Exponential Dose-Response for 65+, (healthy, no underlying conditions)
- Exponential model template is available in FDA-iRISK
- Enter model parameter
  $r = 1.49 \times 10^{-10}$



Probability of adverse effect given

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Data: Health Metric

- Health endpoints and severity weights, duration, fraction of cases, and mortality rate were based on data from scientific literature Kemmeren et al. (2006) and McLauchlin et al. (2004).
- Assumed these data (mostly from the Netherlands and the U.K.) are applicable to the U.S. population
- Adapted where necessary

Data: Health Metric for Listeriosis in Adults 65+

Health Endpoint	Duration	Unit	Severity	DALY	Fraction of Cases	Weighted DALY
Gastroenteritis: Visiting GP	10 [illegible]	D	[illegible]	0.011467	[illegible]	0.0025227
Meningitis	0.5	Y	0.32	0.16000	0.22	0.035200
Mortality in Adults 60 and over	14	Y	1	14.000	0.177	2.4780
Neurological Sequelae from Acquired	7	Y	0.2857	1.9999	[illegible]	0.061597
Pneumonia	0.02	Y	0.04	0.00080000	0.15	0.00012000
Sepsis	0.02	Y	0.93	0.018600	0.37	0.0068820
		Y				
Totals:					1.167800 (> 1)	2.58

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Data: Process Model – Initial Conditions

- Based on preliminary data obtained for RTE cut cantaloupe at retail from a market basket survey (unpublished FDA data)
- 425 samples collected across four states (Maryland, California, Connecticut, Georgia) over one year with 5 positives in 25g detection test
- An MPN assay (4 dilutions x 3 tubes protocol, corresponding to 10g, 1g, 0.1g, 0.01g) was used for enumeration of the level in the positive
- The MPN patterns observed were (3,0,0,0), (2,1,0,0), (2,1,0,0), (2,0,0,0) and (0,1,0,0).

Assumption: the data can be used to describe the contamination pattern of all cantaloupe consumed by the population of interest.

Data: Process Model – Initial Conditions

- Using method presented by Pouillot et al (2013), we determined

  Prevalence = 1.3% in cut cantaloupe

  Concentration = Normal (-0.97, 0.34) log CFU/g

- Initial unit size = 25g (corresponding to prevalence in study)

- Maximum Population Density = 9 Log CFU/g (based on multiple studies)

Process Model:

Two stages of interest: Handling at home & consumer storage

- Handling at home
  - A hypothetical process step illustrating the use of "Increase Addition" to represent a rare cross-contamination event during handling in the home
  - A likelihood of occurrence of 1 in 2000 is used for illustrative purposes
- Consumer storage
  - Using data on consumer storage time and temperature distributions for *L. monocytogenes* growth to estimate the distribution of growth
  - Empirical distribution generated from predictive modeling used as input in FDA-iRISK

Scenario Construction

- Food = Cantaloupe
- Population Group = 1 group, adults 65+, 597,500,000 eo/yr

- Hazard = *L. monocytogenes*
- Dose response = Exponential ($r=1.49x10^{-10}$)
- DALY metric = calculated from health endpoints

- Process model = Initial conditions + 2 process stages

FDA-iRISK® food safety modeling tool

Initial Conditions

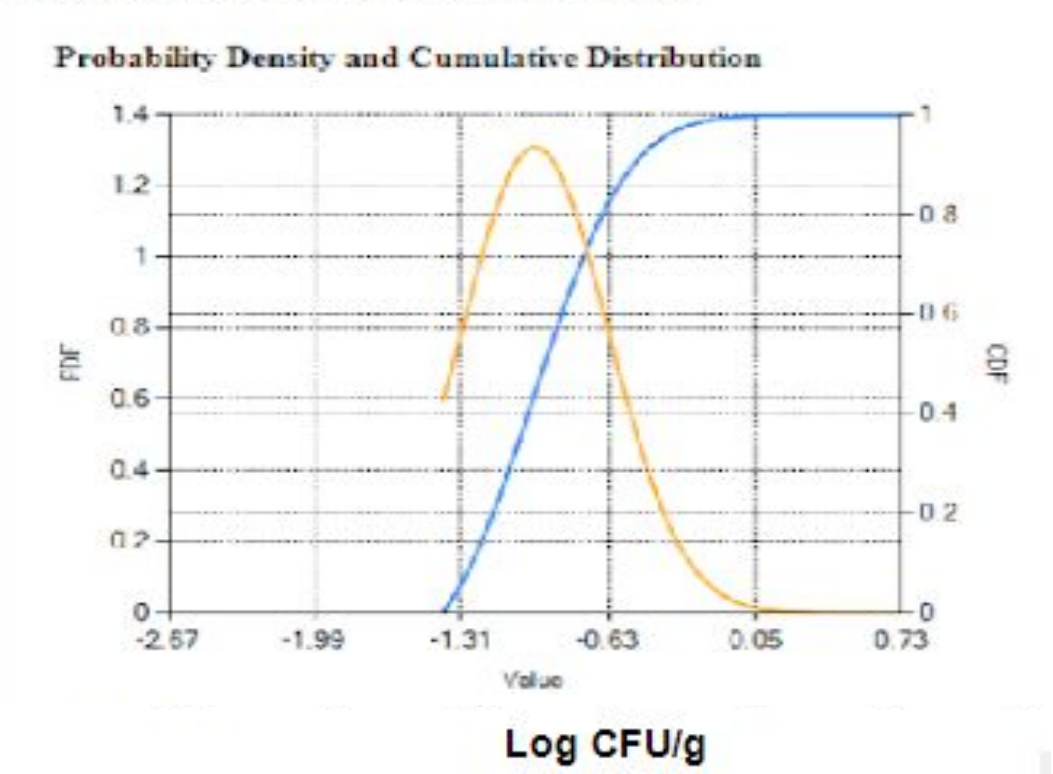
- Prevalence = 0.013
- Concentration = Normal (mean = -0.97, sdev = 0.34) log CFU/g

Please correct the following for initial concentration:

Selected mean and standard deviation will result in values less than the minimum value (-1.398) at points beyond 4 standard deviations. YOUR SETTINGS HAVE BEEN SAVED but this may result in some truncation and/or unexpected results in the model. Consider reducing the standard deviation or using a distribution with a fixed range, such as the beta PERT.

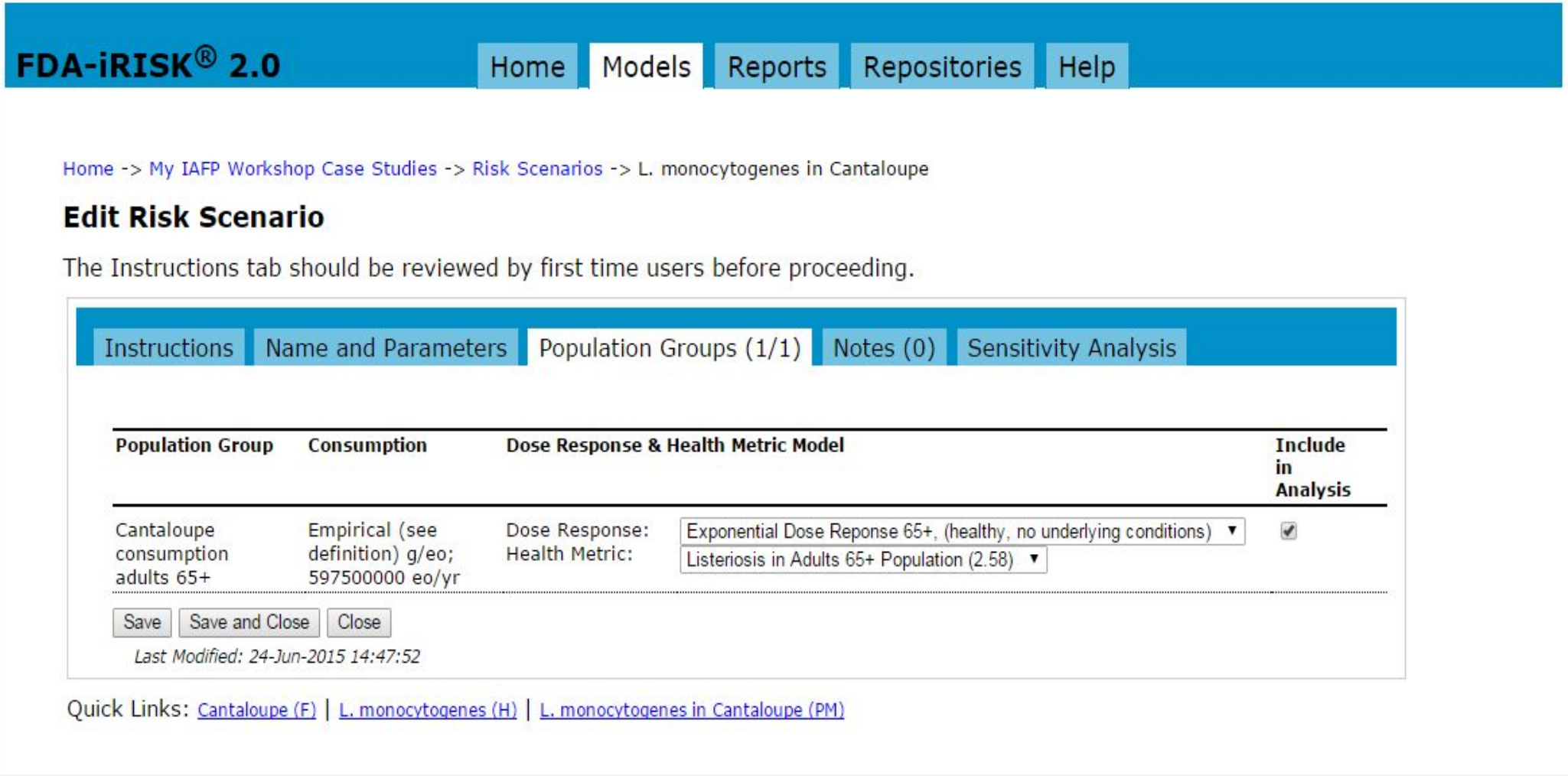
Concentration subtleties

- Normal (-0.97, 0.34)



- FDA-iRISK enforces a “1 CFU per unit” rule
  - Concentration must abide by this
- Unit size 25g, min concentration therefore Log(1/25) = -1.39794
- FDA-iRISK offers a truncated Normal option
- Use min = -1.39794; max = 9

Scenario


FDA-iRISK® 2.0
Home
Models
Reports
Repositories
Help
Home -> My IAFP Workshop Case Studies -> Risk Scenarios -> L. monocytogenes in Cantaloupe
Edit Risk Scenario
The Instructions tab should be reviewed by first time users before proceeding.
Instructions
Name and Parameters
Population Groups (1/1)
Notes (0)
Sensitivity Analysis
Population Group
Consumption
Dose Response & Health Metric Model
Include in Analysis
Cantaloupe consumption adults 65+
Empirical (see definition) g/eo; 597500000 eo/yr
Dose Response:
Exponential Dose Reponse 65+, (healthy, no underlying conditions)
Health Metric:
Listeriosis in Adults 65+ Population (2.58)
Save
Save and Close
Close
Last Modified: 24-Jun-2015 14:47:52
Quick Links: Cantaloupe (F) | L. monocytogenes (H) | L. monocytogenes in Cantaloupe (PM)

Results from Illustrative Scenario

Ranking Summary

All reported summary values are per year. For chronic scenarios, results for the total lifecourse have been divided by the lifecourse duration (e.g. 70 years) specified for the population groups included in the scenario.

Scenario or Scenario Group	Total DALYs per Year
Listeria in Cantaloupe	103

Scenario	Lifecourse Duration	Eating Occasions or Consumers	Total Illnesses	Mean Risk of Illness	Total DALYs per Year	DALYs Per EO or Consumer	Total DALYs per Year (Weighted)
Listeria in Cantaloupe	N/A	5.98E+8	40.0	6.70E-8	103	1.73E-7	103

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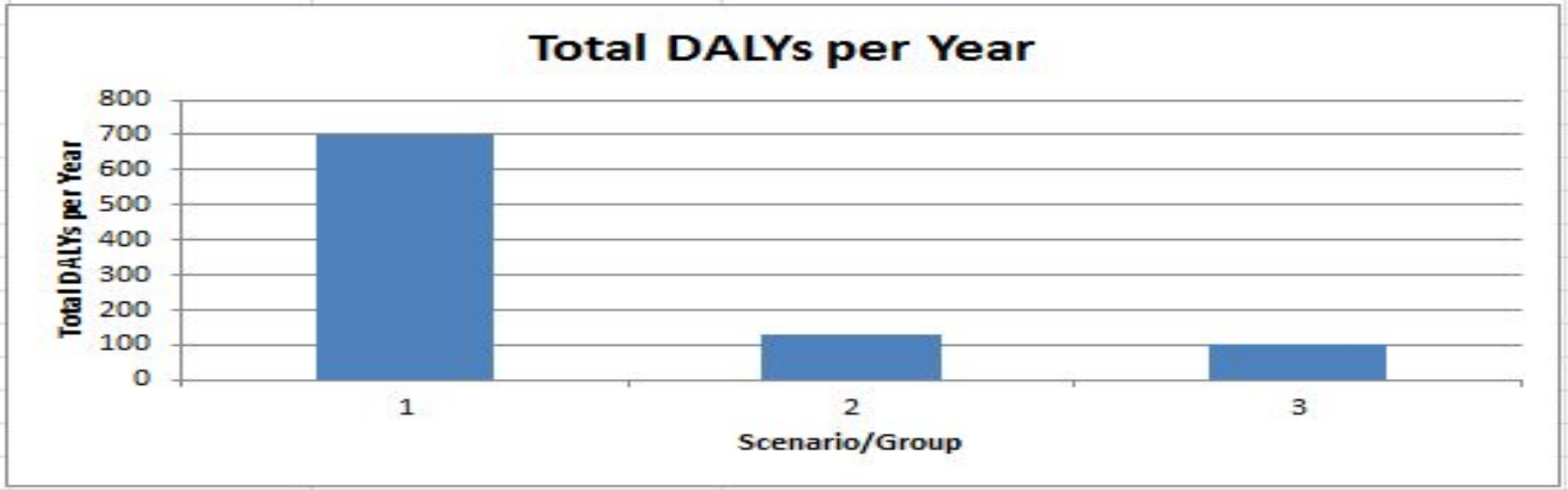
Sensitivity Analysis

- Impact of likelihood of cross-contamination during home prep:

Sensitivity Analysis for Listeria in Cantaloupe



Scenario/Group	Total DALYs per Year	Scenario Name
1	702	Process Stage Handling at home Likelihood: 5E-2
2	129	Process Stage Handling at home Likelihood: 5E-3
3	103	Process Stage Handling at home Likelihood: 5E-4

General Q & A

Open questions on topics covered throughout the training

Self-paced Exercises (see workbook)