Acute and Chronic Lethal Effects to Individuals: Contaminant Interactions and Mixtures

2009
Mixture Effects

Many contamination scenarios reflect exposure to multiple toxicants.

How are combined effects of contaminants assessed?
  - direct measurement preferred; but prediction is most often necessary

Problems include:
  - measuring or predicting effects under equivalent conditions
  - establishing valid interaction models; e.g.
    - potentiation
    - additive
    - comparative
    - multiplicative
    - detecting synergistic or antagonistic interactions

Note – issues are similar for both lethal and sublethal effects
Toxicant Interactions

**Potentiation**: non-toxic chemical enhances the toxicity of another chemical

- naringin, bergamottin (grapefruit, orange, apple)
  - inhibit CYP3A4
- piperonyl butoxide - routinely added to insecticide formulations
  - inhibits cytochrome P450s

![Structure of piperonyl butoxide](image.png)
Toxicant Interaction Models

Potentiation: non-toxic chemical enhances the toxicity of another chemical

Additive: observed effect is the sum of the individual effects

Simple Comparative: observed effect is equal to the single worst effect

Multiplicative: observed effect is the approximate product of the individual effects
Toxicant Interactions

**Synergism**: observed effect is greater than the combination of the predicted individual effects

Additivities/synergism mechanisms:
- concentration additivity
- similar joint action - same mode of action
- independent joint action - different modes of action

**Antagonism**: observed effect is less than the combination of the predicted individual effects

Antagonism mechanisms:
- functional
- chemical
- dispositional
- receptor
**Mixture Effects - Additivity**

**Toxic Unit** approach:

Incipient LCs of the individual compounds are determined; e.g.

Define a Toxic Unit (TU) as the incipient LC$_{50}$ for each compound

- chemical concentrations can be converted to proportional TUs

- TUs can be added to predict mixture effects; e.g. PAH mixtures ....
Calculating PAH Toxicity for Amphipods

**Input**

- Measure PAH bulk
- Predicted PAHs in Interstitial Water
- Toxic Units for each PAH
- Toxic Units for sediments

**Model**

- Equilibrium Partitioning Model
- Toxic Unit: \( TU = \frac{PAH_{iw}}{10\text{-d } LC_{50}} \)
- Additivity Model: Sum TU for all PAHs
- Concentration-Response Model

**Output**

- Predicted PAHs in interstitial water
- Toxic Units for each PAH
- Toxic Units for each sediment sample
- Probability of toxic effect from each sediment sample

Field collected samples

Landis, WG, & Yu, MH, 2004
Mixture Effects - Additivity

**Toxic Equivalency** approach (for compounds with similar MOAs):

- most toxic member of a family is assigned a **Toxic Equivalency Factor (TEF) = 1**
- *similarly acting* compounds given empirically-determined TEFs (< 1)
- **Toxic Equivalency (TEQ) = TEF x concentration**
- mixture TEQ = (TEF_A x [A]) + (TEF_B x [B]) + (TEF_i x [i])
Additivity Isobole

- Toxic Units of Toxicant A
- Toxic Units of Toxicant B

- Additivity
- Synergism
- Antagonism
Choice of interaction models critical for definition of synergistic/antagonistic responses.

Standard models:
- comparative
- additive
- multiplicative
**Synergism/Antagonism Models**

**Simple comparative effect model**: effect of stressors in combination is equal to the effect of the **single worst** or dominant stressor.

Stressor A: results in 55% decreased yield

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\[
\text{Combining A & B:}
\]

Yield with simple comparative effect

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**Synergism**

**Antagonism**

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\% Optimal yield (etc.)

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\[ \text{Combining A \& B:} \]

- Yield with additive effect

\[ \text{Synergism} \quad \text{Antagonism} \]

Synergism/Antagonism Models

**Multiplicative effect model**: Stress from one source can be further operated on probabilistically by another source. Combined effects approximate the product of the individual effects.

Stressor A: results in 55% decreased yield
Stressor B: results in 45% decreased yield

Combining A & B:

Yield with multiplicative effect

Synergism

Antagonism

% Optimal yield (etc.)

Temporal Perspective

Time-response (T-R) approach compliments dose–response approach.

The T-R approach emphasizes exposure duration, not level
- metric: “Time To Death” (TDD)
- \( LT_{50} \) estimates the median time to death.

The T-R approach generates substantially more data than D-R
(see Figure 9.9 in text)
= more statistical power
- requires considerably more effort and resources than D-R

The T-R approach is employed less broadly and used less frequently in Risk Assessments and in the overall regulatory arena.