Health Risk Assessment

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Mixture Risk Summary - 20 minutes

- **Overview of EPA Methods**
  - Exposure issues
  - Component chemicals
  - Whole mixtures

- **Additivity**
  - Response addition
  - Dose addition
  - (Relative Potency Factors)

- **Interaction based Hazard Index**
  - Toxicologic interactions
  - Weight of evidence
  - Modified Hazard Index

- **New Directions**
  - Exposure time
  - Models
  - Cumulative risk

Mixture: definition

Any two or more chemicals contributing to same toxic effect

The two chemicals can:

- Be in different media
- Have exposures at different times
- Cause different effects when alone

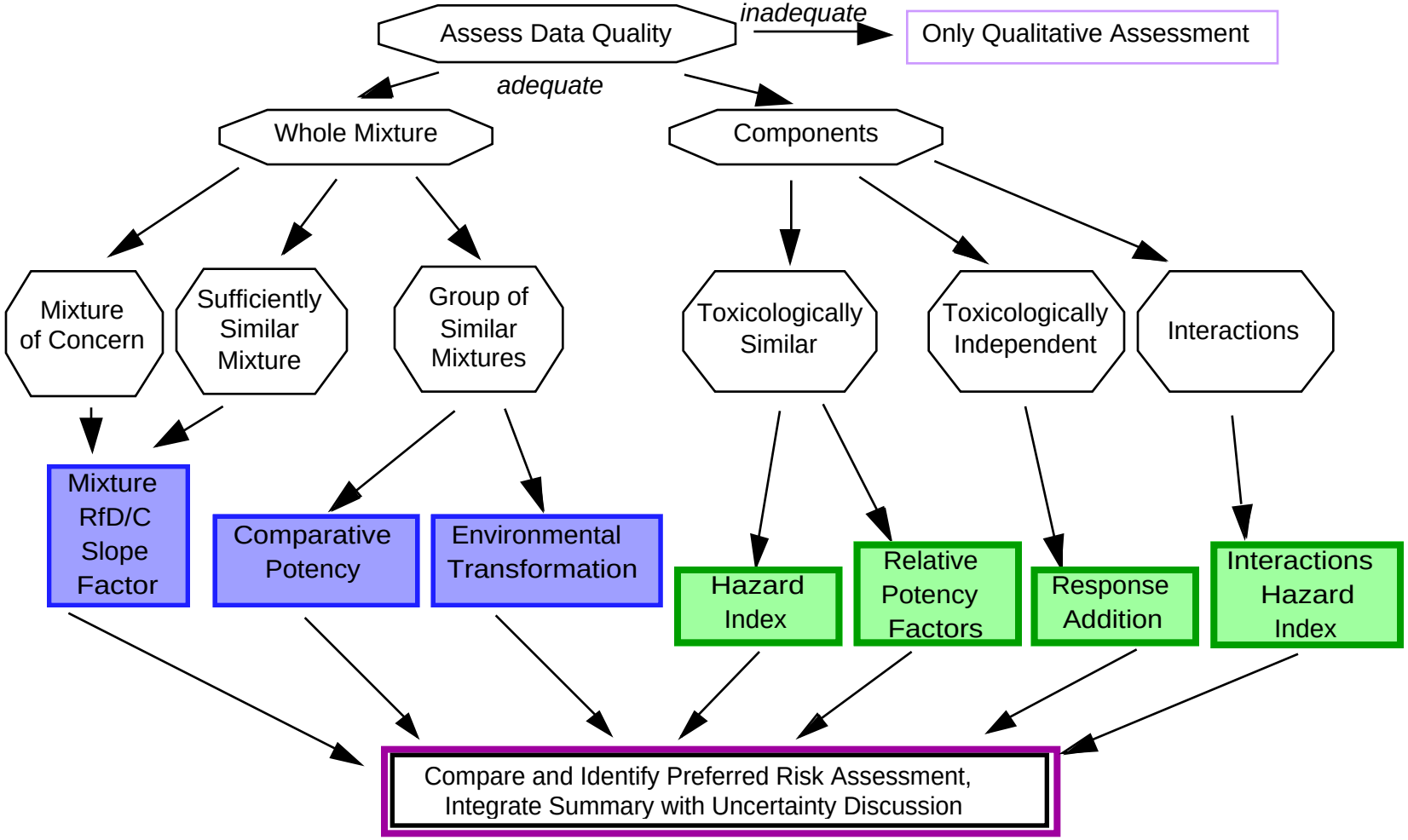
The two chemicals must have some overlap, such as:

- Co-exist in media (external exposure)
- Share metabolic pathway
- Co-exist in target tissue (chem concentration or toxic effect)

User Fact Sheet: Hazard Index

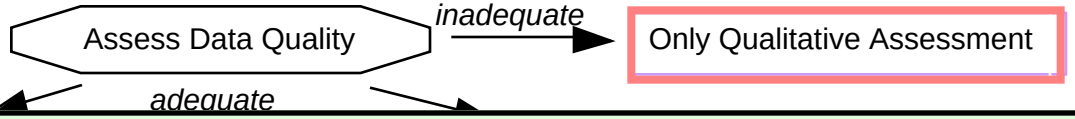
- **Approach:** Hazard Index
  Type of Assessment: Risk Characterization for any Toxic Endpoint
  Section(s): 4.1, 4.2
  References: Used in Superfund site assessments (U.S. EPA, 1989).
  Data Requirements: Method requires both toxicity and exposure data on the mixture's components. Good dose-response data are needed, such as what is available on IRIS (U.S. EPA, 2000).
  Strategy of Method: Scale individual component exposure concentrations by a measure of relative potency (typically, divide by a Reference Dose/Concentration (RfD/C)) for components with a similar mechanism-of-action. Add scaled concentrations to get an indicator of risk from exposure to the mixture of concern.
  Ease of Use: Easy to calculate.
  Assumptions: Applies dose addition which carries with it assumptions of same mode-of-action and similarly shaped dose-response curves across the components. Mode-of-action assumption can be met by using a surrogate of same target organ.
  Limitations: Exposure data must be at relatively low levels (near no-adverse-effect levels) at which interaction effects are not expected. RfD/C values across components vary in their uncertainty, so other measures of potency may be more appropriate.
- **Uncertainties:** Similarity of mechanism-of-action. Accuracy of exposure data.

2000 US EPA Mixture Risk Guidance



All possible assessment paths should be performed.

2000 US EPA Mixture Risk Guidance



Evaluation of Quality of Exposure Information

GOOD Monitoring, perhaps with modeling information well characterizes human exposure to the mixture or its components.

Modeling information reasonably characterizes human exposure to the mixture or its components.

FAIR Exposure estimates for most components - - not likely to substantially affect the risk assessment.

Not all components identified, or exposure levels highly uncertain or variable. The effect on the risk assessment is unknown.

POOR The available exposure information is insufficient for conducting a risk assessment.

Integrate Summary with Uncertainty Discussion

Example: Cancer Risk combining different effects

- US EPA usually treats cancer as probability (risk)
- Superfund criteria for no further action (usually)
  - **Single chemical cancer risk < 10^{-6}**
  - **Mixture cancer risk < 10^{-4}**
- Mixture risk number plausible if low, e.g., $R_{mix} < 0.01$
  - **Otherwise consider possible interactions**

Common Simplification:

surrogate mixture close in composition to mix of concern

- **Similar Mi**

  same mode of action
  similarly shaped dose-response curves

- **Similar Co**

  chemically related mixtures
  similar modes of action and primary effect

  perfund site)

- **Group of Similar Mixtures** (e.g., arachlors, PAH-combustion emissions)

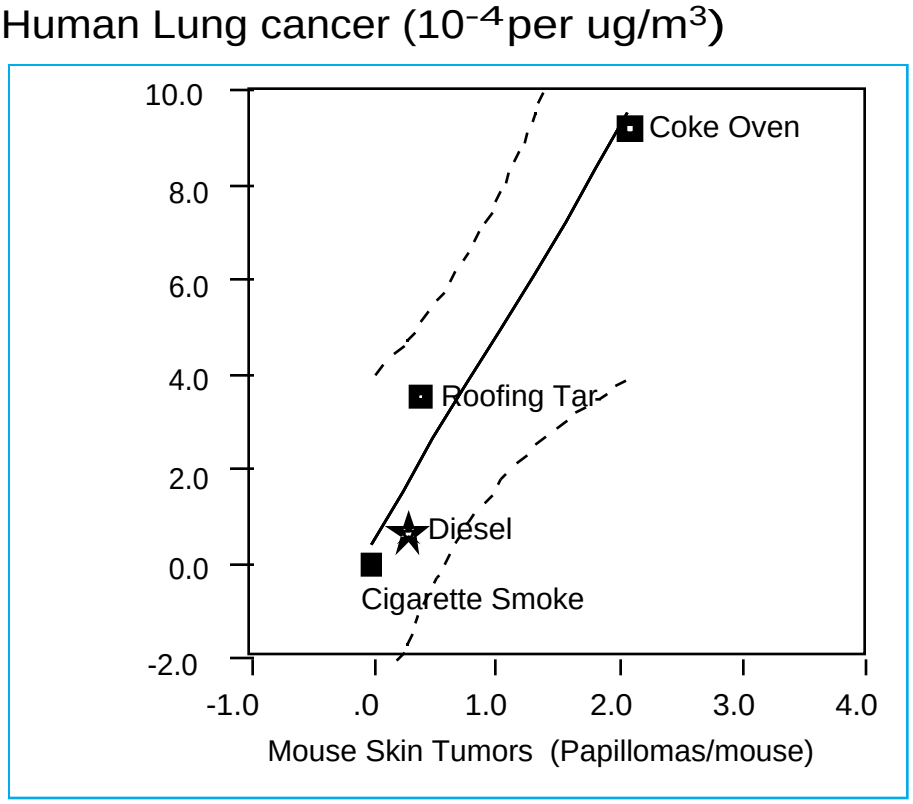
Simplification 2:
Assumption of Independence

Independence of Action

(e.g., carcinogens causing tumors in different organs)

- **The toxicity of one mixture component does not influence the toxicity of the other**

U.S. EPA Methods for Whole Mixtures
Comparative Potency- for combustion mixtures



Linear regression with 95% confidence bands.
Diesel data not used in the regression.

See other in vitro approaches by Texas A&M (Donnelly and colleagues)

Types of Additivity

Dose Addition- cumulative exposure (e.g., Hazard Index, TEFs, RPFs)

- Addition of scaled component doses
- Scaling accounts for relative toxicity
- Assumes same mode-of-action across components
- Assumes similarly shaped dose-response curves of components

Response Addition- cumulative risks (e.g., RAGS method - cancer risks)

- Addition of component risks
- Assumes toxicologic and statistical independence

Effects Addition- cumulative effects (rare, not shown in 2001 Guidance)

- Addition of biological measurements across components
- Assumes toxicologic similarity across components

Response (risk) Addition

survive chemical 1 AND survive chemical 2

For two chemicals:

$$R_m = 1 - (1 - r_1) * (1 - r_2)$$

Simplifies to:

$$R_m = r_1 + r_2 - r_1 * r_2$$

Where:

R_m = mixtures risk

r_i = component risks

Assumes biological and statistical independence of action

What About Noncancer Effects? (or threshold carcinogens)

Is there a risk (probability)?

- Of what? Is there one toxic effect?

- Low dose or risk?

- What risk if all less than threshold dose?

What does Independence Mean?

- Independence if all cause the same effect?

- Example: risk of developmental effects?

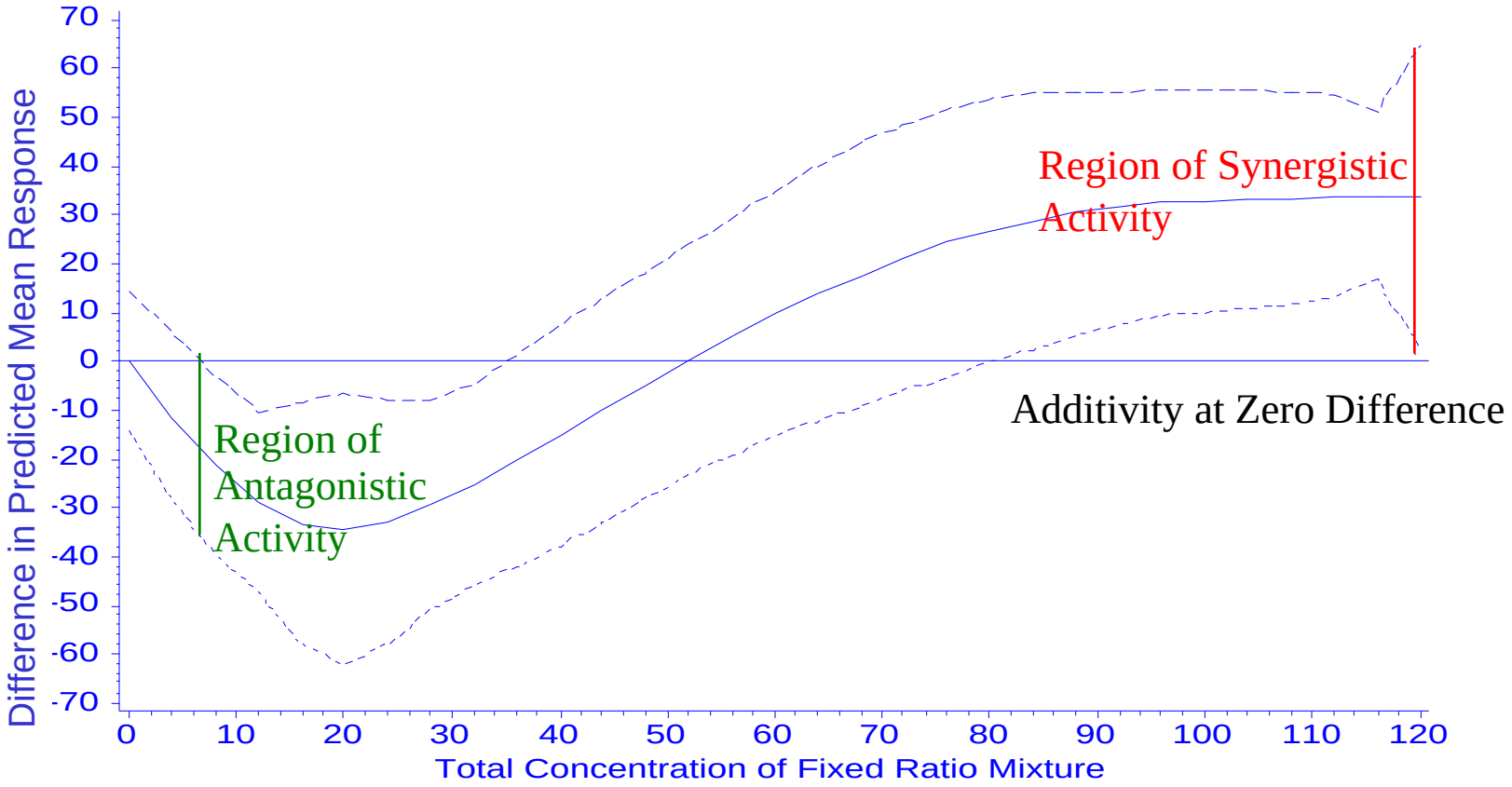
Dose Addition Theory

Let C_1= intake as chemical 1 = $\sum_{i=1}^{n} Intake_i \frac{pot_i}{pot_1}$

Then, the dose-response function for chemical 1 is used to estimate mixture risk. $R_m = f_1(C_1)$

- Assumes same mode-of-action across components
- Assumes similarly shaped dose-response curves across components
- Use is appropriate at low doses where interaction effects are less likely

Modeling of Departures from Additivity (Gennings et al., 1997)



A joint dose-response model is built using single chemical data assuming dose addition. Lab data on the mixture is compared with model predictions.

The Moral

Interaction can change with total dose

Applied Dose Addition: The Hazard Index

$$\mathbf{HI} = \sum_{i=1}^{n} \frac{estimated\ \ intake_i}{RfD_i}$$

- Uses RfDs to scale for toxic potency, usually calculated as RfD = NOAEL / Uncertainty Factors (UF)
- Relaxes same mode-of-action assumption to same target organ affected across components
- Assumption of similarly shaped dose-response curves of components is hard to show in practice
- Recommend use at low exposures where interaction effects are less likely

Uncertainties for Component Based Approaches

- **Limit use to simple mixtures of a dozen or so chemicals**
  - Express how well these chemicals represent the entire mixture's composition and, by extension, the entire mixture's risk
- **In general, the risk assessor must use considerable judgment along with plausible approaches to perform a mixture risk assessment**
  - Results must be presented transparently
  - Assumptions should be confirmed whenever possible
- **Data gaps and differences in data quality among components must be considered and described, such as:**
  - Use of RfDs and RfCs with different UFs, confidence statements
  - Exposure issues: variability, unidentified components, bioavailability

Interactions-Based Hazard Index

- What are Toxicologic Interactions
- When should interactions be included?
- How can we quantify interactions?
- Can we evaluate prediction accuracy?

What is Synergism? (according to US EPA)

Both Chemicals at Toxic Levels

- Synergism Joint toxicity is more than predicted by dose addition
- Antagonism Joint toxicity is < D.A.

One Chemical Does Not Cause that Toxic Effect

- Potentiation Joint toxicity is > D.A.
- Inhibition Joint toxicity is < D.A.

Dose Addition

- All chemicals in the mixture are toxicologically **similar**.
- DoseMIX = sum(scaled doses)

$$d_{M1} = \sum_{i=1}^{n} T_{i1} d_i$$

Response Addition

- Special case where the chemicals act independently

How Can We Quantify Interactions?

- At common lower environmental levels, interaction magnitude < 10-fold

Chemicals	Min toxic dose (ED_{10})
A and B (dose addition)	20
A and B (observed)	4

Interaction magnitude = 5 (= 20/4)

- Few studies quantify interaction.

Hazard Index

$$HI = \sum_{i=1}^{n} \frac{E_i}{RfD_i}$$

$$d_{M1} = \sum_{i=1}^{n} T_{i1} d_i$$

Assumes Dose Addition

- Similar toxic effects only
- Separate index for each major toxic effect

Accounts for Joint Exposure without Synergism

How can We Quantify Interactions?
Weight of Evidence Modification of the Hazard Index

$$HI_{ADD} = \frac{E_1}{RfD_1} + \frac{E_2}{RfD_2} = HQ_1 + HQ_2$$

$$HI_{INT} = \sum_{j=1}^{n} HQ_j \sum_{k \neq j}^{n} f_{jk} M^{B_{jk} g_{jk}}$$

$$f_{jk} = \frac{HQ_k}{HI_{ADD} - HQ_j}$$

$$g_{jk} = \frac{\sqrt{HQ_1 \bullet HQ_2}}{(HQ_1 + HQ_2)/2}$$

Weight of Evidence Modification of the Hazard

$$HI_{INT} = \sum_{i=1}^{n} HQ_i$$

Fraction of all interacting chemicals: f

$$f_{ij} = \frac{HQ_j}{HI_{add} - HQ_i}$$

Interaction magnitude: M

Equitoxicity measure: g

Weight-of-evidence score:

$$g_{ij} = \frac{\sqrt{HQ_i HQ_j}}{\left(HQ_i + HQ_j\right) \div 2}$$

Hypothetical Example

response predicted by dose addition

Three Chemicals, constant HI=1

All pairwise synergistic, M=5 for each pair

B_{jk}=1 (excellent data)

Proportions	HI_{INT}
1 : 1 : 1	**5**
8 : 1 : 1	**2.8**
98 : 1 : 1	**1.4**

Weight of Evidence Scores

Category	Description	Greater than Add	Les than Add
I.	Directly relevant to humans	1.0	1.0
II.	Animal studies, but relevant	0.75	0.5
III.	Plausible evidence, relevant?	0.5	0.0
IV.	Additivity demonstrated or accepted because poor data	0.0	0.0

e.g.: *in vitro* studies given less importance

Antagonism given less influence

Example: antagonism needs more proof

Region III- Palmerton site

- Zn, Cd, Pb all at high levels in soil
- Zn is known inhibitor of Cd and Pb
- Can Region relax Pb soil standard because of Zn?

Data support?

- Pb and Cd are synergistic
- Zn inhibits the synergy and entire toxicity of Pb+Cd
- 3-metal interaction study is on testicular atrophy,
  Does not consider neurodevelopmental effects in children

Decision- **NO**

The Moral

Interaction can change with total dose

Reported interaction may be irrelevant to situation or effect being considered

Is cumulative risk, even mixture risk,

too inconsistent or complicated?

how to stop forest fires...

8.27.02

Good and Bad Qualities

- **Assumptions**
  - Pairwise interactions are all that is needed
  - Interaction magnitude of 5 as default
- **Plausible**
  - Toxic interaction mechanisms work in pairs
    3-chemicals: C influences the A*B interaction
  - At low doses, interactions = small change from dose addition
- **Unknowns**
  - The dose-dependent functions
  - WOE judgments and scores- reasonable? reproducible?
  - Is there a limit on the number of chemicals?

Can We Evaluate the Prediction Accuracy?

Sort of . . .

- Plausibility of the formula structure
  - Do the functions make sense?

- Numerical agreement with simple cases
  - Reduce to HI if interaction magnitude=1
  - If all M=5, HI_{INT} =5*HI

- Plausibility of assumptions and defaults
  - Any data showing pairwise interactions are sufficient for more complex mixture?

(still looking for good data...)

Mixtures Risk Assessment

A combination of scientific information and judgment

Difficult to evaluate accuracy

- Methods judged by plausibility

Requested by stakeholders and regulatory agencies

Always room for improvement by smart people!

- Still using dose addition as default, BUT
- Many issues to discover and resolve

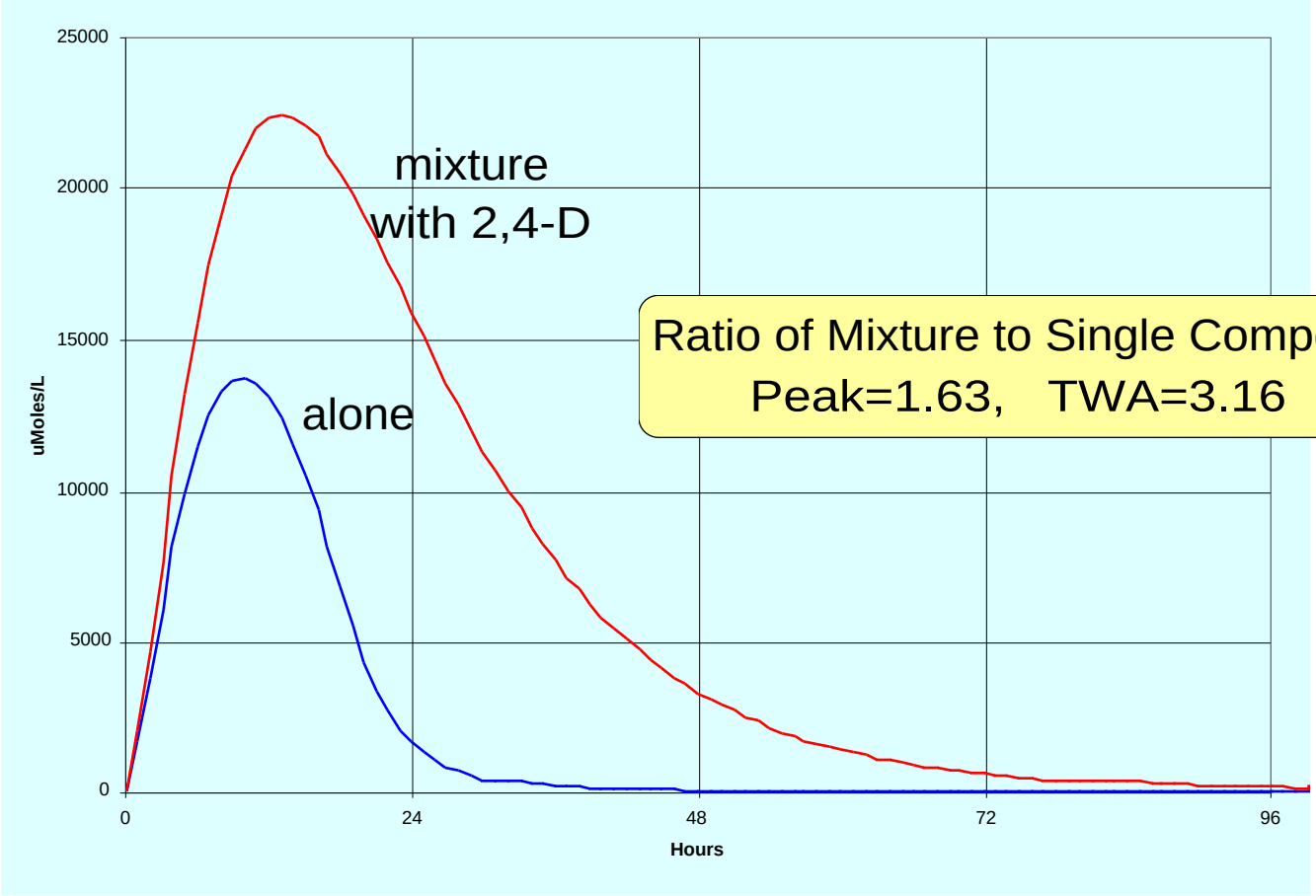
New Directions
(and problems with present methods)

- Complex Toxicity

  - Multiple population susceptibilities

  - Multiple endpoints and severities

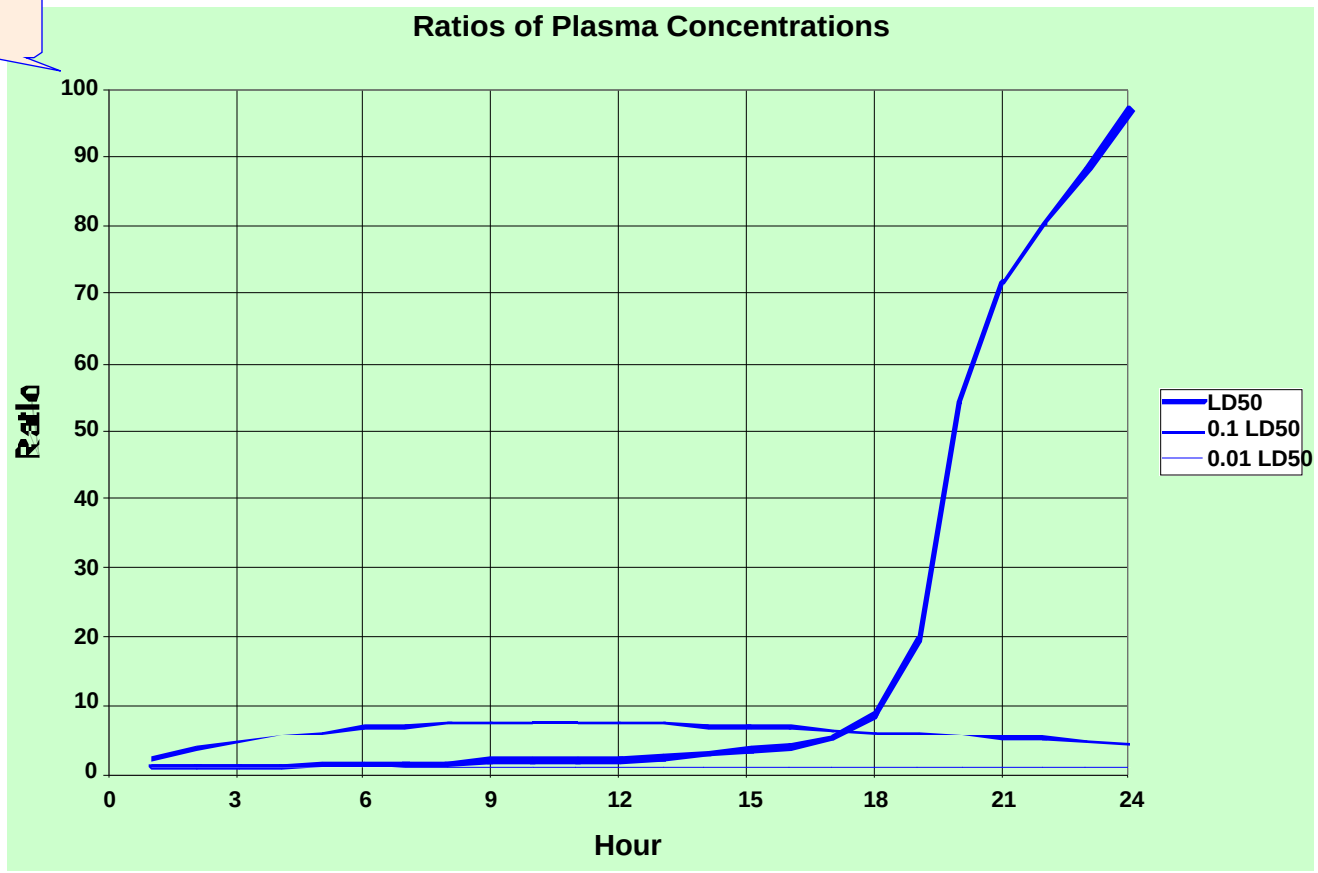
Effect on Picloram in Liver Mixture at LD_{50} Levels

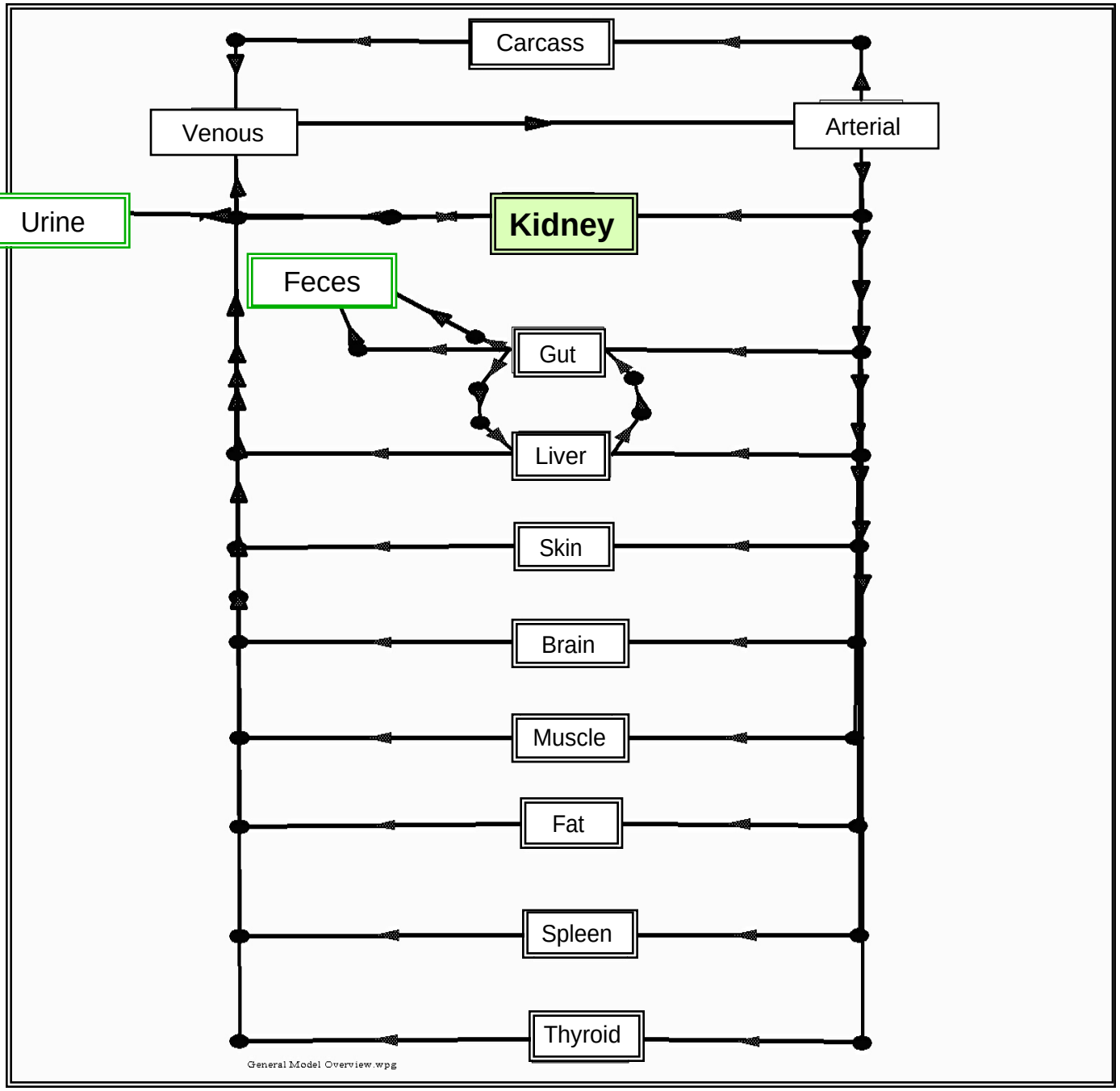


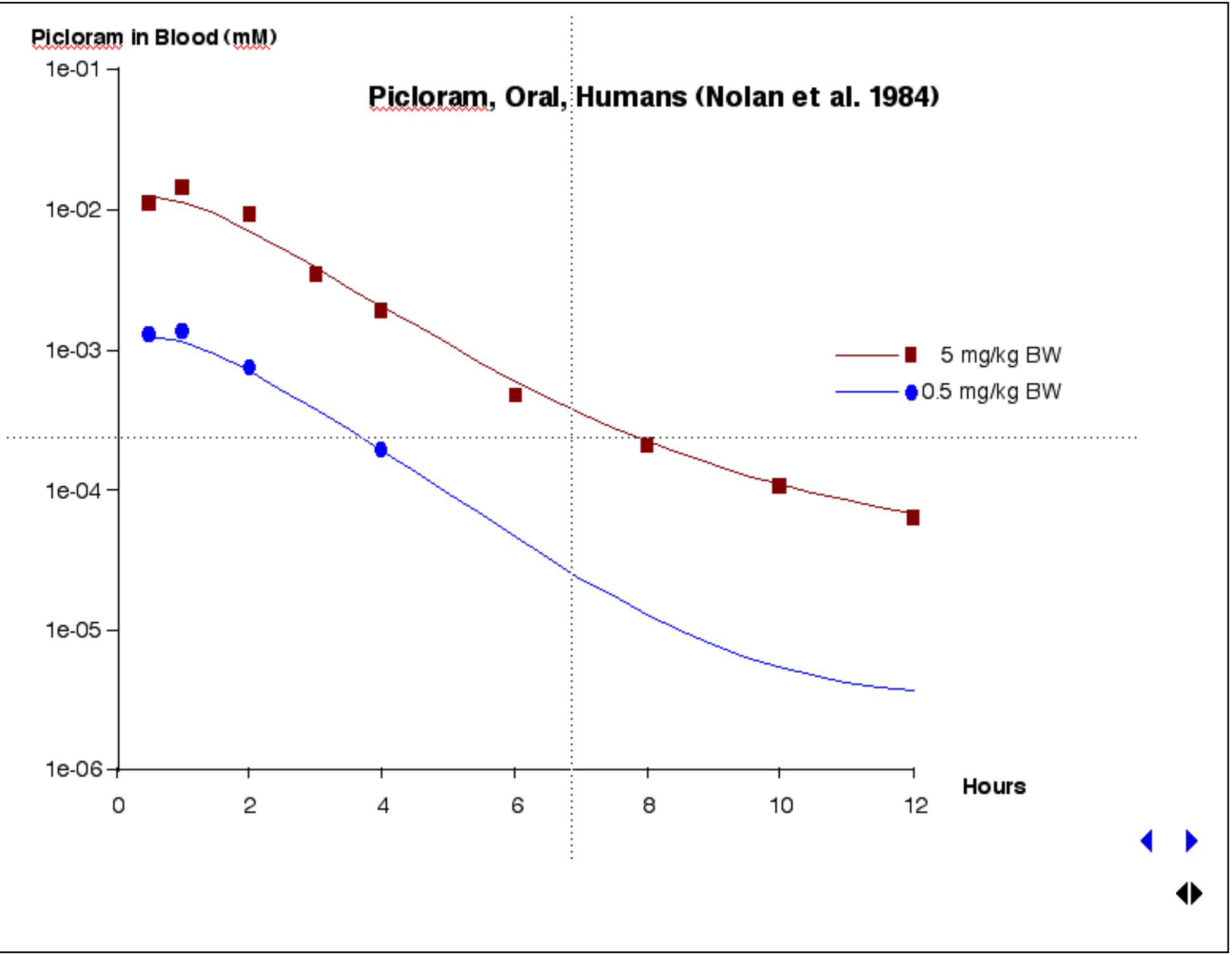
Ratio of Mixture to Single Compound
Peak=1.63, TWA=3.16

Picloram in the Liver at LD_{50} and Lower Doses

100




Carcass
Venous
Arterial
Urine
Kidney
Feces
Gut
Liver
Skin
Brain
Muscle
Fat
Spleen
Thyroid
General Model Overview.wpg


Picloram in Blood (mM)
Picloram, Oral, Humans (Nolan et al. 1984)
1e-01
1e-02
1e-03
1e-04
1e-05
1e-06
0
2
4
6
8
10
12
Hours
5 mg/kg BW
0.5 mg/kg BW

Physiologically Based Pharmacokinetic Models

- Mechanistic foundation
  - believable
- Adaptable
  - cross species, routes, ..
- Predictive
  - testable
- Expensive, specific to mixture under study

Toxicologic Examples
Chemical-Chemical Interactions

- Synergism
  - Formation of nitrosoamines from nitrites and amines
- Antagonism
  - Depletion of tissue levels of Vitamin B6 due to interaction with dimethyl hydrazine

Toxicologic Examples
Pharmacokinetic Interactions- Absorption

- Synergism
  - Enhanced neurotoxicity of EPN due to increased skin absorption by aliphatic hydrocarbons
- Antagonism
  - Inhibited lead toxicity due to decreased lead absorption in presence of zinc

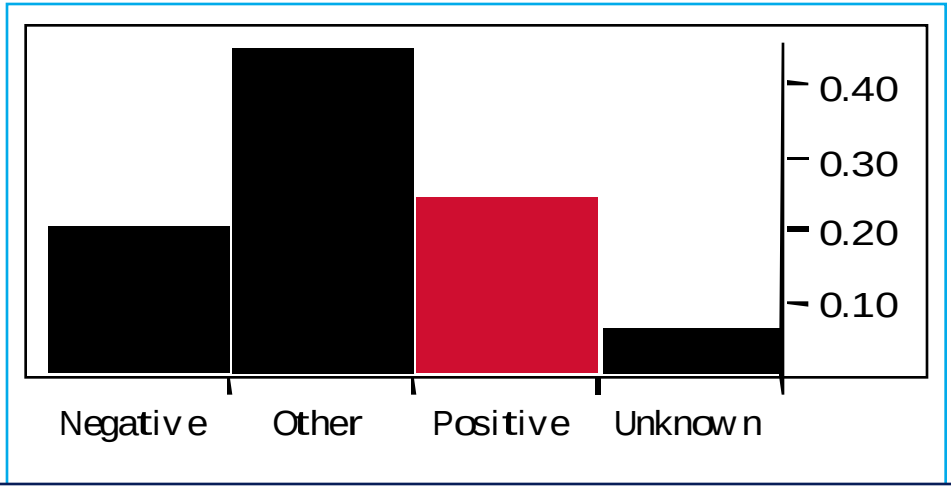
Toxicologic Examples
Pharmacokinetic Interactions- Distribution

- Synergism
  - Increased lead levels in brain following treatment with dithiocarbamate derivative
- Antagonism
  - Protection of cadmium toxicity by selenium through decrease of cadmium concentration in liver and kidney

Toxicologic Examples
Pharmacodynamic Interactions- at DNA

- Antagonism
  - Copper DNA binding antagonism by other metals

How Often is Synergism?



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Very few inhalation studies

IRSST (Montreal) updating all TLV chemicals to include interactions

xicity

rs, 1990.

Summary and Guesses?

- Synergy magnitudes not large
- Info available for many priority chemical combinations
- Research still needed, e.g.,
  - particulates potentiating other airborne chemicals' toxicity

Relative Potency Factors

- Dose Addition Basis
- Procedures for RPF Development
- Risk Characterization using RPFs

Differences between the TEF and RPF

TEF Specific Type of RPF	RPF General Case
All health endpoints	May be limited
All routes	May be limited
All timeframes of exposure	May be limited
Implies more abundant data are available	May be based on lower quality/ fewer data
Implies greater certainty about mode-of-action	May be more accurate because application can be constrained given available data
Less emphasis on analytic uncertainty	Greater emphasis on characterization of uncertainty

Process

1. Demonstrate the Need
2. Define the Class of Compounds

   -common MOA

3. Develop the RPFs

   -Index Chem.Test value/test value of component

4. Characterize Uncertainty

   -identify health endpoints, exposure routes, durations, and dose ranges covered and not covered by approach

5. Evaluate the RPF Process
6. Identify Research Needs

CASE STUDY:
Example - Toxicologic Properties of 5 Cholinesterase Inhibitors

Chemical	Study ED10 (mg/kg/day)	Test Species	Duration Critical Study	Data Set Characteristics
Alphaphos	1.0	Rat	90 days	Poor. Few poor studies.
Betaphos	10.0	Rat	90 days	Good. Many good studies, many endpoints, multiple species
Chlorophos	0.3	Rat	90 days	Extensive. Human confirmation of effects
Ethaphos	0.06	Rat	90 days	Good
Deltaphos	1.5	Rat	90 days	Limited. Few well-conducted studies.

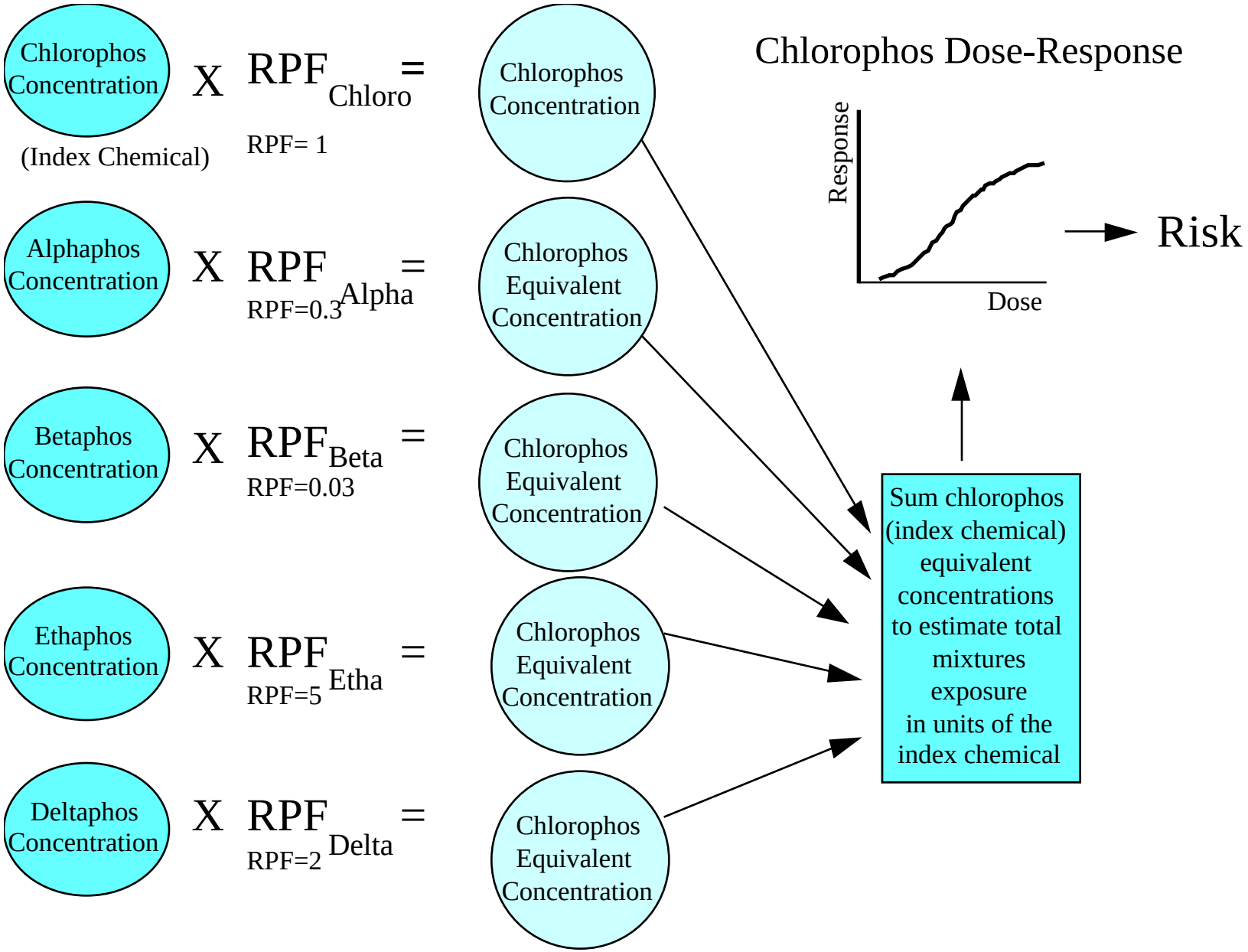
RPFs and Equivalent Exposures

Chemical	Study ED10 (mg/kg/day)	RPF	Exposure (mg/kg/day)	Chlorophos Equivalent
Alphaphos	**1.0**	**0.3**	**0.15**	**0.045**
Betaphos	**10.0**	**0.03**	**0.02**	**6E-4**
Chlorophos	**0.30**	**1.0**	**0.25**	**0.25**
Ethaphos	**0.06**	**5.0**	**0.05**	**0.25**
Deltaphos	**0.15**	**2.0**	**0.15**	**0.30**
TOTAL			**0.62**	**0.85**

Chlorophos ED_{10} = 0.30, Chlorophos equivalent exposure = 0.85

Index Compound is associated with 29% of the RPF Predicted Toxicity

Index Compound is associated with 40% of the Exposure to Class


Chlorophos Concentration
X
RPF Chloro =
RPF= 1
(Index Chemical)
Alphaphos Concentration
X
RPF Alpha =
RPF=0.3
Betaphos Concentration
X
RPF Beta =
RPF=0.03
Ethaphos Concentration
X
RPF Etha =
RPF=5
Deltaphos Concentration
X
RPF Delta =
RPF=2
Chlorophos Concentration
Chlorophos Equivalent Concentration
Chlorophos Equivalent Concentration
Chlorophos Equivalent Concentration
Chlorophos Equivalent Concentration
Sum chlorophos (index chemical) equivalent concentrations to estimate total mixtures exposure in units of the index chemical
Chlorophos Dose-Response
Response
Dose
Risk