ECOTOXICOLOGY

Lecture 4

Pesticides


敌敌畏


精制敌百虫
（水产用）
Jingzhi Dibaichong Fen
Purified Trichlorphon Powder


氧化乐果


对硫磷粉剂
净含量

Regulatory Definition of Pesticide

- FIFRA (1947)
- Any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest
- Pest: insect, rodent, plant, or animal life or viruses, bacteria, or other microorganisms, except viruses, bacteria, or other microorganisms on or in living man or other animals
- Pesticide includes plant regulators, defoliants, or desiccants 干燥剂 脱叶剂
- Pesticide includes disinfectants 消毒剂

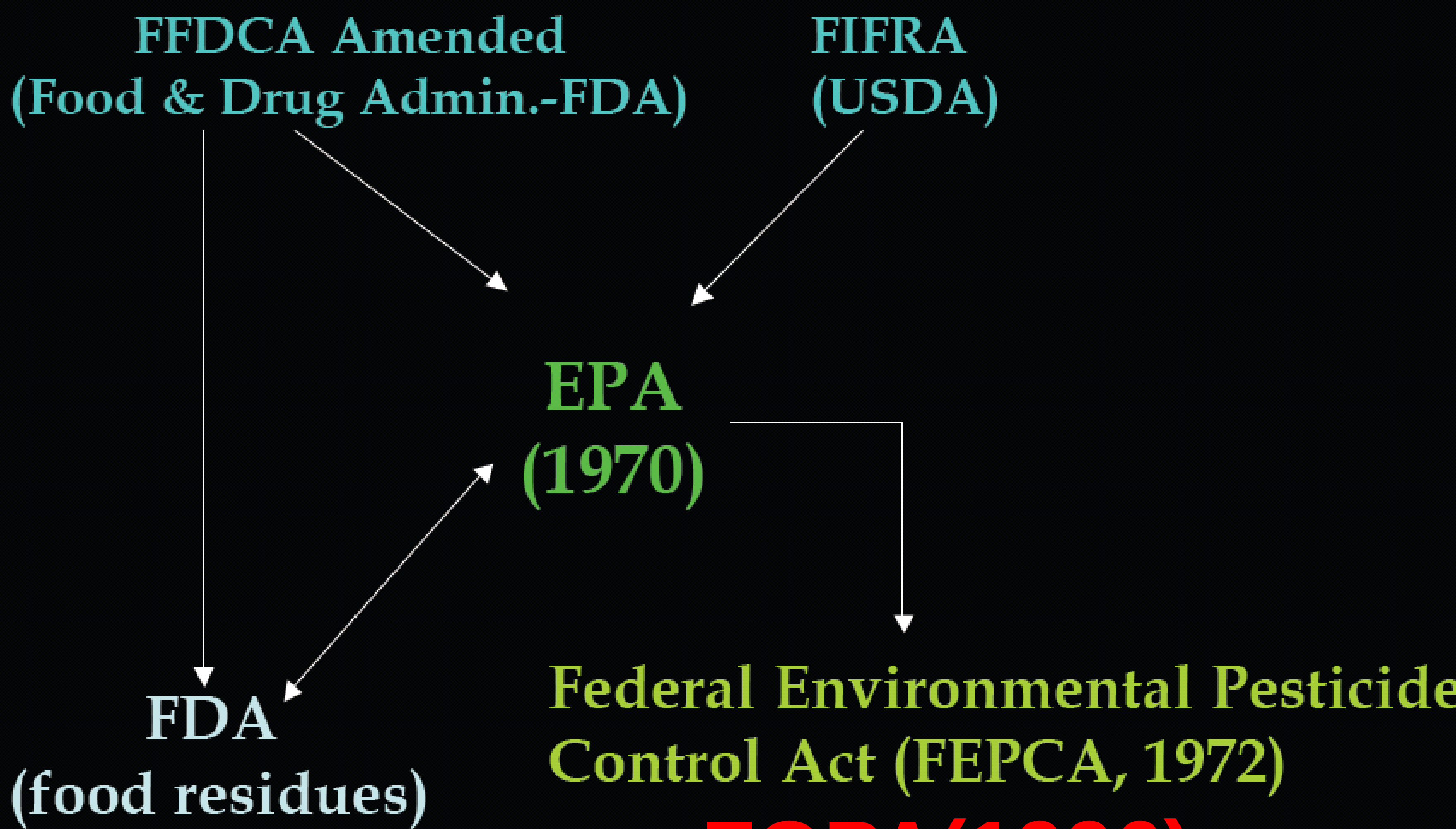
Why Use Pesticides
Natural vs. Agricultural Ecosystem Characteristics

Natural Ecosystems

- Self-sustaining as a result of biological (genetic) diversity
  – Diverse in species and function
- Responsive to system perturbations
  – System can quickly recover after disruptions

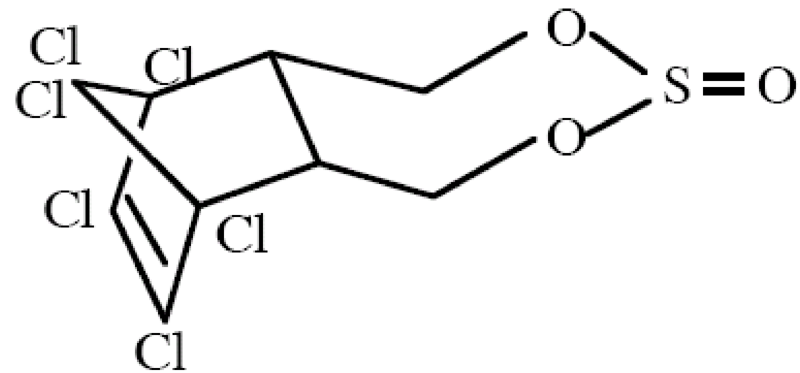
- Energy flow balanced
  – Nutrients recycled
  – Soil stores plant nutrients

Shared Responsibilities



FQPA(1996)

Naming Pesticides



endosulfan

硫丹（一种烈性杀虫剂）

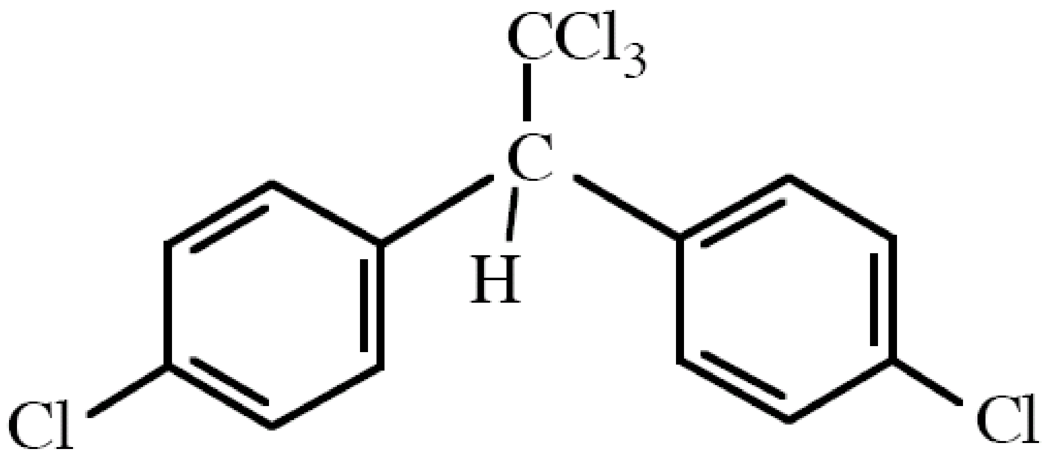
- Common chemical name
  - Endosulfan
- Formulation name
  - Thiodan 硫丹（农药）
- IUPAC approved chemical nomenclature 命名法
  - 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide

国际理论和应用化学联合会

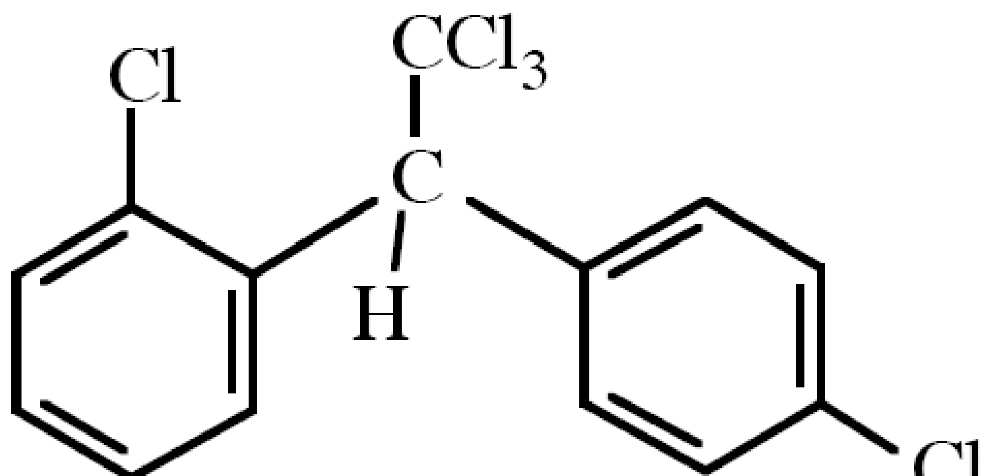
Chlorinated Hydrocarbons & Chlorinated Cyclodienes

环戊二烯类杀虫剂

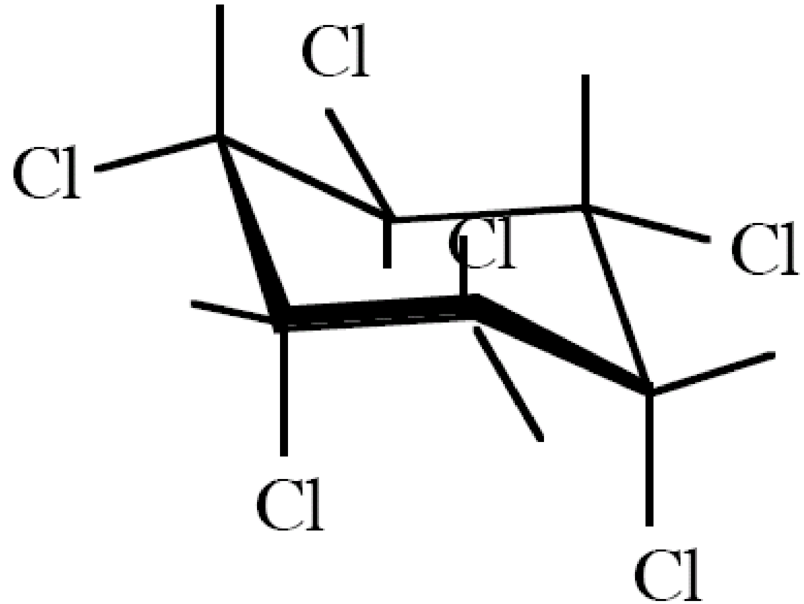
- Almost all (except) endosulfan, banned
- Persistent Organic Pollutants (POPs) classification



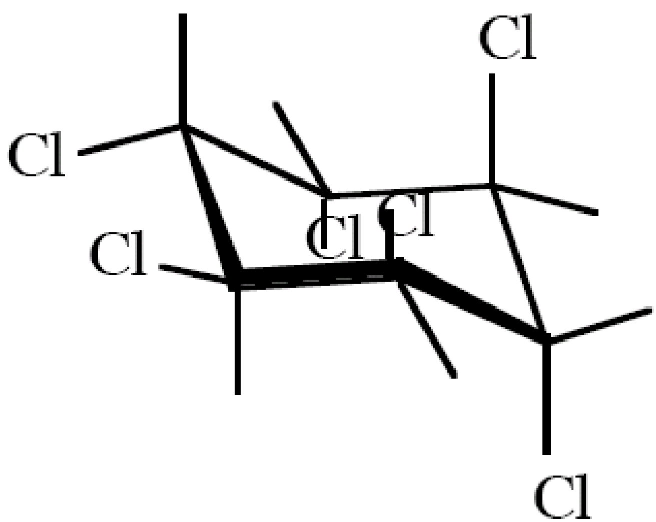
p,p'-DDT



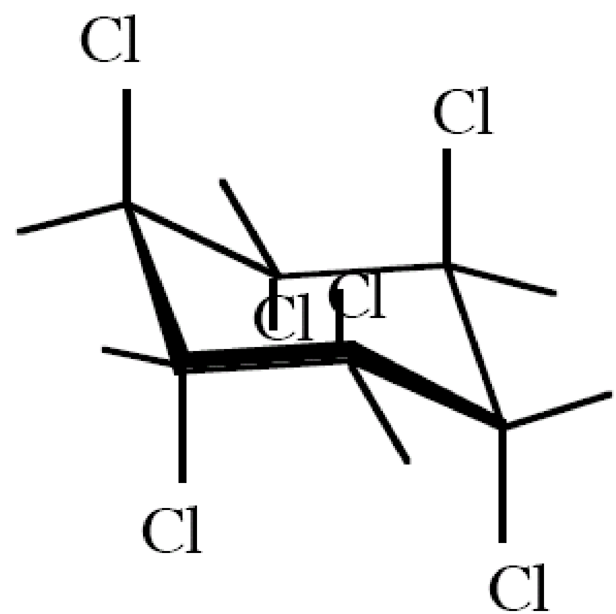
o,p'-DDT



gamma hexachlorocyclohexane (lindane)

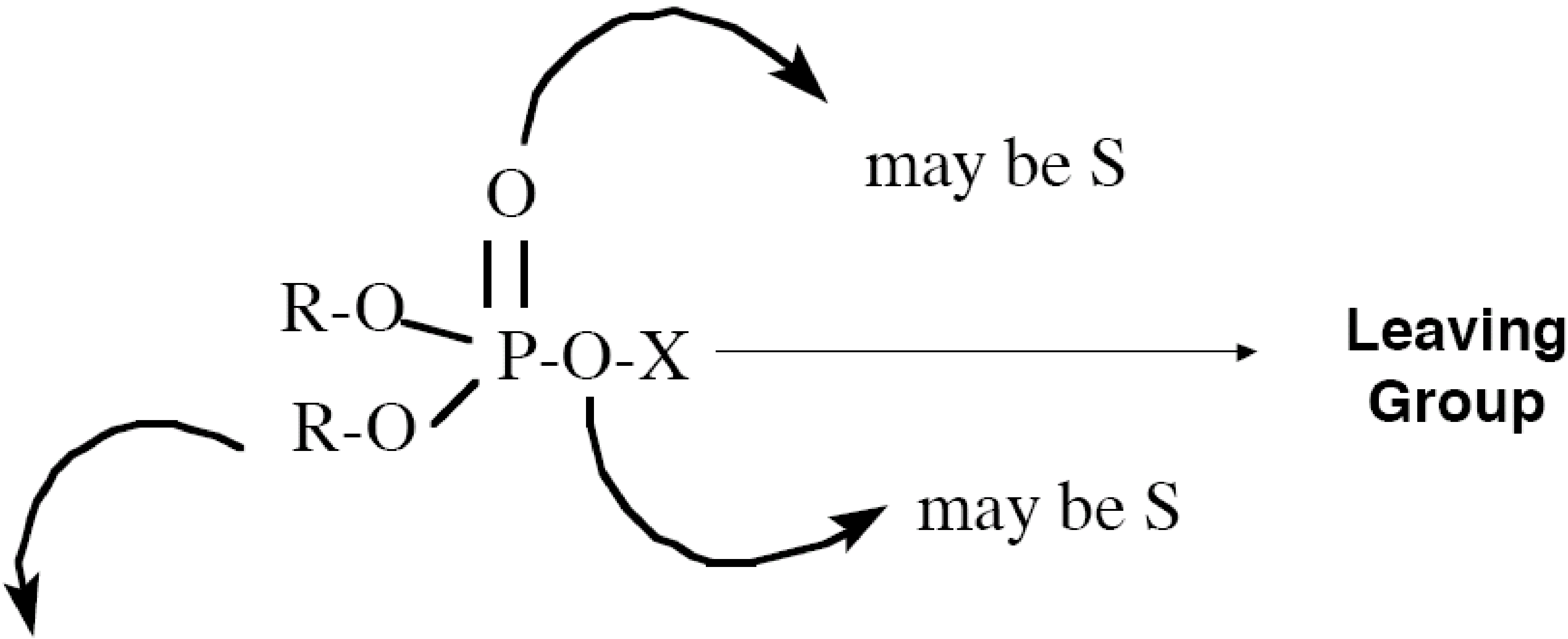


alpha HCH



beta HCH

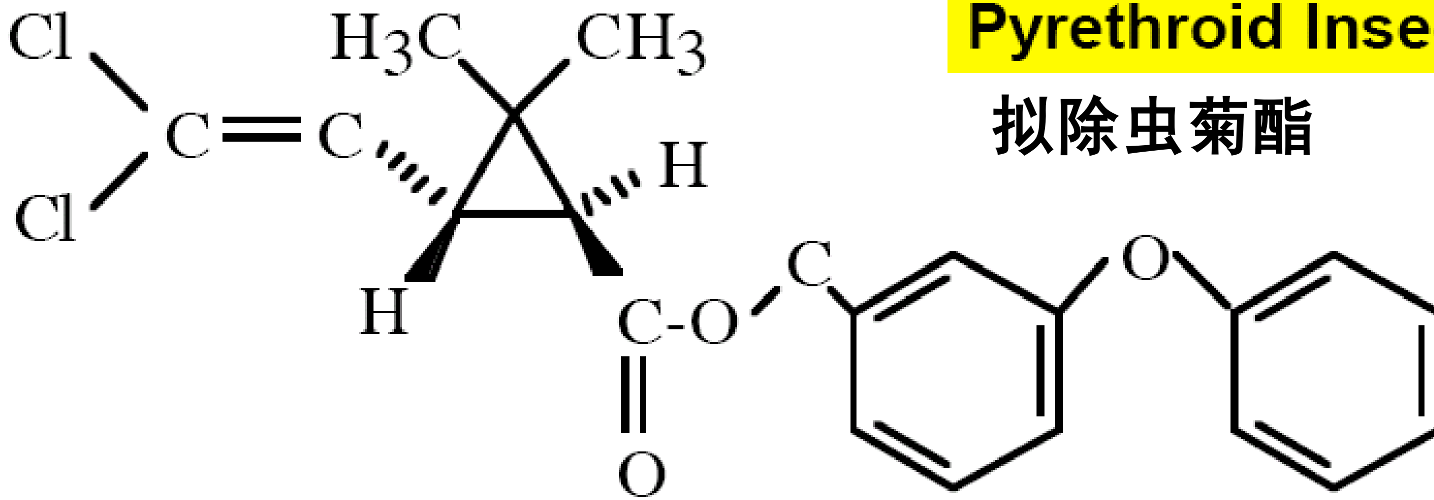
Basic Structure of Organophosphorus Insecticides



R is an alkyl group
usually of 1 or 2 C;
both R groups usually the same

Pyrethroid Insecticides

拟除虫菊酯

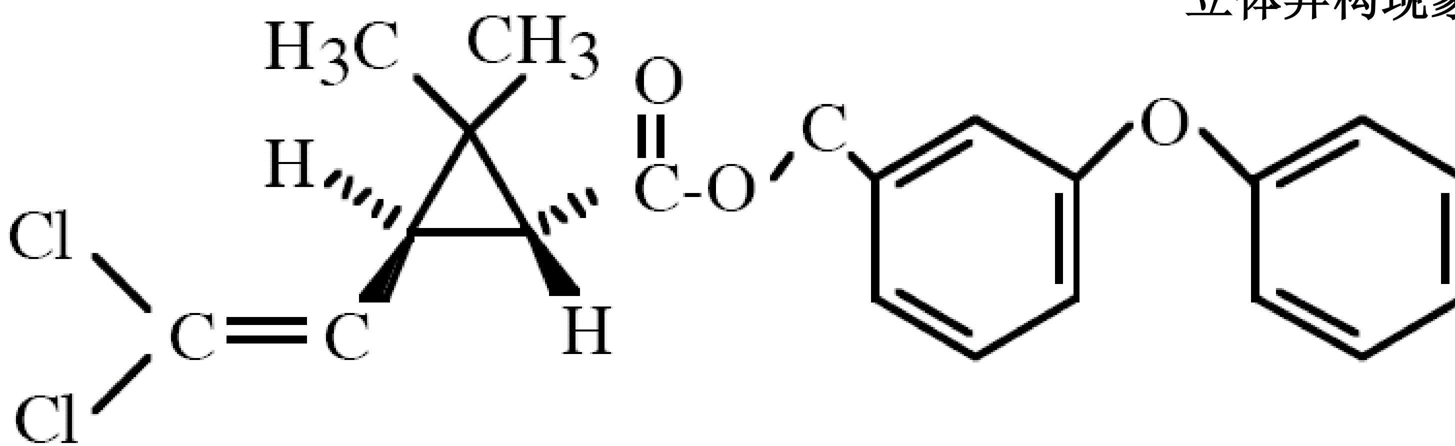


1S trans permethrin

百灭宁

Stereoisomerism

立体异构现象



1R trans permethrin

For Risk Characterization, Acute Toxicity Is Less Important than the NOAEL for the Most Sensitive Effect

NOAEL Data from EPA REDs (Registration Eligibility Decision Documents

合格

Doses in mg/kg/day

Pesticide	Acute or Subchronic NOAEL	Acute or Subchronic LOAEL	Chronic NOAEL	Chronic LOAEL	Chronic RfD	Chronic PAD
azinphosmethyl 谷硫磷	0.3	1	0.149	0.688	0.00149	0.00149
chlorpyrifos 毒死蜱	0.5	1	0.03	0.22	0.0003	0.00003
atrazine 阿特拉津	10	70	1.8	3.65	0.018	0.0018
2,4-D	67	227	1	5	0.01	0.01
glyphosate 草甘膦	<63	63	175	350	2	2

Dermal Absorption

- Many pesticides are inefficiently absorbed through the skin
  - Azinphos-methyl: 42% in 24 h
  - Chlorpyrifos: 3%
  - Atrazine: 5.6%
  - 2,4-D: 6%

Long Term DDT Experiment

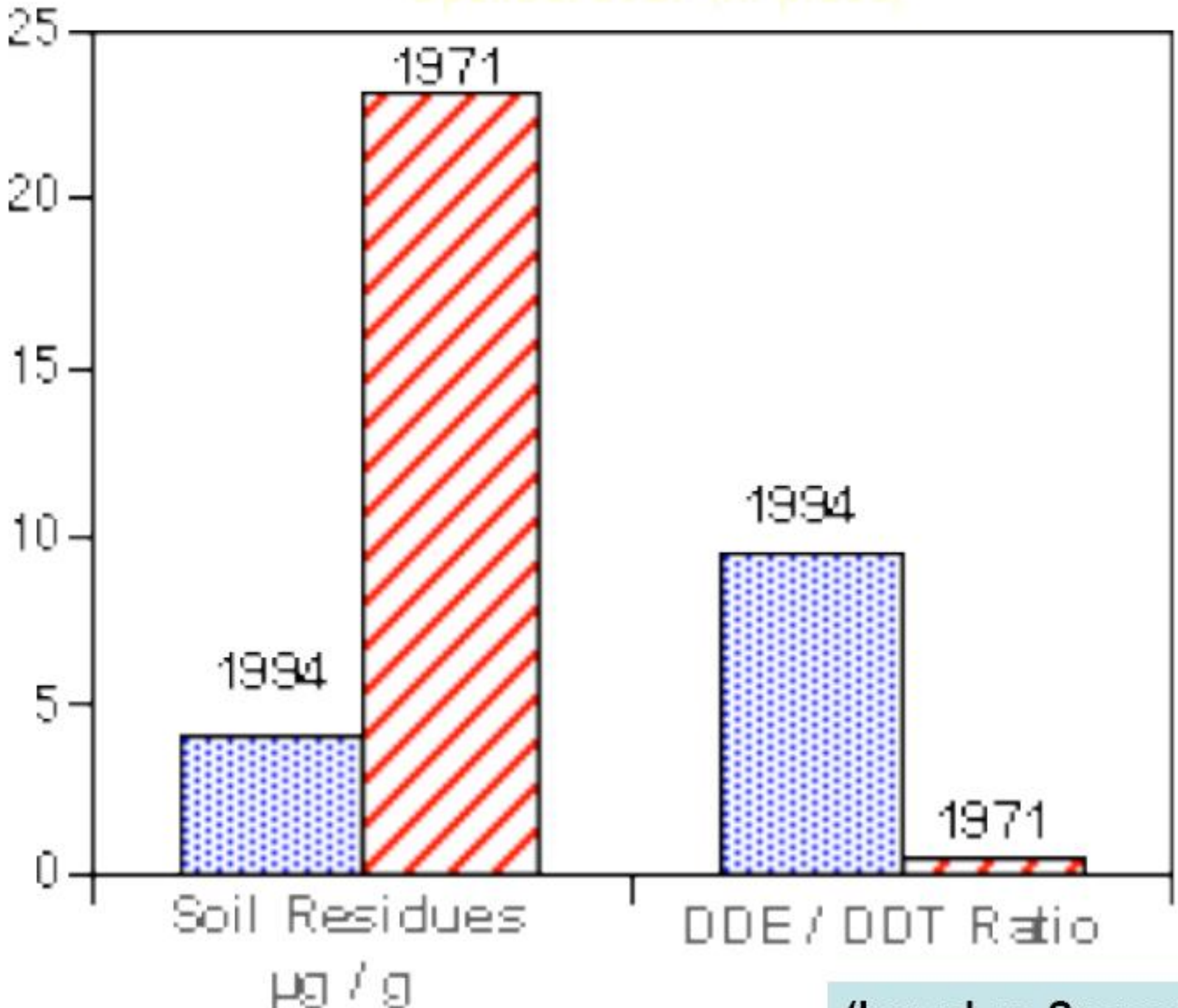
(Spencer et al. 1996, JEQ)

- Treat plots in 1971
- Measure air and soil residues after application and in 1994

Effect of Time on Recovery of Total DDT Residues

Coachella Valley, CA

Spencer et al. (in press)



(based on Spencer et al. 1996)

Effect of Time on Recovery of Total DDT Residues

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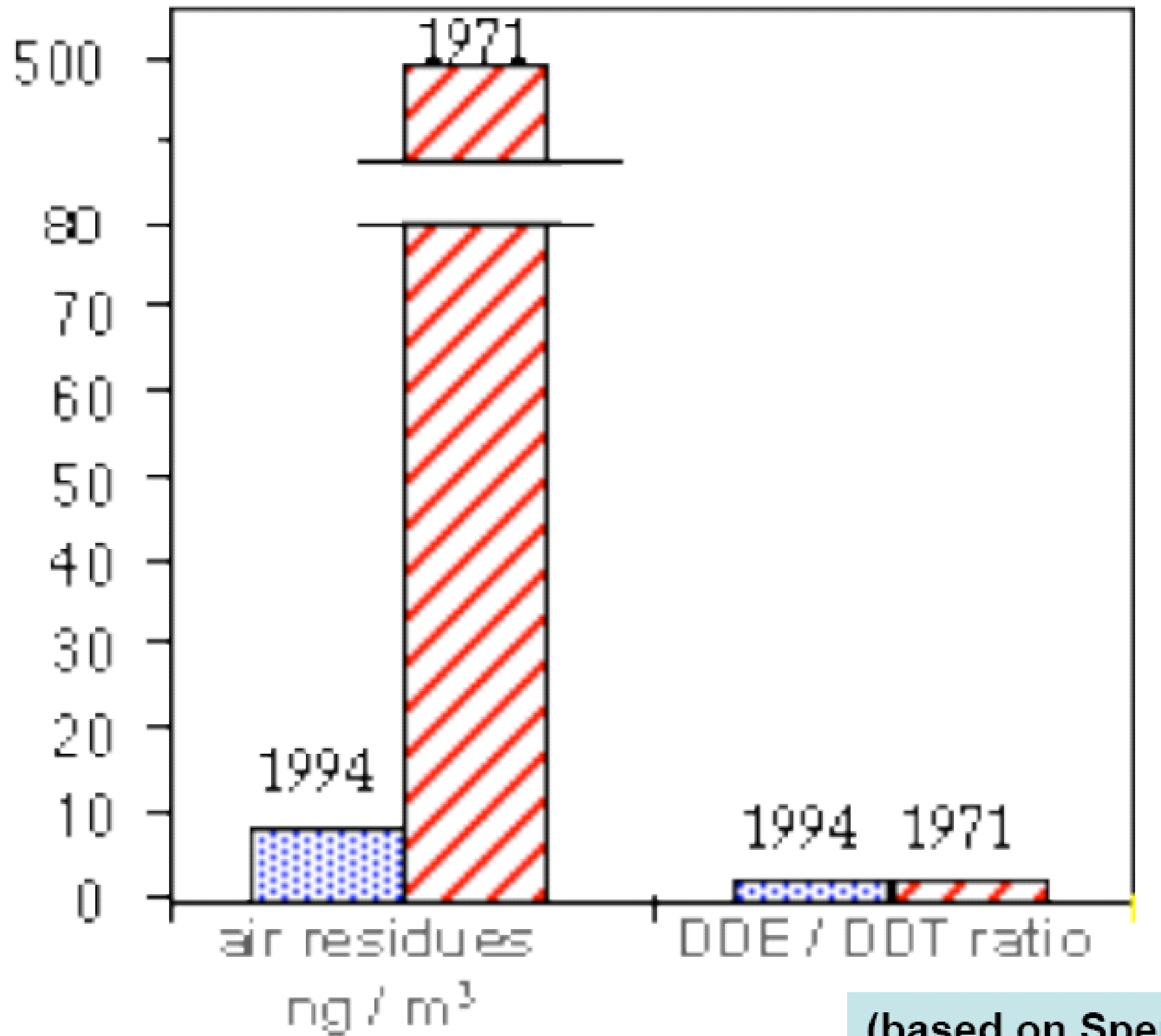


(based on Spencer et al. 1996)

Pesticides: Human Health Risk Assessment

(How EPA Assesses Aggregate & Cumulative Exposure & Characterizes Risk)

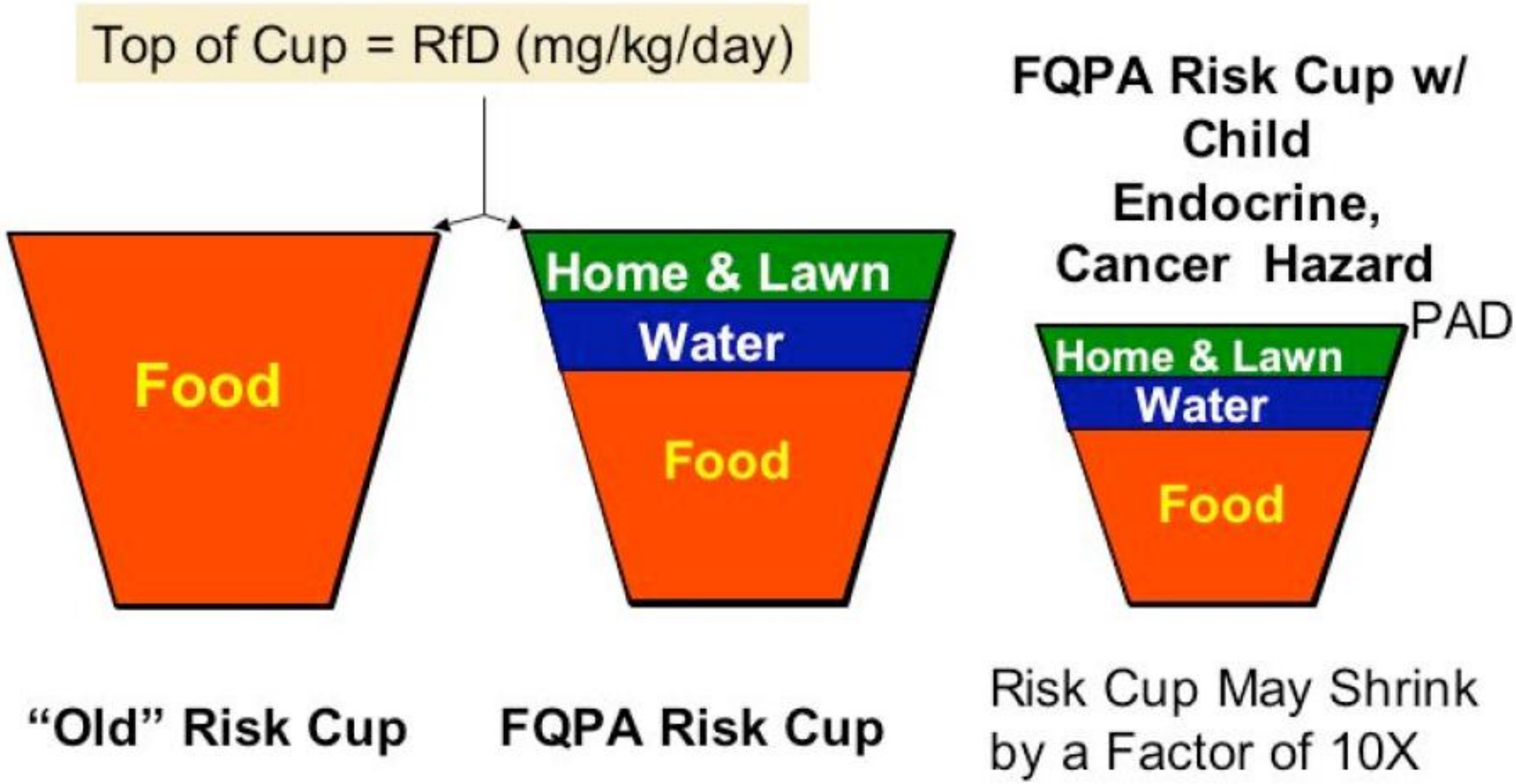
Tolerance
容许量

- Legal limit of residues on food
  - Mechanism of satisfying the mandates of the Federal Food Drug and Cosmetic Act (FFDCA), which is risk oriented, and Federal Insecticide, Fungicide, and Rodenticide Act, which is benefits oriented
- NOT a safety standard
- Expression of pesticide residues on food
  - ppm
  - mg/kg
  - μg/g

TMRC
(Theoretical Maximum Residue Contribution)

- Tolerances are residues
- Toxicological endpoints are doses relative to an effect and body weight
- The sum of all exposures to residues at the tolerance level cannot exceed the Reference Dose, the “safe” level by policy design
  - Pre-FQPA: considered food residues only
  - Post-FQPA: tolerance would have to account for aggregate exposures

The Risk Cup Metaphor



Example

- Tolerance (old) for chlorpyrifos on apples at 1.5 ppm
  毒死蜱
- Tolerance for chlorpyrifos on wheat at 0.5 ppm
- Average male eats 100 g /day wheat and 75 g/day apples

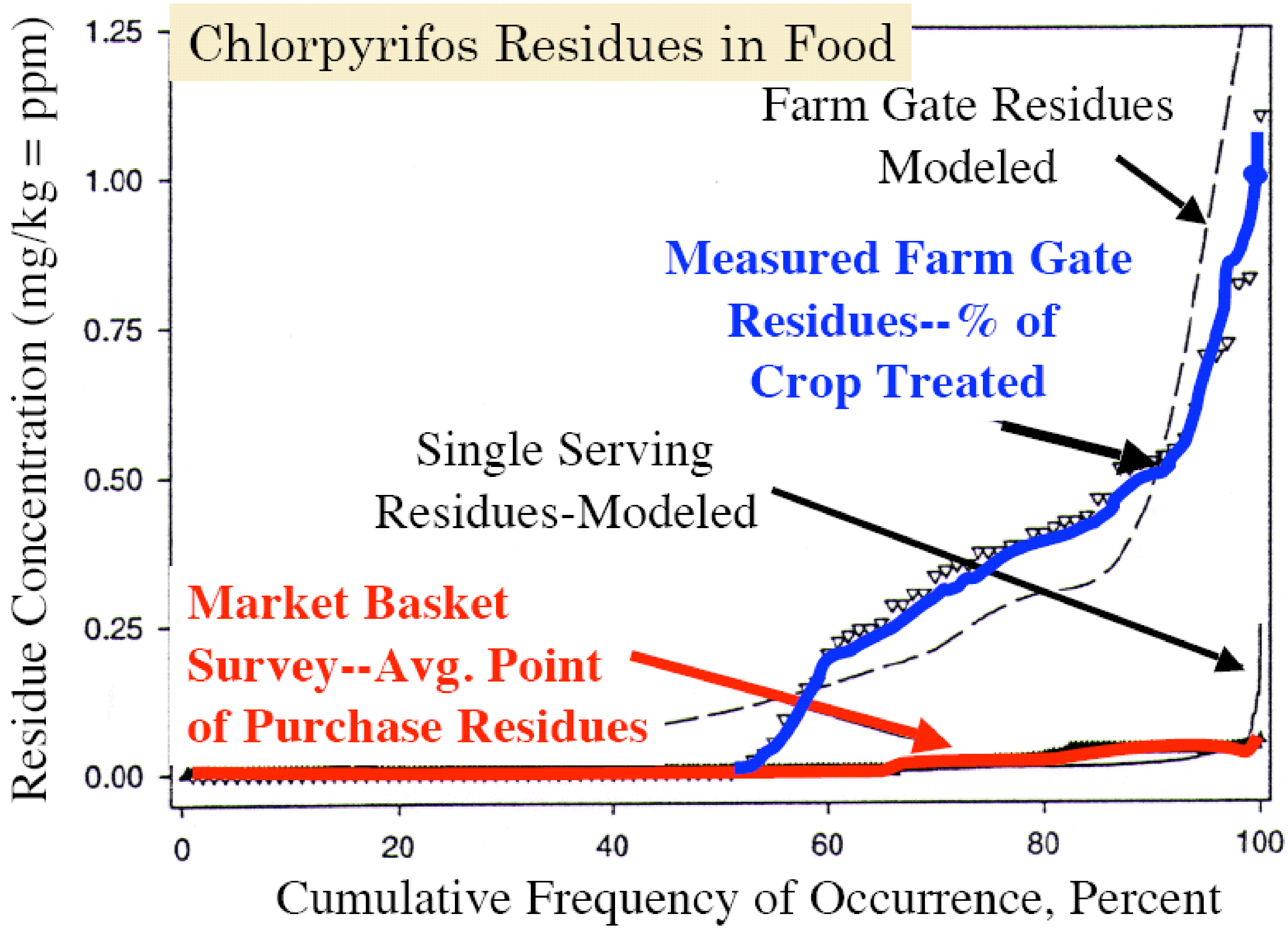
Sum (1.5 μg/g x 75 g/day) + (0.5 μg/g x 100 g/day) = 162.5 μg/day (0.1625 μg/day)

Daily Exposure = (162.5 μg/day) /70 kg bw = 2.32 μg/kg bw/day = 0.00232 mg/kg

Example (cont'd.)

- The RfD for chlorpyrifos is 0.0003 mg/kg/day for chronic exposure
- Thus, just from the two commodities alone, the RfD is exceeded for an adult
- Note that average consumption based on the FDA Total Diet Study is only 0.000015 mg/kg/day (for an infant of 10 kg)

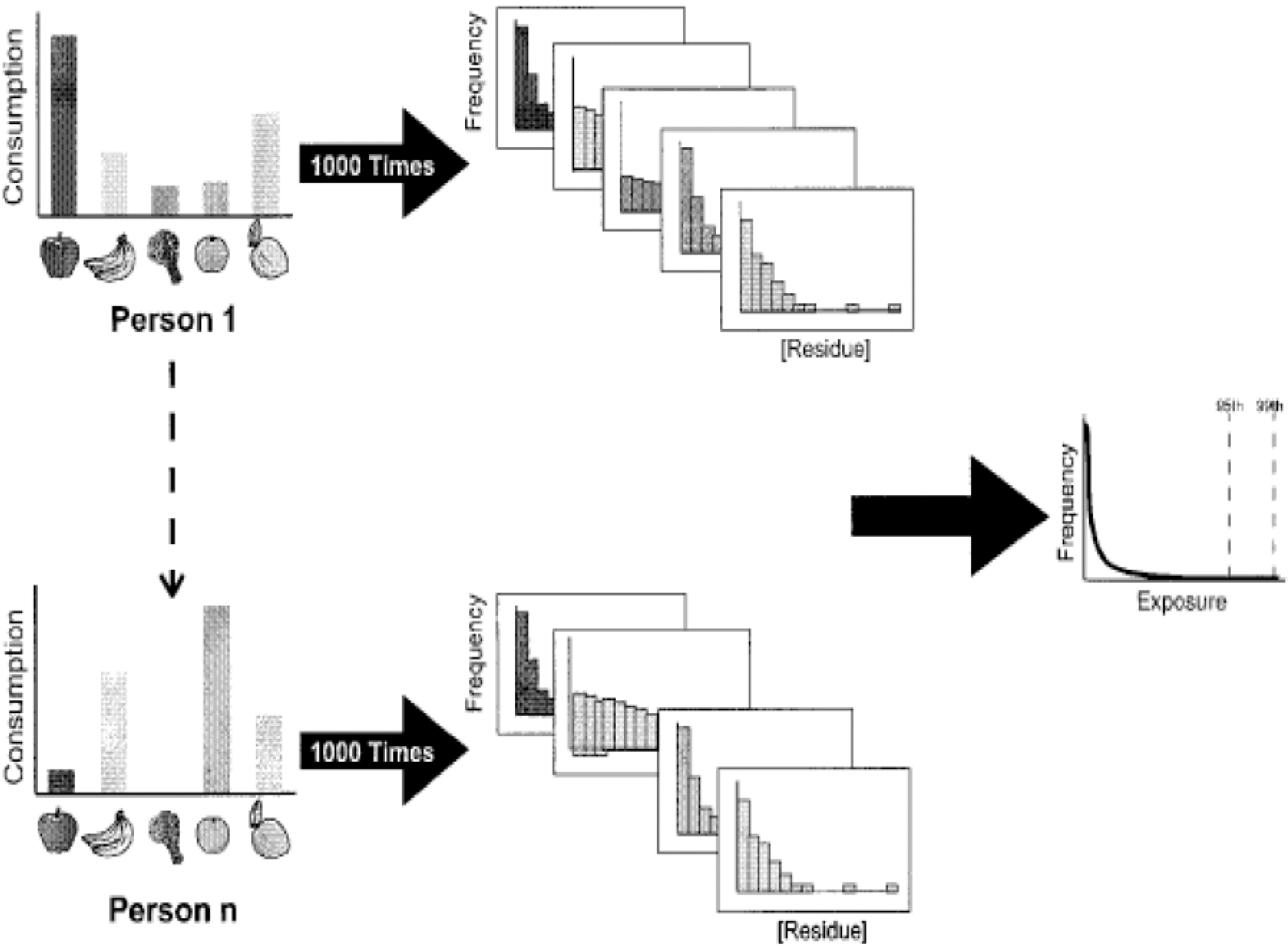
Real Residue Data Advantages



Wright '99 (DowAgro)

Acute Dietary Exposure

- Probabilistic assessment employing Monte Carlo analysis
  - The entire distribution of food consumption and food residue data are used
  - Essentially, the two distributions are multiplied together to yield a distribution of exposures
- Chronic exposure assessment is deterministic
  - Point estimates of food consumption and residues are used


Consumption
Person 1
1000 Times
Frequency
[Residue]
Consumption
Person n
1000 Times
Frequency
[Residue]
Frequency
Exposure

Food Consumption Matrix (kg/day)

Food matrix	Person 1 Day 1	Person 1 Day 2	Person 1 Day 3	Person 2 Day 1
Apple	0.10	0.15	0.00	0.05
Peach	0.02	0.10	0.00	0.10
Raisins	0.03	0.05	0.01	0.00
Corn flakes	0.00	0.75	0.04	0.10
Pizza	0.06	0.00	0.05	0.20
Cookies	0.04	0.06	0.04	0.03
Granola Bar	0.02	0.03	0.06	0.02
Hot Dog	0.08	0.08	0.00	0.00
French Fries	0.08	0.06	0.04	0.00
Milk	0.06	0.20	0.10	0.03

Residue Data Matrix (mg/kg)

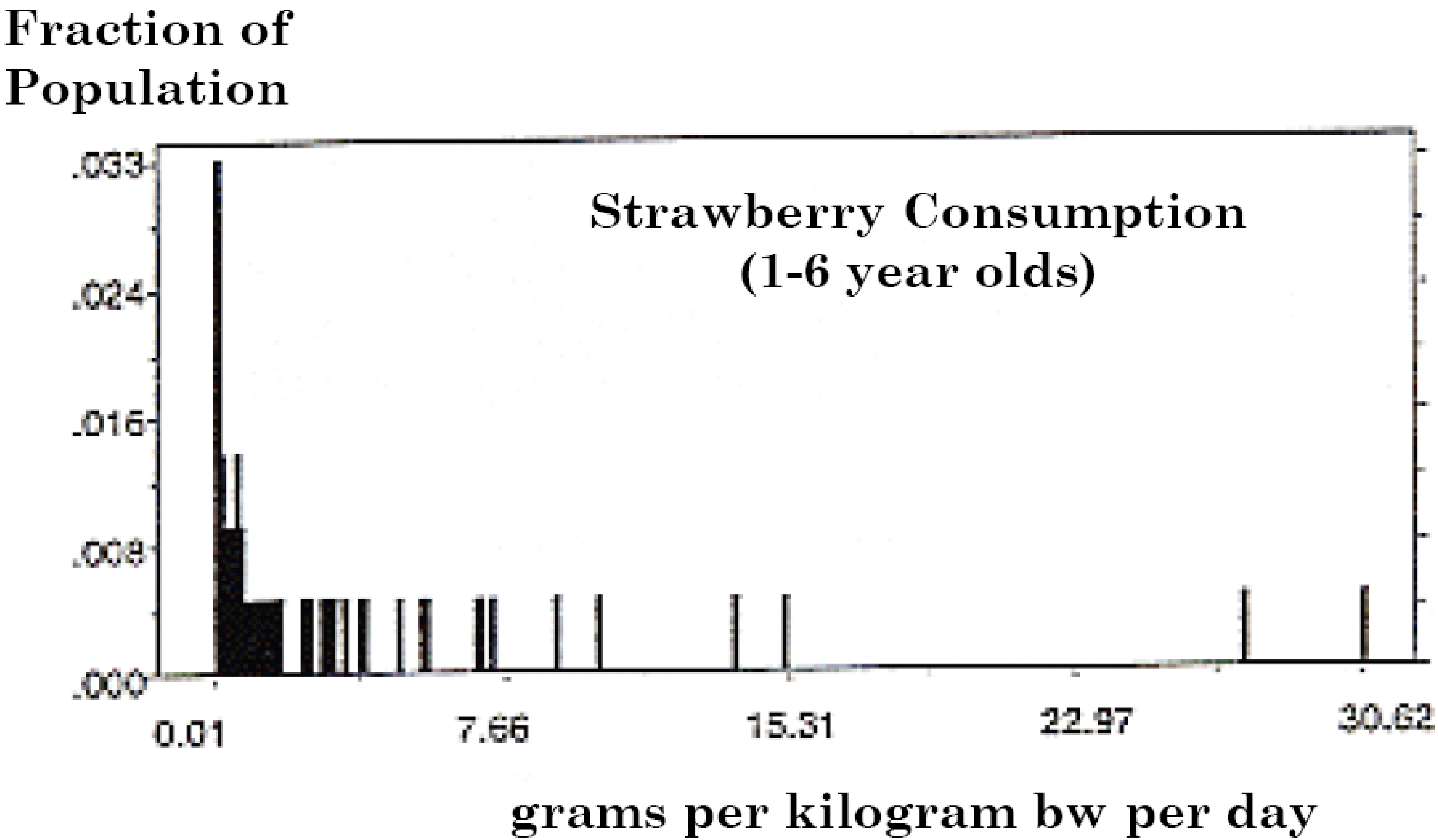
Food matrix	Sample 1	Sample 2	Sample 3	Sample 4
Apple	0.00	0.05	0.02	0.00
Peach	0.01	0.02	0.00	0.00
Raisins	0.03	0.01	0.00	0.00
Corn flakes	0.00	0.02	0.04	0.00
Pizza	0.06	0.00	0.05	0.20
Cookies	0.00	0.00	0.01	0.02
Granola Bar	0.02	0.00	0.00	0.02
Hot Dog	0.00	0.00	0.00	0.00
French Fries	0.00	0.00	0.00	0.00
Milk	0.00	0.00	0.00	0.00

In probabilisitic dietary exposure assessment, the distribution of weights of specific foods consumed are multiplied by the distribution of pesticide residues in those food. The Monte Carlo technique samples from each distribution, multiplies them, and then repeats the process for as many iterations as the risk assessor wants.

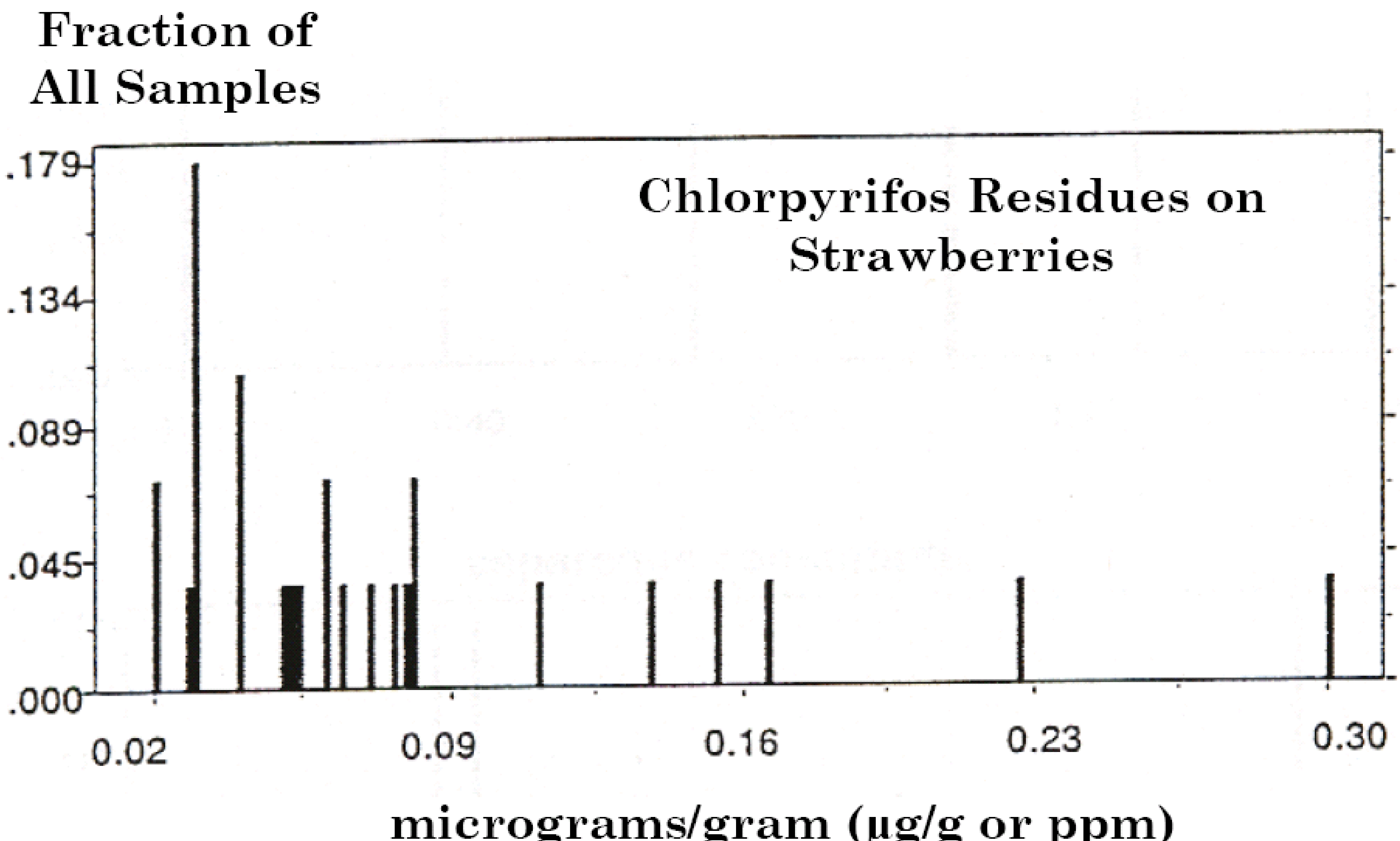
	Food Consumed (kg/day)	X	Pesticide Residue (ppm = mg/kg	
Apple	{0.100, 0.150, 0.000, 0.050}	X	{0.003, 0.054, 0.023, 0.002}	= 16 possible exposures
Peach	{0.020, 0.100, 0.000, 0.100}	X	{0.010, 0.020, 0.002, 0.002}	= 16 possible exposures

Monte Carlo Technique

- The Monte Carlo program randomly selects a food consumption value for each type of food and matches it to a randomly selected residue value for that food
  - The food consumption and residue value are multiplied together to yield the exposure
- For every food consumption and residue selection, the process is repeated hundreds or thousands of time to obtain a stable distribution of exposures


Fraction of Population
Strawberry Consumption
(1-6 year olds)
.033
.024
.016
.008
.000
0.01
7.66
15.31
22.97
30.62
grams per kilogram bw per day

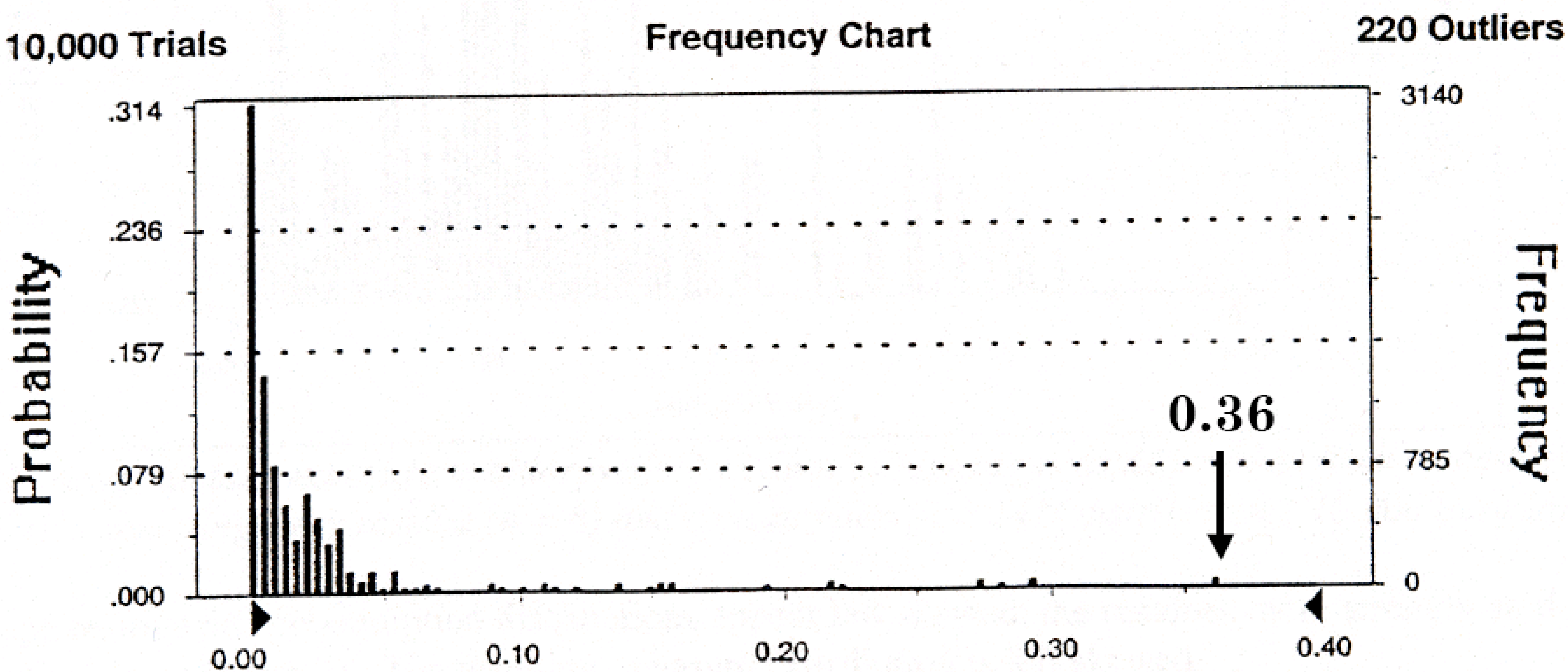
DAS 1999



Fraction of
All Samples
Chlorpyrifos Residues on
Strawberries
.179
.134
.089
.045
.000
0.02
0.09
0.16
0.23
0.30
micrograms/gram (µg/g or ppm)

DAS 1999

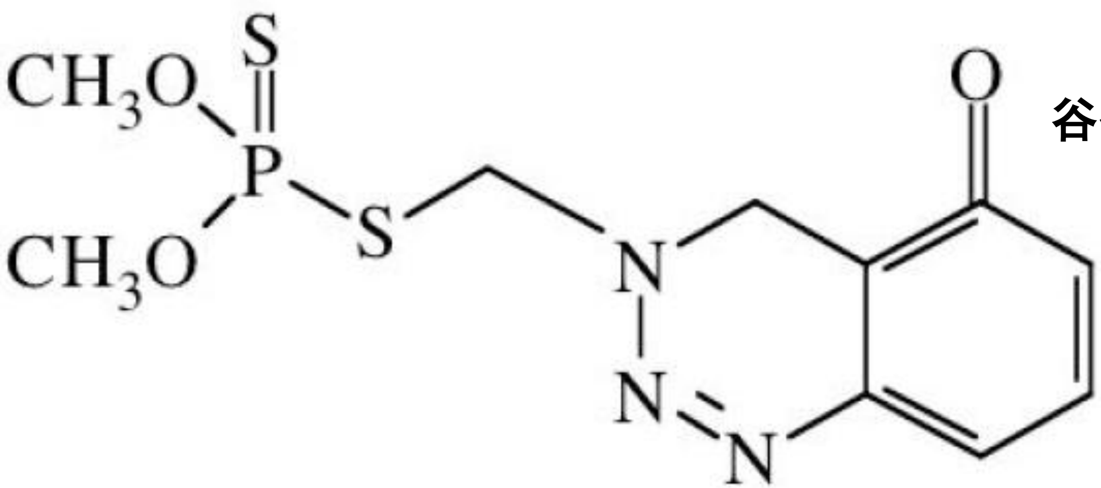
Estimated Exposure to Chlorpyrifos in Strawberries Using a Monte Carlo Analysis (1-6 year old)



microgram per kilogram bw per day

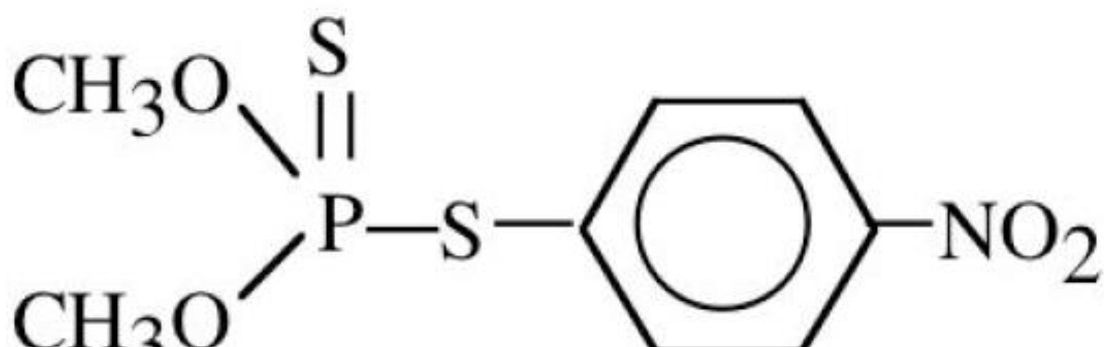
DAS 1999

A Tale of Two Risk Assessments



谷硫磷, 保棉磷(一种杀虫农药)

Azinphos-methyl



Methyl parathion

甲基对硫磷

Toxicity Parameter	mg/kg/day Azinphos-methyl	 Methyl Parathion
Acute Oral LD50	4.5	4.5
Acute Dermal LD50	2000 Rabbit 200 Rat	6
Acute NOEL	0.3	0.11
Chronic NOEL	0.149	0.02

mg/kg/day

Exposure Endpoints	Azinphos-methyl	Methyl Parathion
Acute Reference Dose	0.003	0.0011
Acute Population Adjusted Dose	0.003	0.00011
Chronic Reference Dose	0.00149	0.0002
Chronic Population Adjusted Dose	0.00149	0.00002

Methyl Parathion--Acute Dietary Risk Characterization

99.9th Percentile Exposure

Population Group	Pre-Mitigation Exposure mg/kg/day	Pre-Mitigation % aPAD	Post-Mitigation Exposure mg/kg/day	Post-Mitigation % aPAD
U.S. Population	0.000416	378	0.000068	60
All infants < 1 yr	0.000415	377	0.000067	61
Children 1-6 yrs	0.000969	881	0.000086	78
Children 7-12 yrs	0.000428	388	0.000087	78

Azinphos-Methyl--Acute Dietary Risk Characterization

99.9th Percentile Exposure

Population Group	Tolerance Residues: Exposure mg/kg/day	Tolerance Residues: % aRfD	"Real" Residues: Exposure mg/kg/day	"Real" Residues: % aRfD
U.S. Population	0.005519	85	0.001781	59
All infants < 1 yr	0.009934	331	0.003003	100
Children 1-6 yrs	0.010343	202	0.003913	130
Children 7-12 yrs	0.006556	129	0.002704	90

Risk Characterization

- **Part Science**
  - Divide the dose **observed** to cause no effect by the exposure level
  - State the ratio (the MOE)
    - MOE = NOAEL (mg/kg/day) ÷ exposure (mg/kg/day)
- **Part Risk Management**
  - Divide the estimated level of exposure by the dose **believed** to be "safe" (Exposure/RfD)
  - Determine if the ratio is **acceptable or not**

Risk Characterization
MOE vs. RfD

Margin of Exposure (MOE) =

$$\frac{\text{NOAEL (mg/kg/day)}}{\text{Exposure (mg/kg/day)}} \geq 100 \text{ (EPA not concerned)}$$

$$\text{Reference Dose (RfD)} = \frac{\text{NOAEL}}{100}$$

Risk =(Exposure/RfD) x 100
if < 100, EPA not concerned

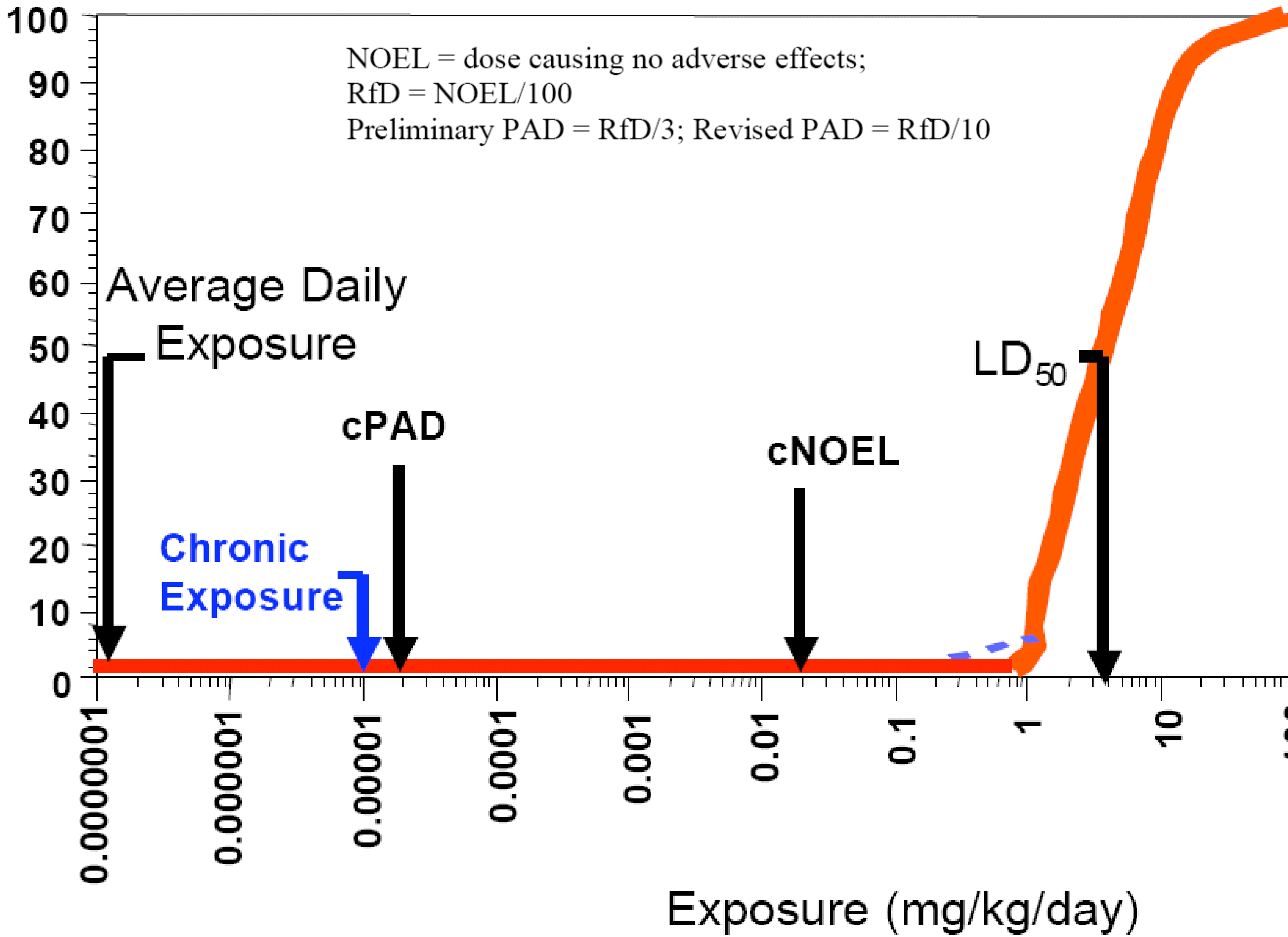
Child Sensitivity Is Considered

- If fetal and newborn rats are more sensitive at a given dose than adult rats, then up to an extra 10-fold safety factor may be applied to the RfD
- The RfD divided by this FQPA Safety Factor is called the
  - **Population Adjusted Dose (PAD)**

$$\frac{\text{NOEL}}{100} = \text{Reference Dose (RfD)}$$

$$\frac{\text{RfD}}{10} = \text{Population Adjusted Dose (PAD)}$$

Hypothetical Dose-Response Curve for Methyl Parathion



Hypothetical Dose-Response Curve for Methyl Parathion

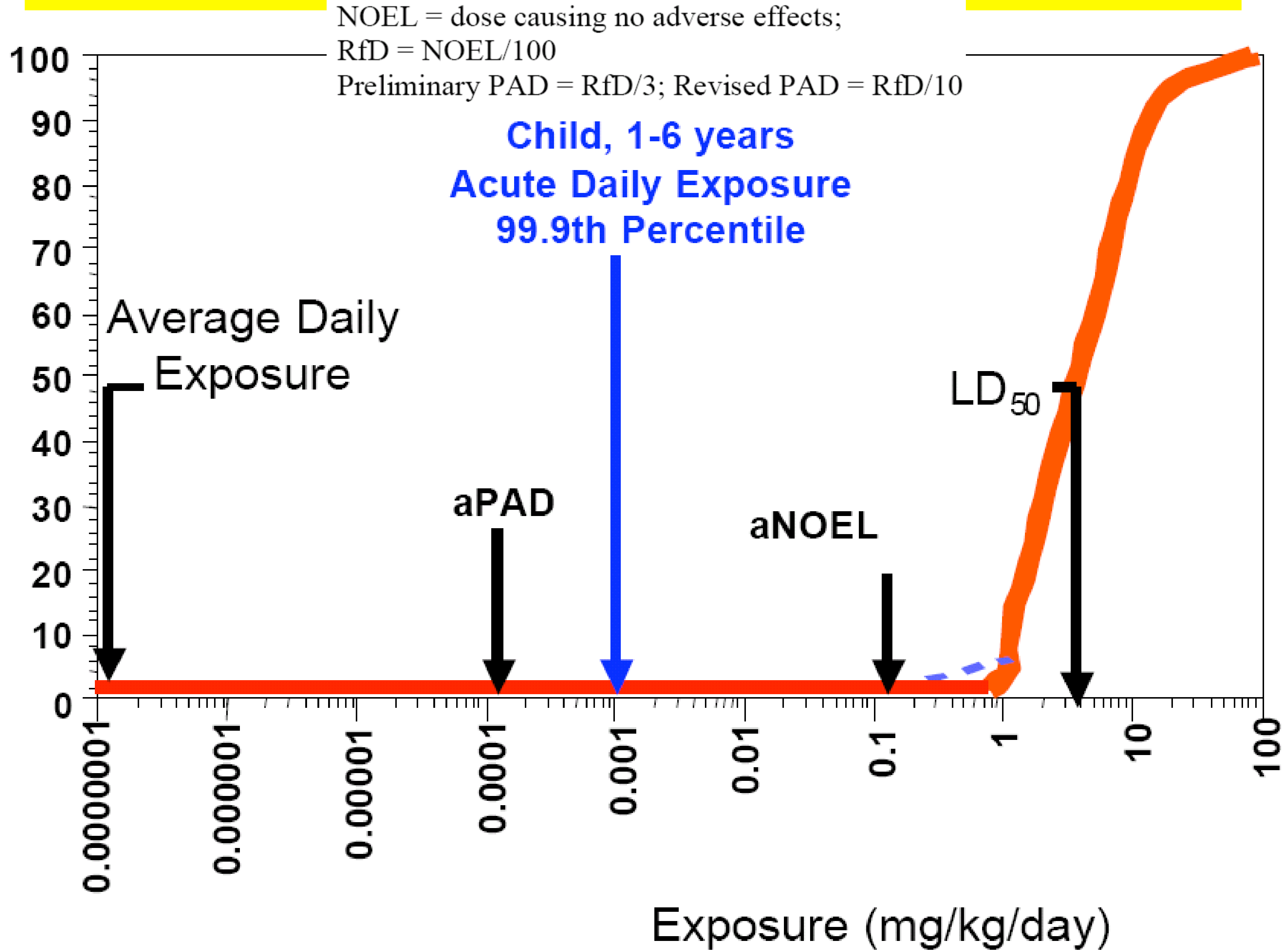
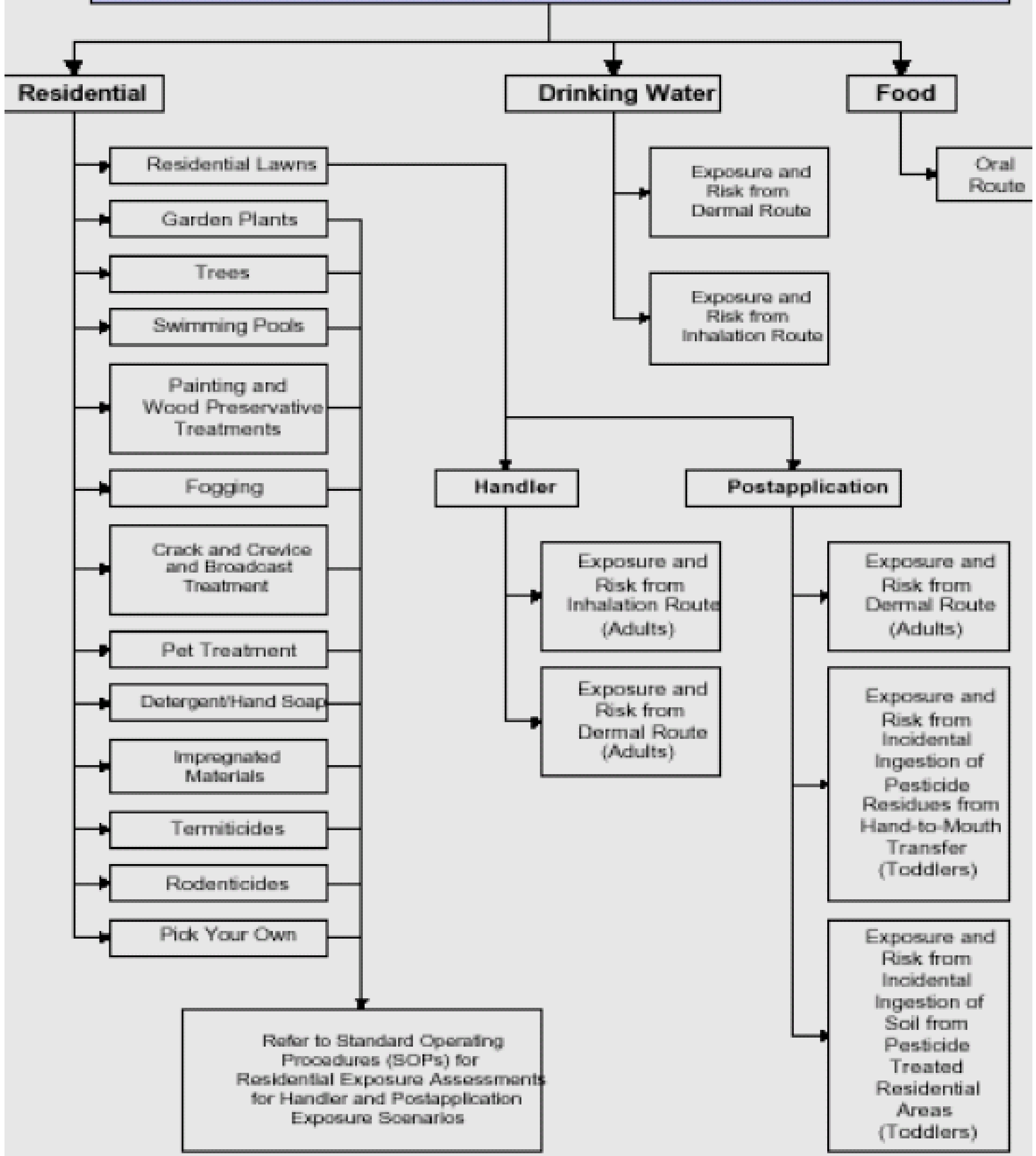
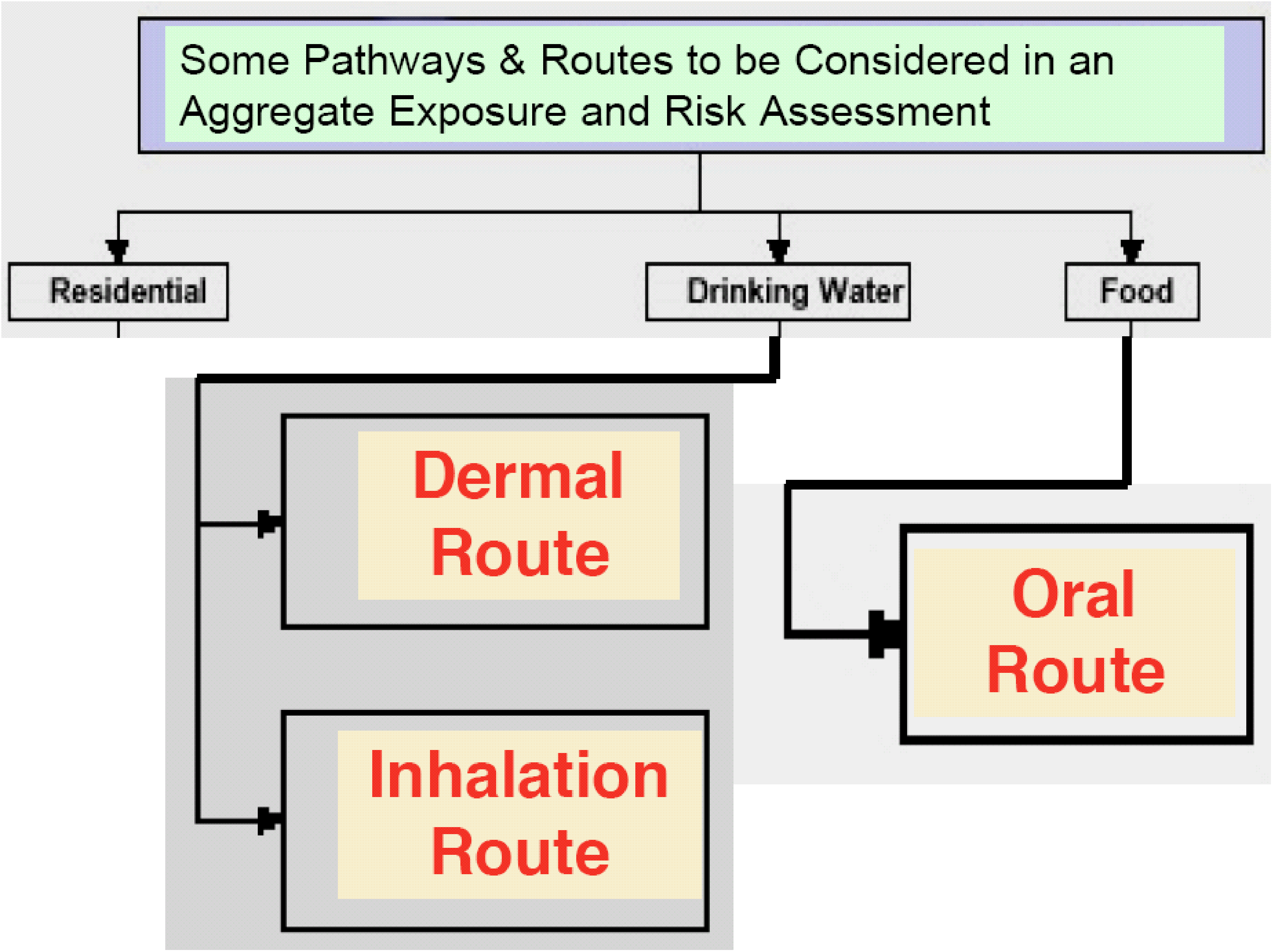
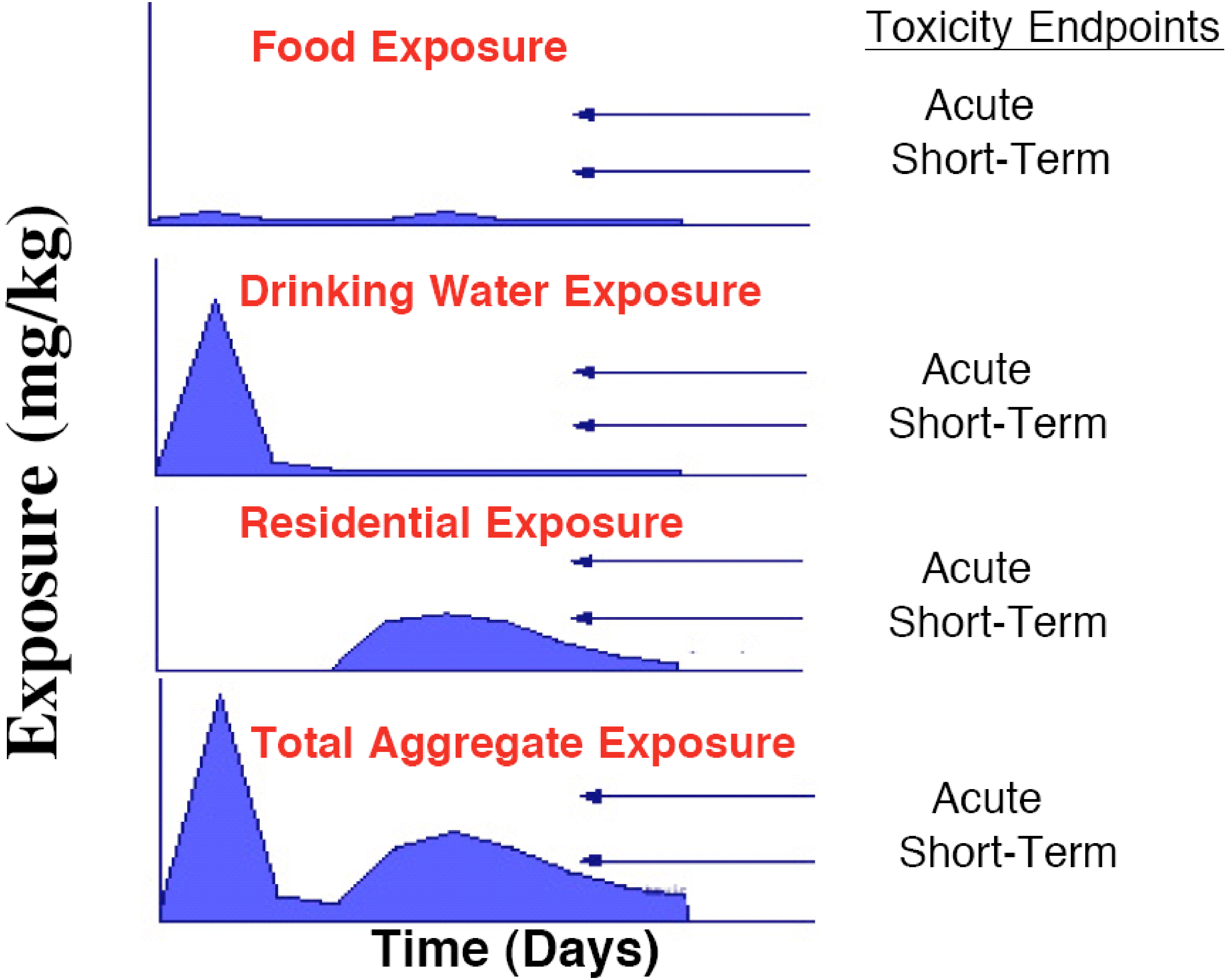


Figure 1. Some Pathways and Routes to be Considered in an Aggregate Exposure and Risk Assessment




Some Pathways & Routes to be Considered in an Aggregate Exposure and Risk Assessment
Residential
Drinking Water
Food
Dermal Route
Inhalation Route
Oral Route


Toxicity Endpoints
Food Exposure
Acute
Short-Term
Drinking Water Exposure
Acute
Short-Term
Residential Exposure
Acute
Short-Term
Total Aggregate Exposure
Acute
Short-Term
Exposure (mg/kg)
Time (Days)

Residential Exposure Assessment--Applying

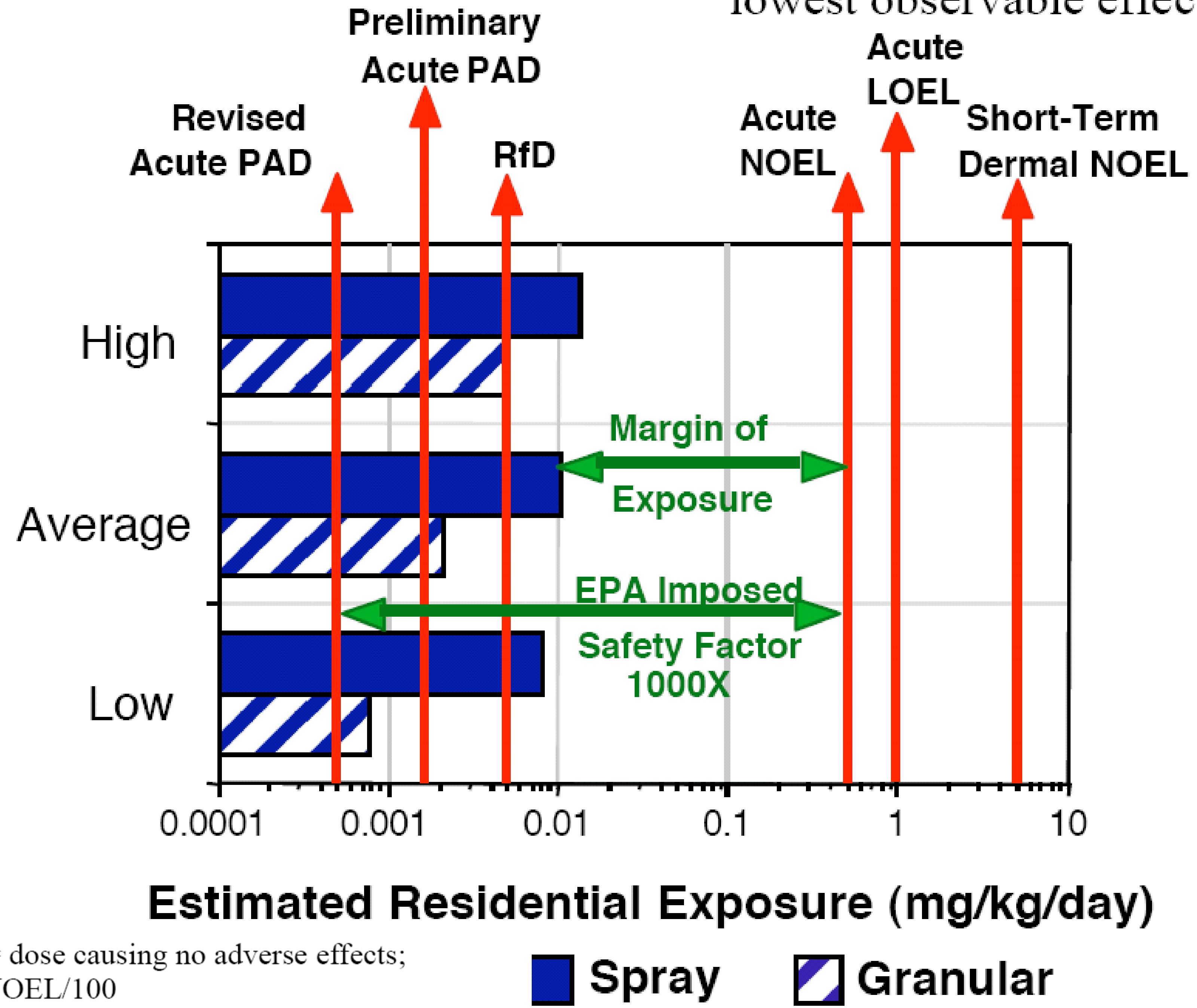
- PDR = UE x AR x A
  - PDR = potential dose rate (mg/day)
    - Empirical
    - PHED (Pesticide Handler Exposure Database)
  - UE = unit exposure (mg/lb AI) **AI=ai, active ingredient**
  - AR = application rate (lb AI/acre; lb AI/gallon)
  - A = area treated (acres/day or gallons/day)
- Exposure = PDR/kg body weight
  - (mg/kg/day)

PDR (mg/kg/day) = (3.0 mg/lb ai x 1 lb ai/acre x 0.5 acre/day)/71.8 kg = 0.02

Residential Exposure Assessment

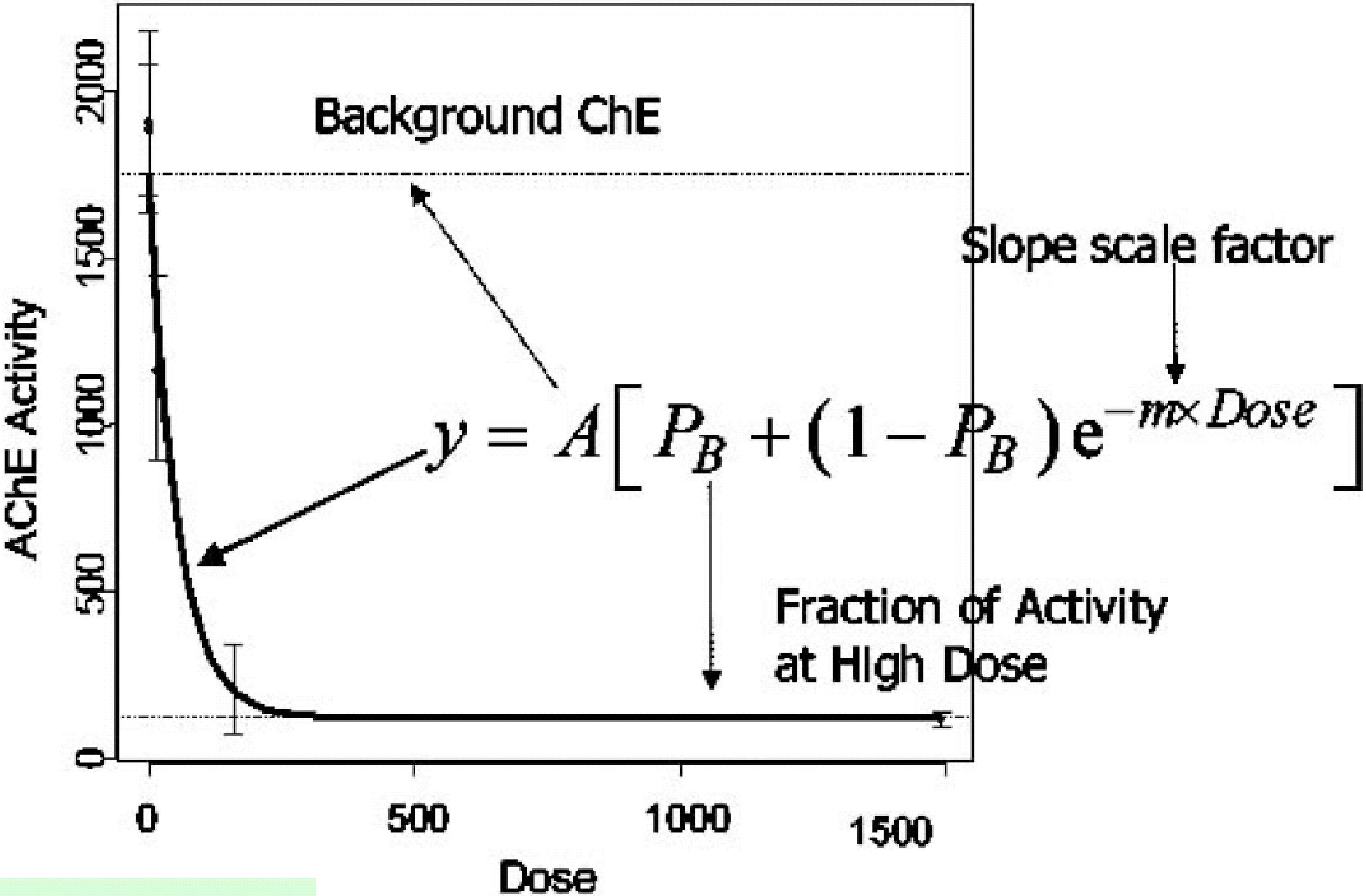
- Biomonitoring
  - Volunteers carry out “residential activity”
    - Extract clothes
    - Extract gloves; wash hands
    - Air monitoring in breathing zone using portable sampler
  - Assess biomarkers
    - For ex., metabolite in urine
      - Back calculate whole body exposure

lowest observable effect level



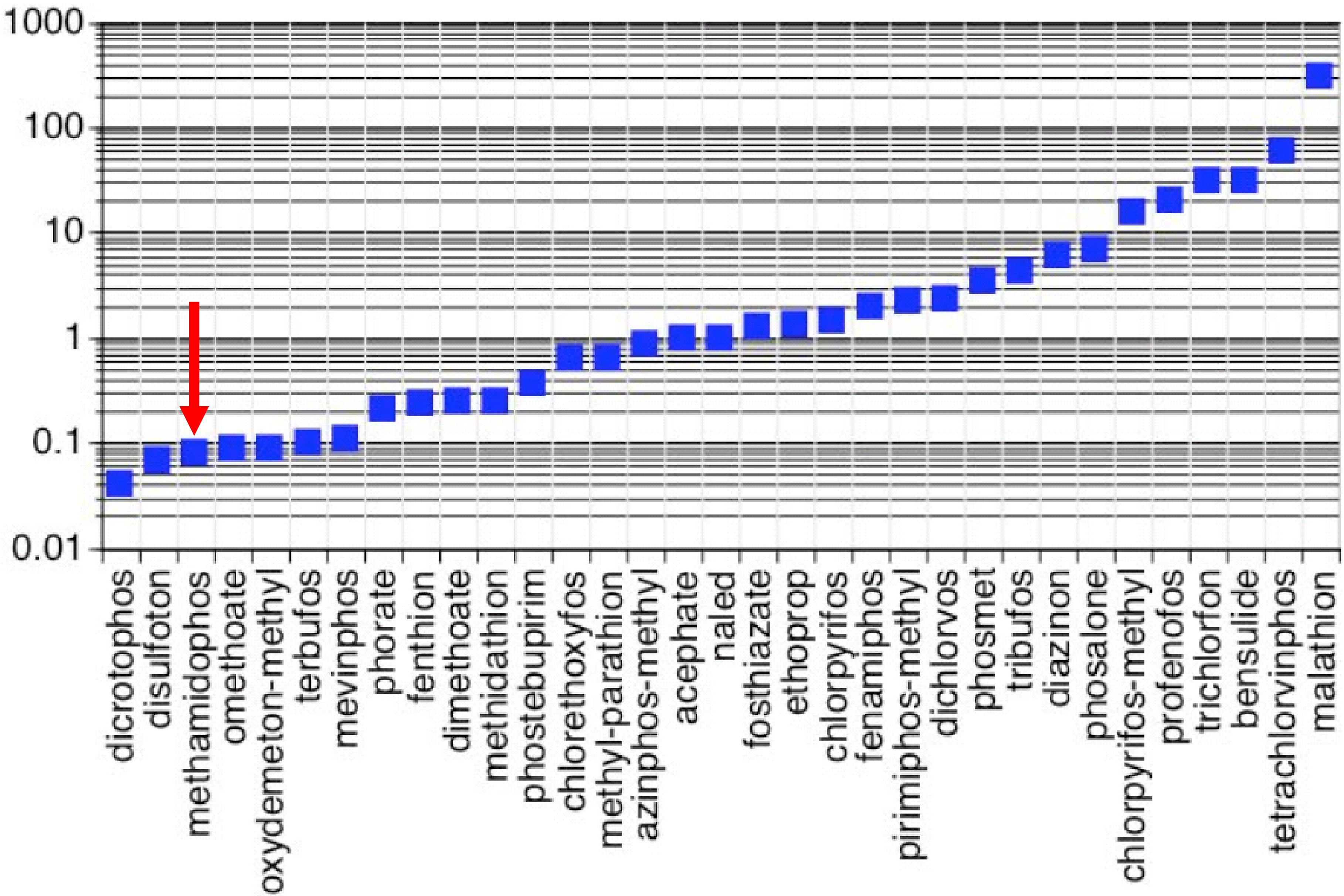
NOEL = dose causing no adverse effects;
RfD = NOEL/100
Preliminary PAD = RfD/3; Revised PAD = RfD/10

Basic Exponential Dose-Response Model for Estimating 10% ChE Inhibition Benchmark Dose (BMD10)

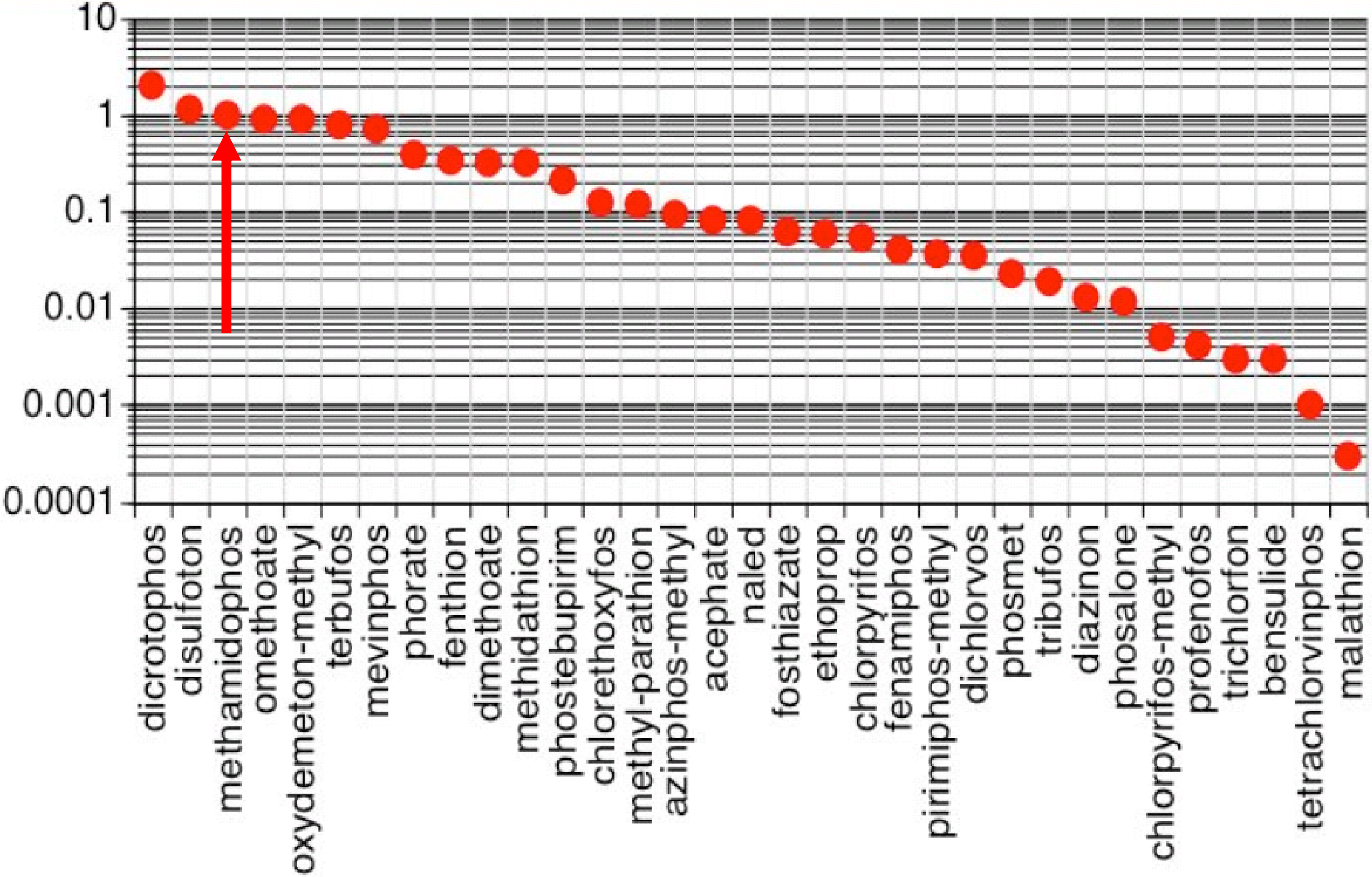


EPA CRA revised

Female BMD10s (Dose Inhibiting Brain AChE by 10%)



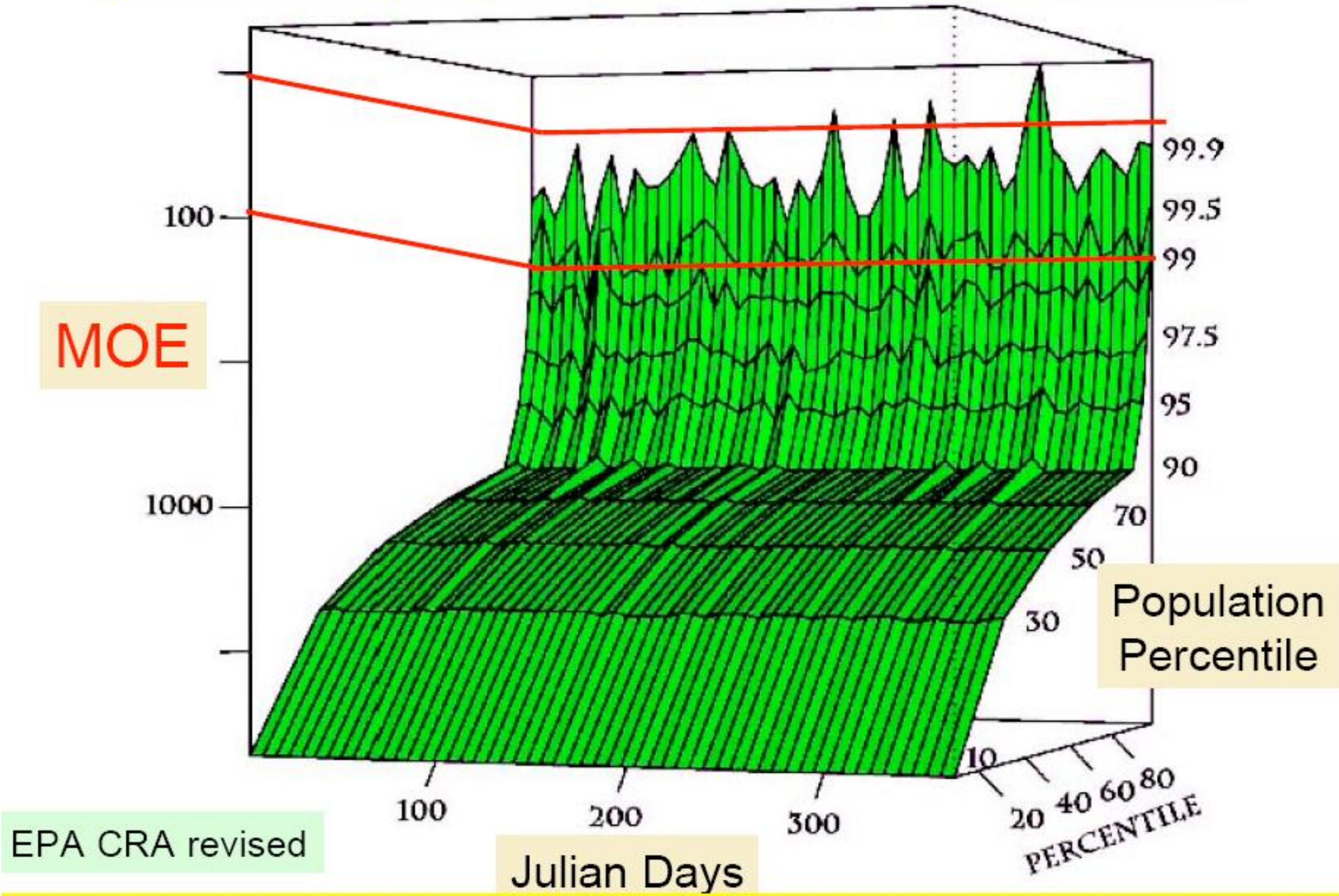
Relative Potency Factors Based on Female Brain Acetycholinesterase Inhibition



Exposure Determination

- Multiply RPF by residue concentrations resulting from each exposure scenario to create index equivalent residue
  - Sum all the index equivalent residues for each exposure scenario
- Add all index equivalent residues across exposure scenarios employing a one-day time step for each individual modeled by Calendex
  - Repeat modeling for each person represented in the CFSII database

Total MOE by Day of Year and Percentile of Exposure



Note: overall MOE @ 99.9th percentile of exposure lies somewhere between 100 & ~50

EPA’s Conclusions

- Drinking water contributed very little to cumulative exposure
- Residential exposure was the major contributor to cumulative exposure
  - DDVP pest strips (inhalation exposure)
  - Hand-to-mouth behavior in children
- Certain foods contributed more to dietary exposure than others (for example, grapes, apples, pears)
- Even with the extra FQPA safety factor of 3 incorporated into the RPFs, MOE for 1-2 year old was about 50 or greater

Ecorisk Dilemma

- Too many species to protect
- Must accept some adverse effects (practically speaking)
  - Habitat destruction dominates any possible effect that pesticides could have (absent a spill or other intentional misuse)
- Desire to know the likelihood that communities and ecosystems will be affected
  - However, studies are largely based on examining individuals, not higher levels of hierarchy

EPA Objective

- Choose most sensitive organism
- If can protect that organism, then there is a reasonable certainty of no environmental harm

Giddings et al., ETAC v. 15, 1996

Summary of Effects-LOECs

- Zooplankton
  - Total numbers--4.3 μg/L
  - Taxonomic richness--2.4 μ/L
- Insects
  - Total numbers--9.2 μg/L
  - Taxonomic richness--9.2 μg/L
- Fish
  - Survival--54 μg/L
  - Biomass--22 μg/L
- Aggregate LOEC & NOECs
  - LOEC (70-day, 9.2 μg/L)
  - NOEC (70-day, 4.3 μg/L)

Thank you for your attentions!