Impact of Grouping Misclassification on Risk Prediction when using the Relative Potency Factors Method to Assess Mixtures Risk

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The authors have no conflicts of interest to report.

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TOPICS

- Grouping chemicals for mixture risk prediction
  - Extrapolations to environmental exposures
  - In the absence of mixture data
  - Using the index chemical, relative potency factor approach
  - Is it dose addition or response addition (independence)?
- Grouping misclassification effect on mixture risk prediction
  - What can go wrong?
  - How bad is it?
  - Can we fix it?

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GROUPING CONCEPTS

- Toxicologic similarity groups for dose addition
  - Similarity of toxic action
  - Common key dose-additive process
    - Not necessarily the full MOA/AOP
- Independent action groups
  - Completely independent MOA (still the same endpoint)
    - No shared key events
  - Dose addition within, response addition across (integrated addition)

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INDEX CHEMICAL, RELATIVE POTENCY FACTOR MODEL

IC_RPF = index chemical, RPF dose addition model

Assumes constant relative potency

$$Prob_{mix} = f\left(\sum_{i=1}^{n} d_{\mathrm{i}} \cdot \mathrm{RPF_i}, \Theta_{IC}\right)$$

$$Prob_{mix} = f\left(d_{\mathrm{IC}} + d_1 \cdot \mathrm{RPF_1} + d_2 \cdot \mathrm{RPF_2} \ldots + \ d_{\mathrm{n}} \cdot \mathrm{RPF_n}, \Theta_{IC}\right)$$

IC = index chemical

RPF = relative potency factor

$$\mathrm{RPF_i} = \mathrm{ED}x_{\mathrm{IC}} \div \mathrm{ED}x_{\mathrm{i}}$$

EDx = effective dose associated with response x

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GROUPING MISCLASSIFICATION: Where can we go wrong?

- Getting the RPF wrong
- Assigning a compound to the wrong dose-additive group
- Failing to allow for differently-shaped dose-response curves
- Mistaking dose additivity for response additivity
- Failing to account for different control values
- Failing to account for partial agonists
- Improper application of effect summation
- Low-dose extrapolation

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GROUPING MISCLASSIFICATION I: Getting the RPF wrong

- Getting the RPF wrong
  - Error depends on the magnitude of the RPF error, the mass-fraction contribution of the chemical to the mixture, and the group IC dose-response function
- Assigning a compound to the wrong dose-additive group
- Failing to allow for differently-shaped dose-response curves
- Mistaking dose additivity for response additivity
- Failing to account for different control values
- Failing to account for partial agonists
- Improper application of effect summation
- Low-dose extrapolation

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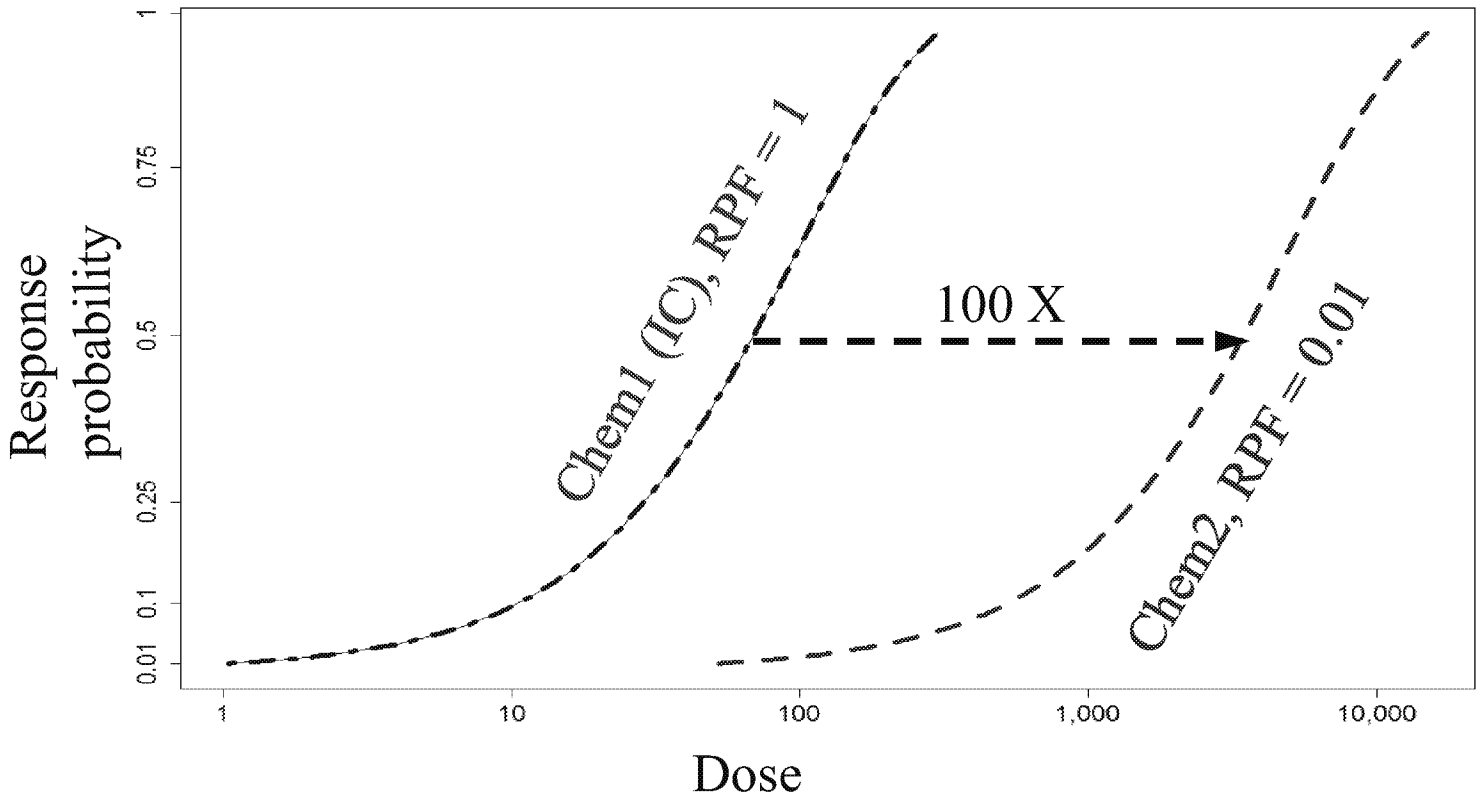
GROUPING MISCLASSIFICATION I:
Getting the RPF wrong

Chemical components of mixture
Weibull power = 1



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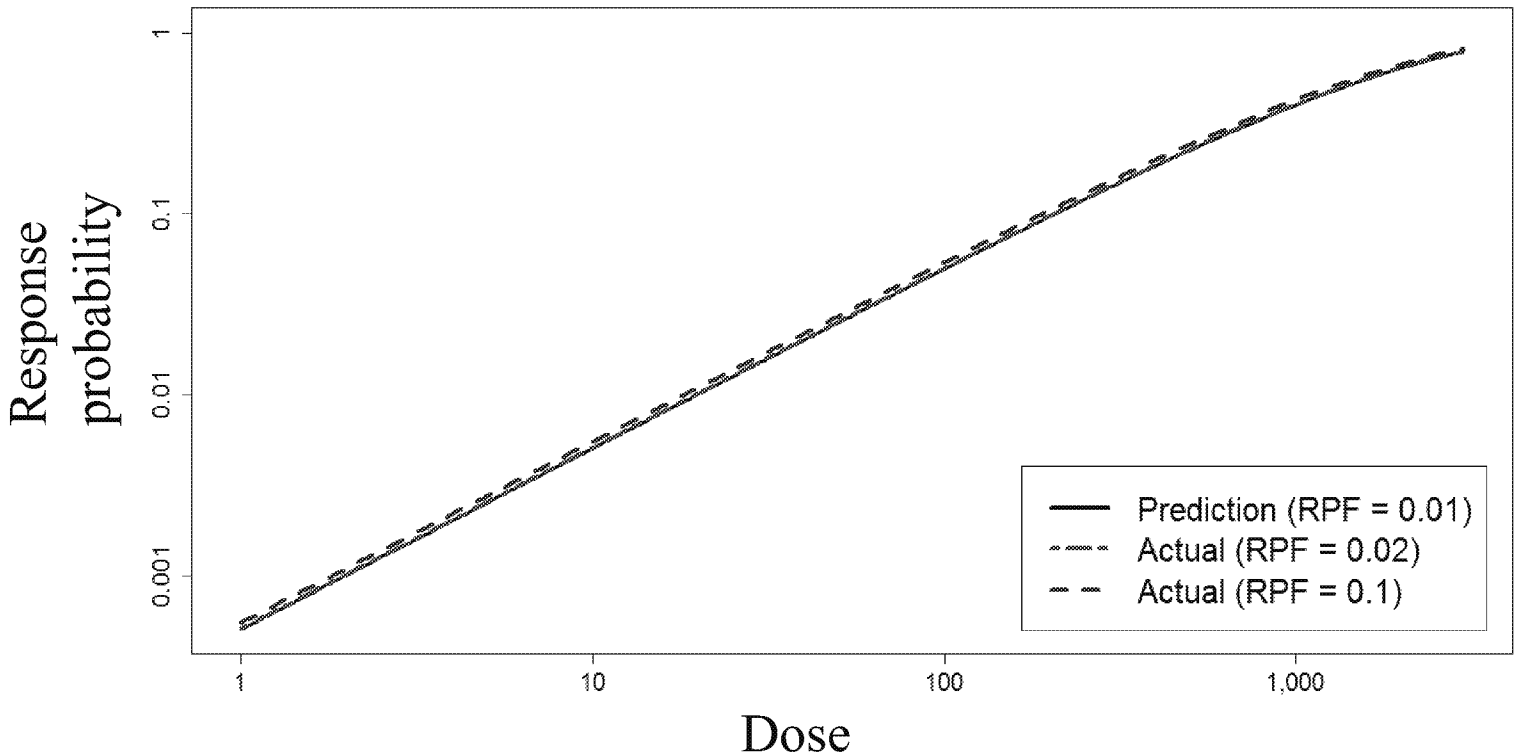
GROUPING MISCLASSIFICATION I: Getting the RPF wrong

2-chemical mixture of equal doses

[Chem2]:[Chem1] = 1

Weibull power = 1



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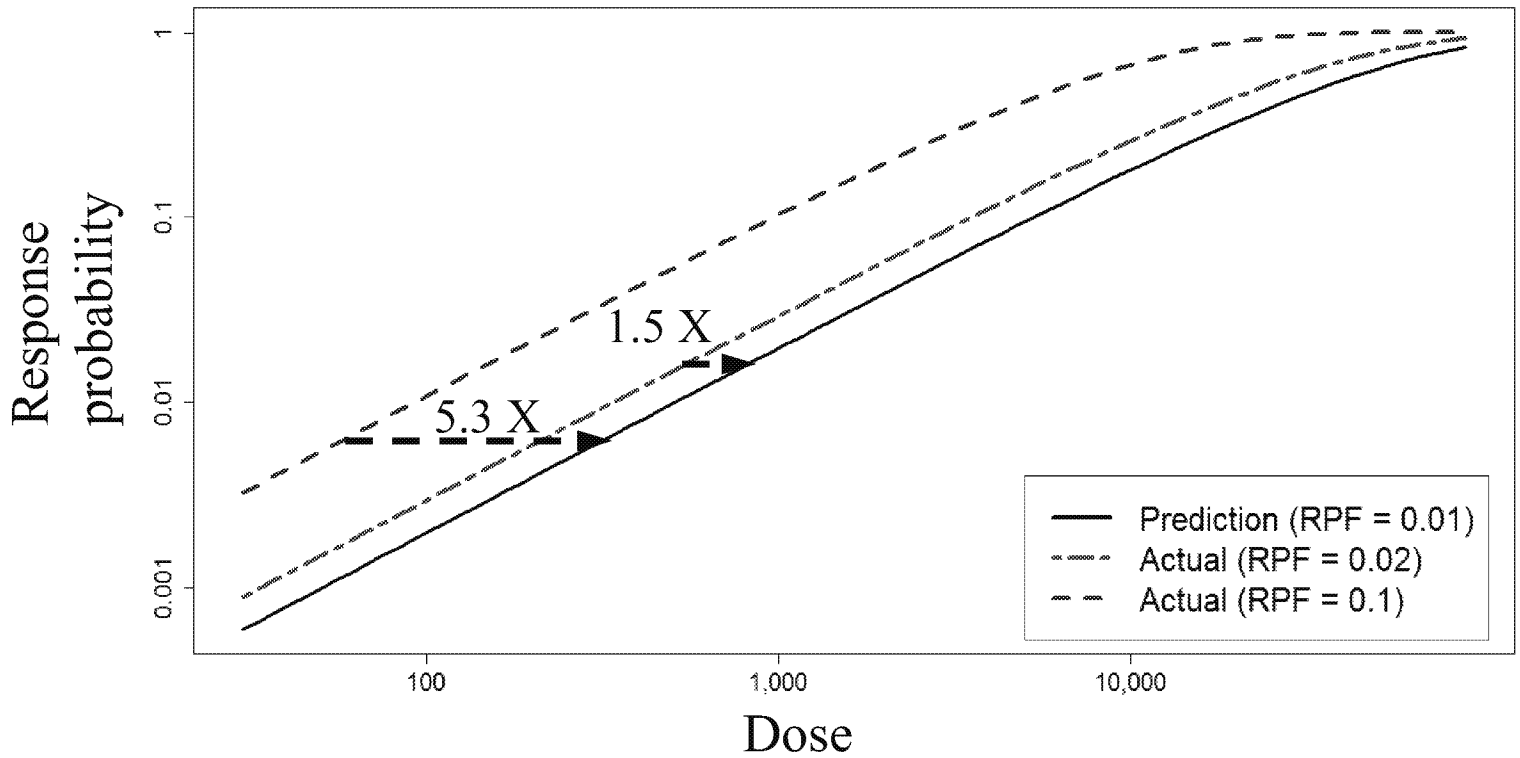
GROUPING MISCLASSIFICATION I:
Getting the RPF wrong

2-chemical mixture of equi-toxic doses

[Chem2]:[Chem1] = 100

Weibull power = 1



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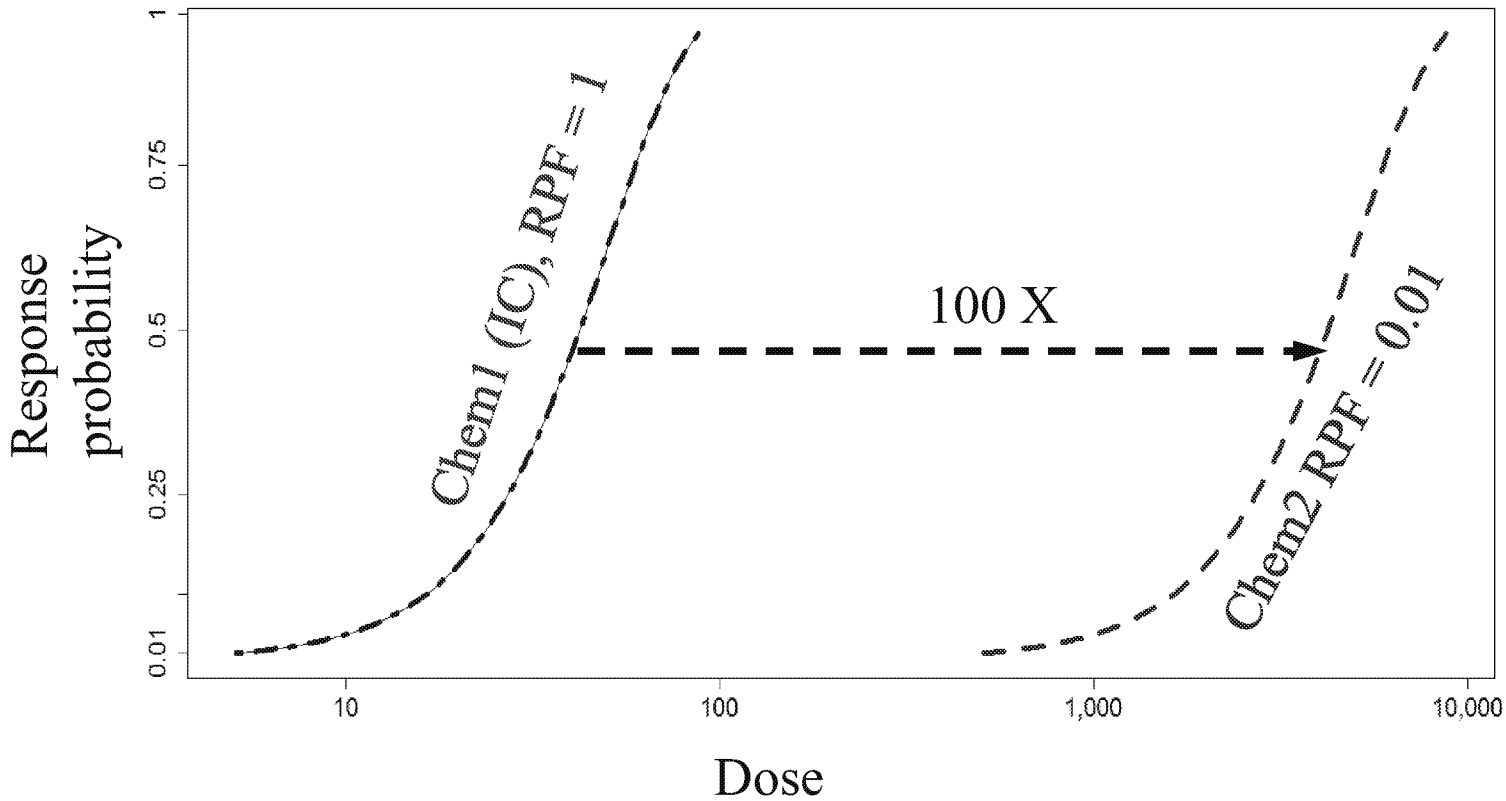
GROUPING MISCLASSIFICATION I:
Getting the RPF wrong

Chemical components of mixture
Weibull power = 2



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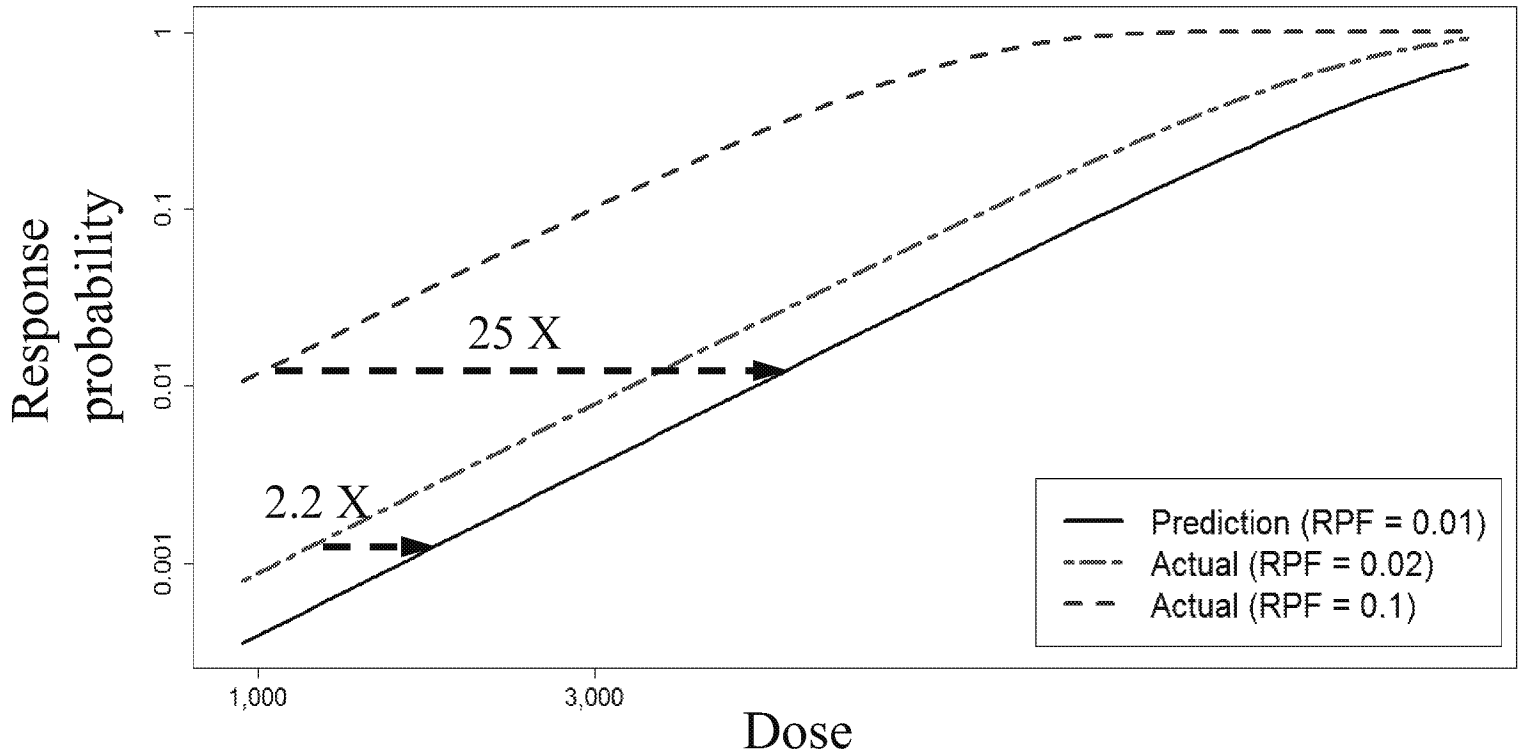
GROUPING MISCLASSIFICATION I: Getting the RPF wrong

2-chemical mixture of equi-toxic doses

[Chem2]:[Chem1] = 100

Weibull power = 1



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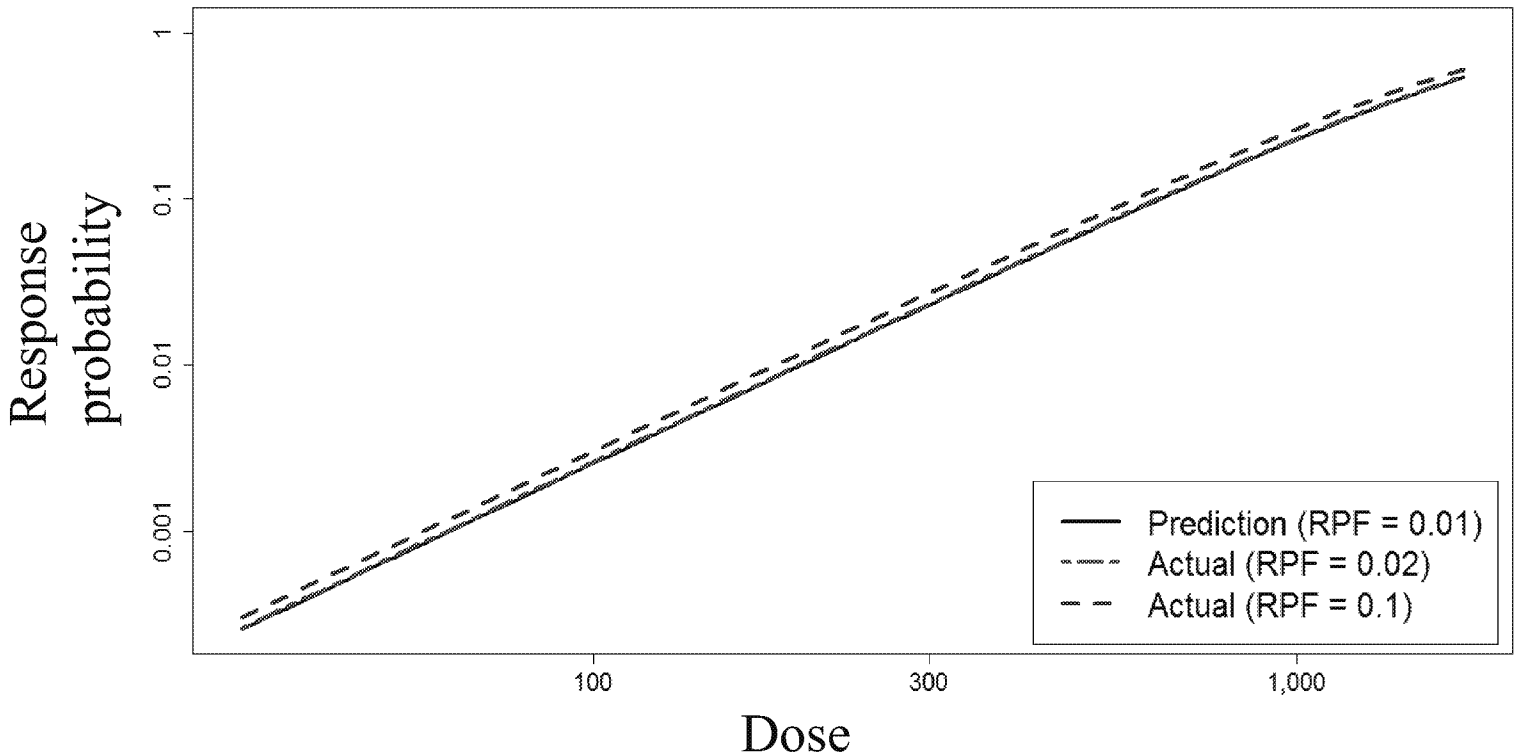
GROUPING MISCLASSIFICATION I: Getting the RPF wrong

2-chemical mixture of equal doses

[Chem2]:[Chem1] = 1

Weibull power = 2



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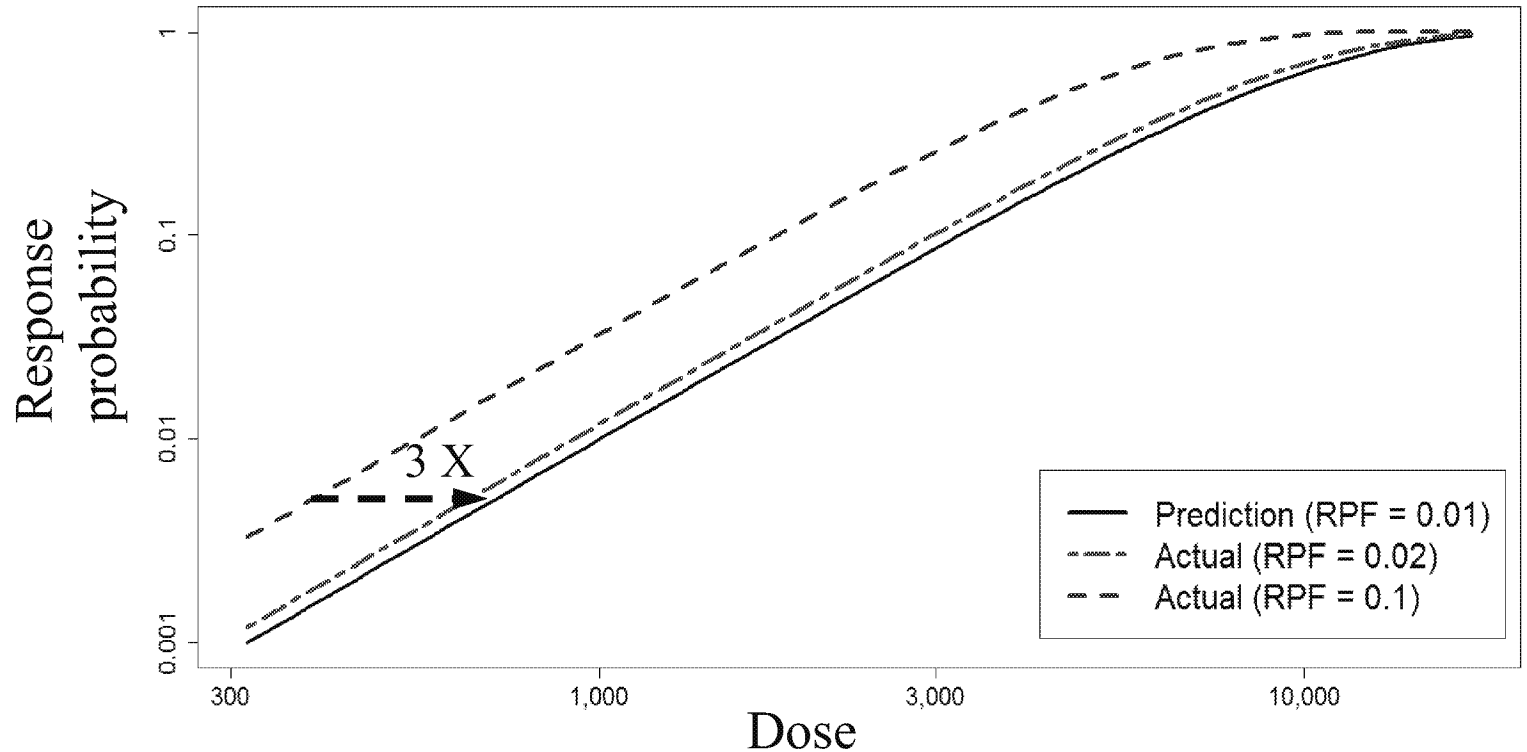
GROUPING MISCLASSIFICATION I:
Getting the RPF wrong

10-chemical mixture of equi-toxic doses

[Chem2]:[Chem1] = 10

Weibull power = 2



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GROUPING MISCLASSIFICATION II: Wrong Group Assignment

- Getting the RPF wrong
- **Assigning a compound to the wrong dose-additive group**
  - Applies to integrated addition of independent action groups
  - Error depends on the relative potency of the chemical, the mass-fraction contribution of the chemical to the group, and the group IC dose-response function
- Failing to allow for differently-shaped dose-response curves
- Mistaking dose additivity for response additivity
- Failing to account for different control values
- Failing to account for partial agonists
- Improper application of effect summation
- Low-dose extrapolation

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GROUPING MISCLASSIFICATION III:
Dose-Response Curve Shape

- Getting the RPF wrong
- Assigning a compound to the wrong dose-additive group
- **Failing to allow for differently-shaped dose-response curves**
- Mistaking dose additivity for response additivity
- Failing to account for different control values
- Failing to account for partial agonists
- Improper application of effect summation
- Low-dose extrapolation

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DOSE-RESPONSE CURVE SHAPE

- Same shape required (mathematically) for constant relative potency at all doses and full applicability of IC_RPF model
- Different shape does not mean dose addition does not apply (as previously interpreted by many)
  - High-dose non-proportionalities in the toxicokinetics, but additivity at a common molecular initiating event (MIE)
- Failing to allow for differently-shaped dose-response curves can result in potentially significant error when using the IC_RPF method
  - Assuming same shape when they are different
  - Assuming different shapes when they are the same
  - Mistaking dose additivity for response additivity

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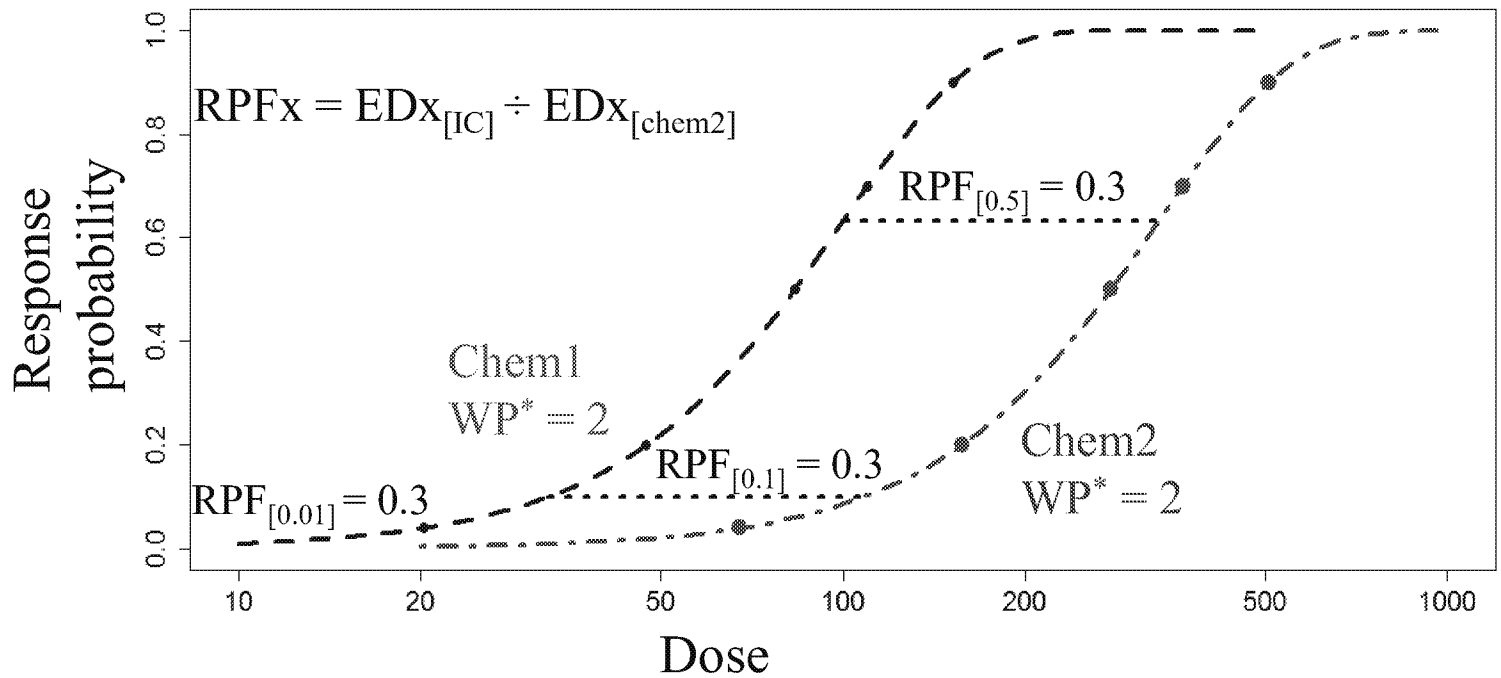
DOSE ADDITION FOR CHEMICALS WITH SIMILAR DOSE-RESPONSE SHAPES

- Simple similar action at the MIE
- Proportionality in toxicokinetics & toxicodynamics
  - RPF-scaled external doses are additive (constant relative potency)



*WP = Weibull power

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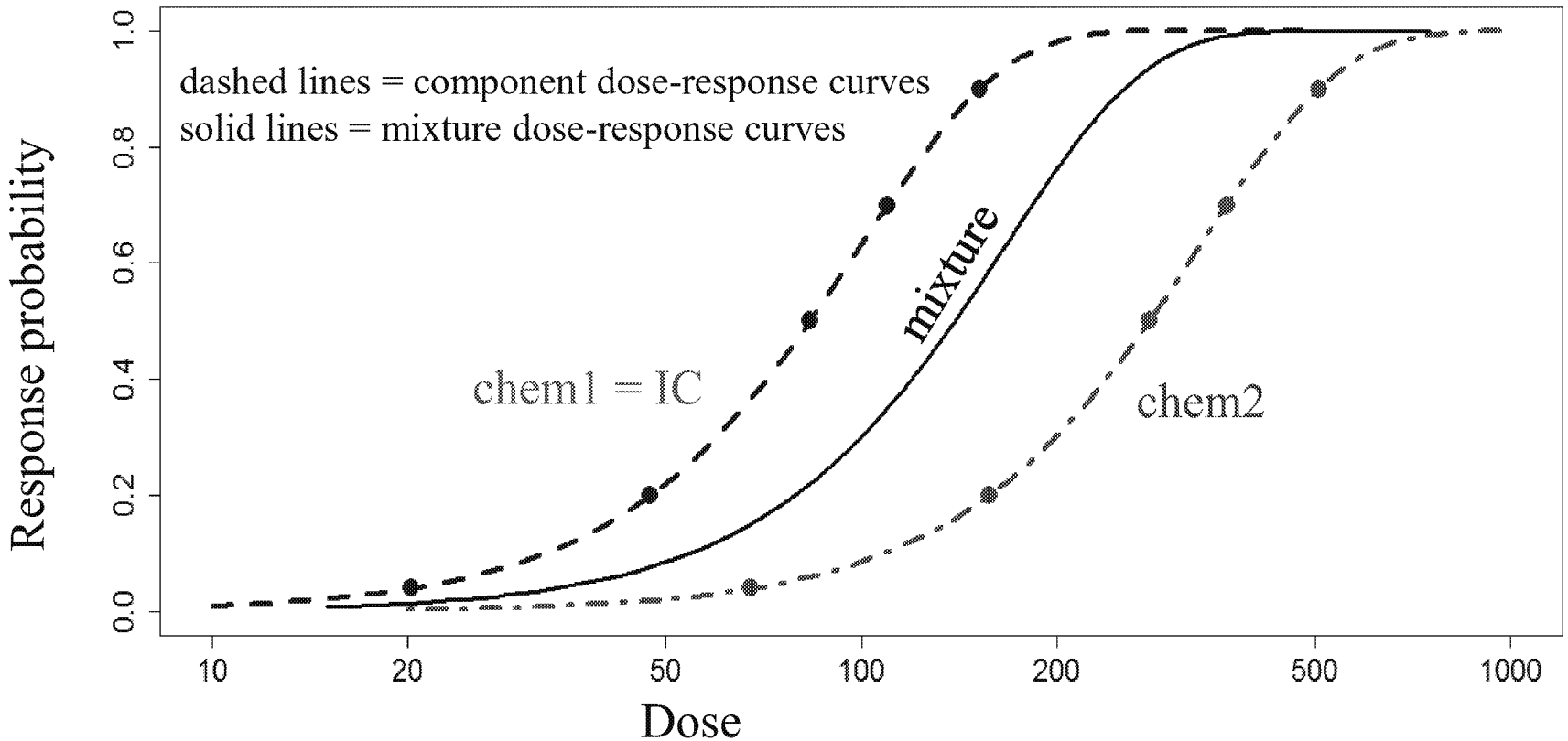
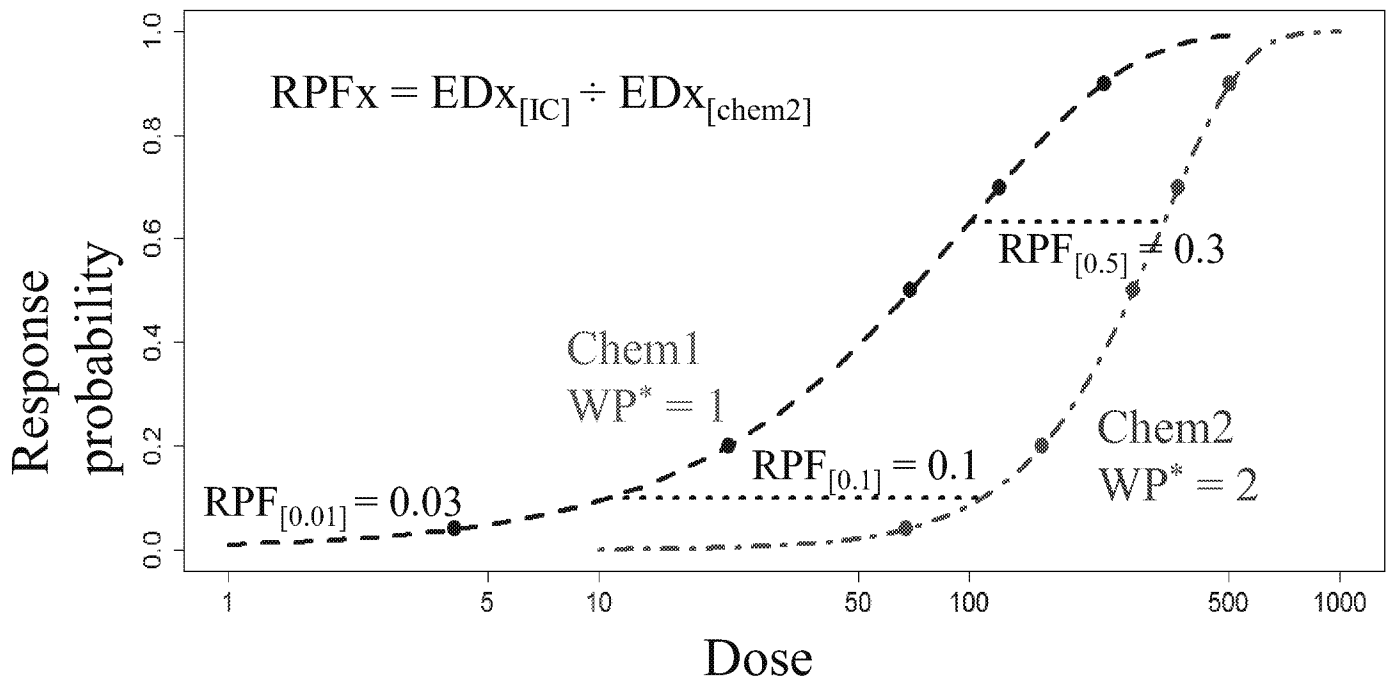
DOSE ADDITION FOR CHEMICALS WITH SIMILAR DOSE-RESPONSE SHAPES



- Mixture for any combination of fixed-proportion doses will have same shape

DOSE ADDITION FOR CHEMICALS WITH DISSIMILAR DOSE-RESPONSE SHAPES

- Simple similar action at the MIE
- Non-proportionalities in toxicokinetics
  - RPF-scaled external doses are **not** additive (non-constant relative potency)
  - Predicted mixture risk dependent on choice of IC (Chen et al., 2003)
  - Addition of internal component doses



*WP = Weibull power

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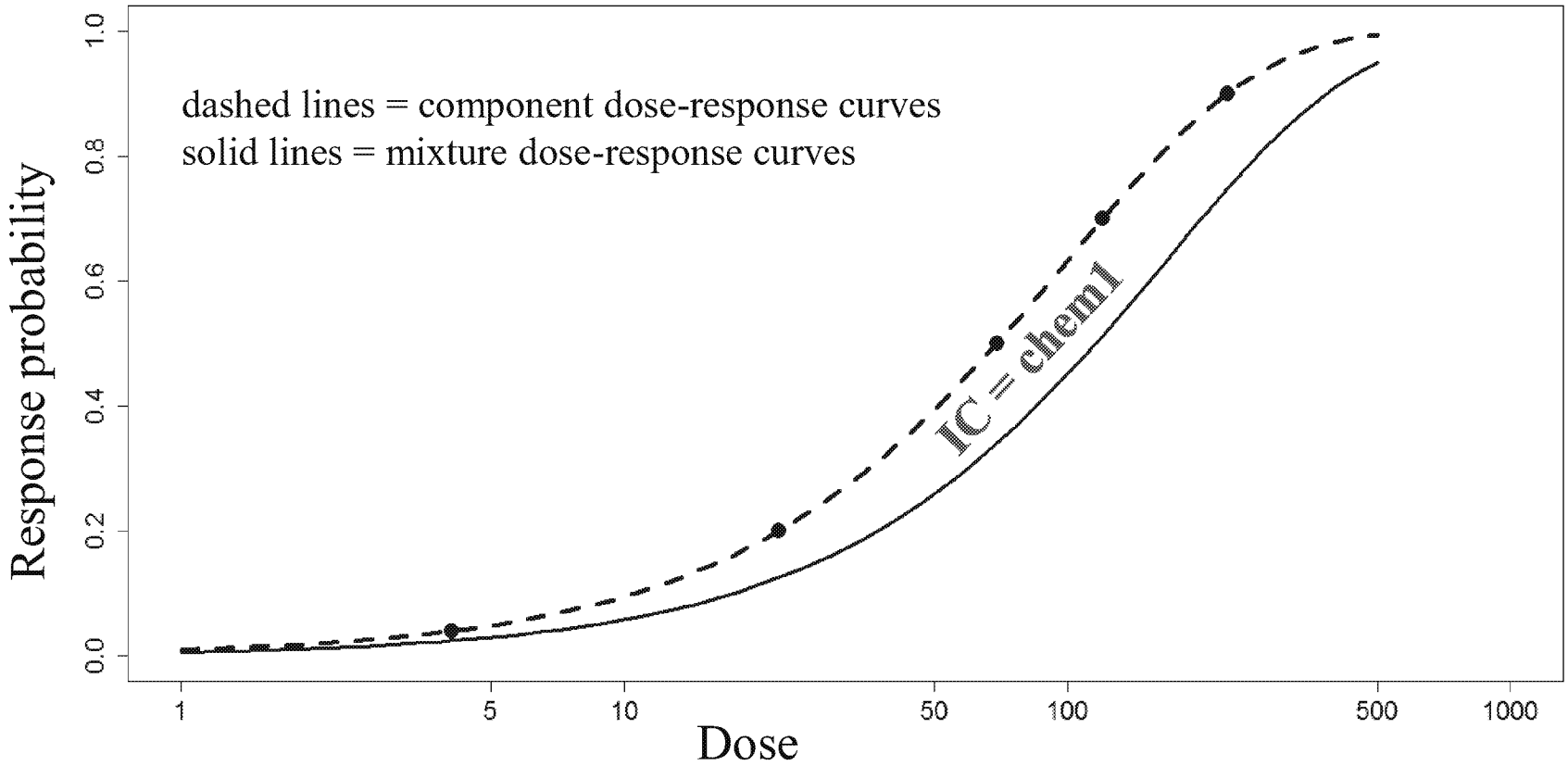
DOSE ADDITION FOR CHEMICALS WITH DISSIMILAR DOSE-RESPONSE SHAPES



- Mixture response prediction is dependent on the choice of IC

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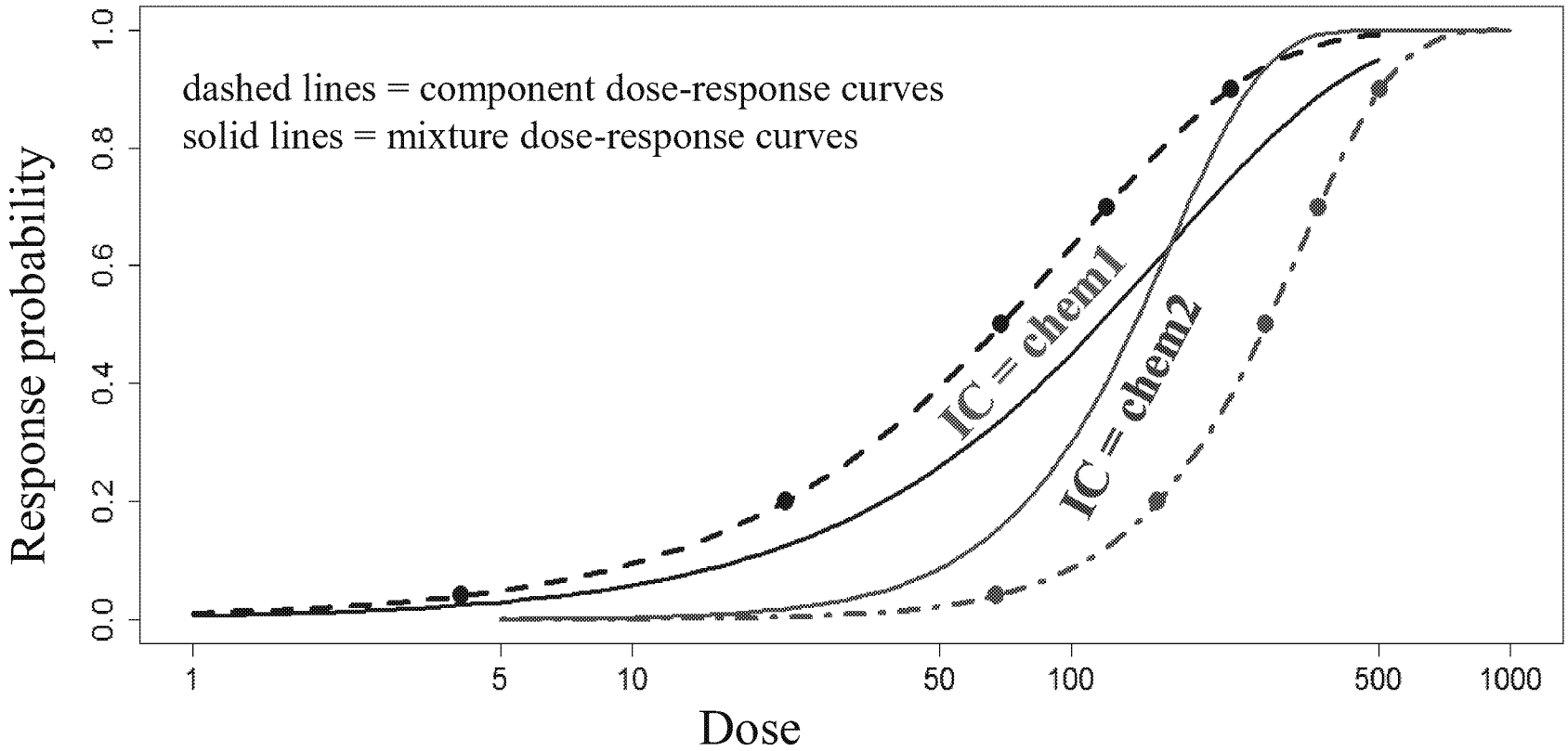
DOSE ADDITION FOR CHEMICALS WITH DISSIMILAR DOSE-RESPONSE SHAPES



- Mixture response prediction is dependent on the choice of IC

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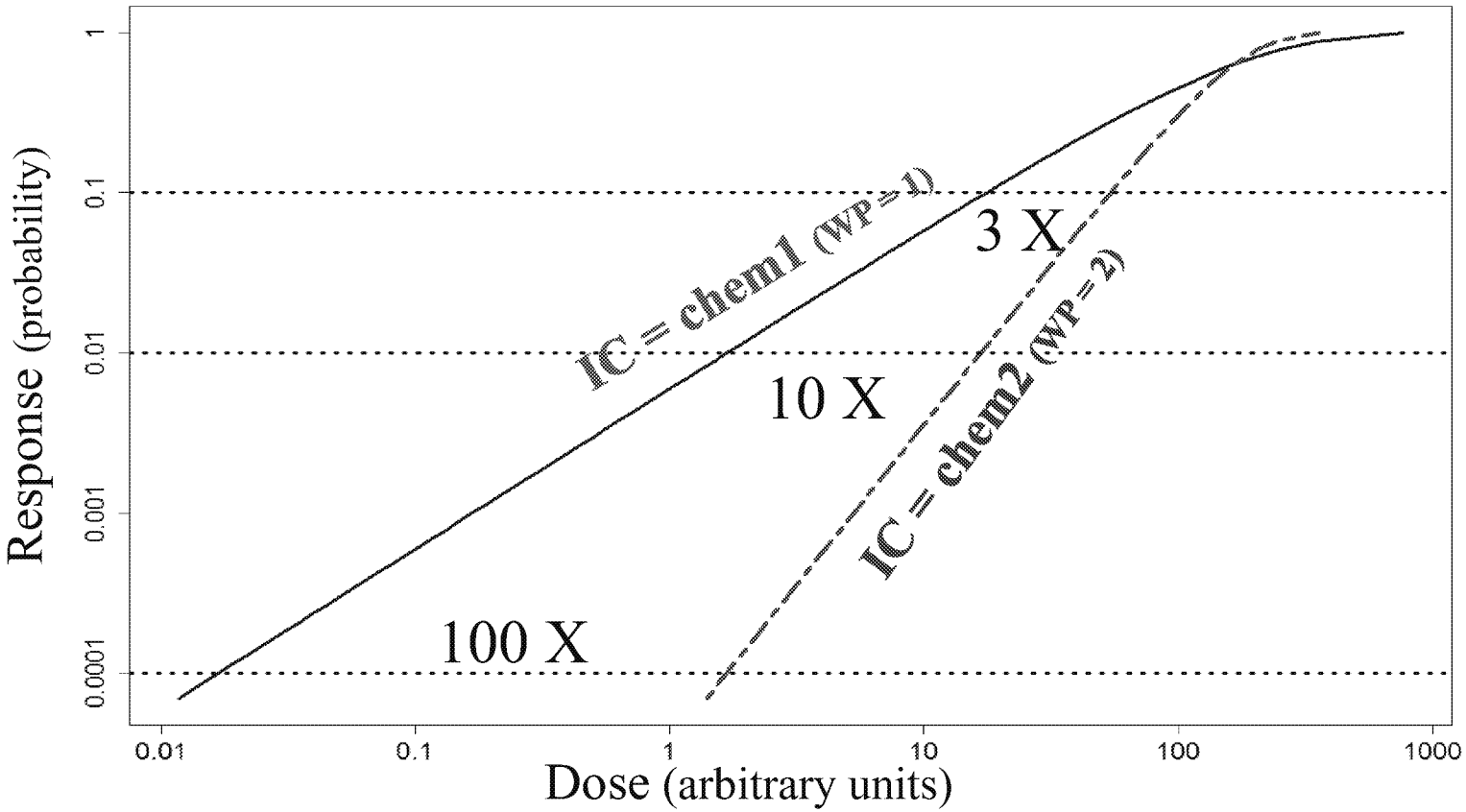
VARIABLE RELATIVE POTENCY: IC DEPENDENCE ERROR

Two component mixture: component dose-response shape parameters are 2-fold different



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GROUPING MISCLASSIFICATION IV: Dose Additivity vs. Response Additivity

- Getting the RPF wrong
- Assigning a compound to the wrong dose-additive group
- Failing to allow for differently-shaped dose-response curves
- **Mistaking dose additivity for response additivity**
- Failing to account for different control values
- Failing to account for partial agonists
- Improper application of effect summation
- Low-dose extrapolation

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DOSE ADDITION INTERPRETED AS RESPONSE ADDITION

- The case of differently-shaped component dose-response curves (DRCs)
  - If one assumes Bliss "dilution" concept applies to both toxicokinetics and toxicodynamics
- The case of different MIEs
  - Could be assumed to be evidence for total independence of toxicodynamic pathways
- Result is likely to be under-predictive
  - Except for thresholds

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DOSE ADDITION INTERPRETED AS RESPONSE ADDITION

- The case of differently-shaped component dose-response curves (DRCs)
  - If one assumes Bliss "dilution" concept applies to both toxicokinetics and toxicodynamics
- The case of different MIEs
  - Could be assumed to be evidence for total independence of toxicodynamic pathways
- Result is likely to be under-predictive

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DIFFERENT MIEs

- Often interpreted as definitive for independence and use of response addition
- Dose addition, however, can apply for downstream concentrations of common or similarly-acting products in the toxicodynamic pathways (shared dose-additive event).
  - Hormone-driven outcomes (androgen insufficiency; Rider et al., 2010)
  - Reactive oxygen species toxicity (PaH's ?)
  - Ion channel blockers (Norberg & Wahlstrom, 1988 ?)

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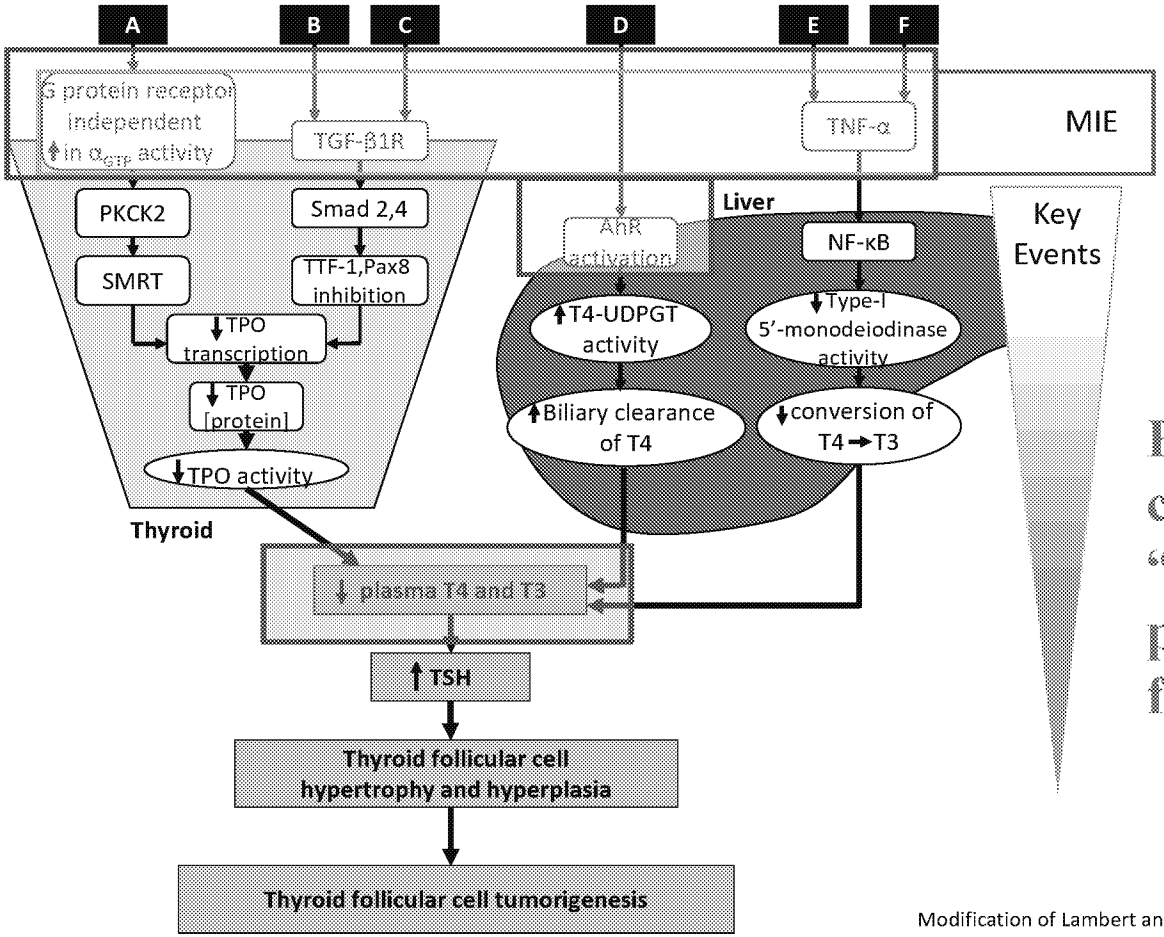
DOSE ADDITION FOR INITIALLY INDEPENDENT PATHWAYS



Independent MIE suggests response addition may apply

Pathway convergence at "dose"-additive process may allow for dose addition

Modification of Lambert and Lipscomb (2007)

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GROUPING MISCLASSIFICATION V: Continuous Measures

- Getting the RPF wrong
- Assigning a compound to the wrong dose-additive group
- Failing to allow for differently-shaped dose-response curves
- Mistaking dose additivity for response additivity
- **Failing to account for different control values**
- **Failing to account for partial agonists**
- **Improper application of effect summation**
- Low-dose extrapolation

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GROUPING MISCLASSIFICATION VI: Low-dose Extrapolation

- Getting the RPF wrong
- Assigning a compound to the wrong dose-additive group
- Failing to allow for differently-shaped dose-response curves
- Mistaking dose additivity for response additivity
- Failing to account for different control values
- Failing to account for partial agonists
- Improper application of effect summation
- **Low-dose extrapolation**
  - All mixture risk models assume some form of continuation of component dose-response curve shape below the tested range, but how can we know?
  - Need a way to inform low-dose mixture shape prediction *experimentally*

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SUMMARY & CONCLUSIONS

- Grouping for dose additivity starts with similarity of toxic action
  - Key dose-additive event is required, but does not have to be the MIE
- Dose addition can still apply with dissimilar dose-response curve shapes
  - IC_RPF model is impacted adversely
- Dose addition can still apply with independent MIEs
  - Downstream toxicodynamic pathway convergence
- Grouping errors can be substantial but could be "diluted" out with large number of chemicals
- Low-dose extrapolation is a major issue
  - Need a way to predict dose-response shape below the tested range (other than mathematical speculation)
  - How about some of that 21st Century Toxicology?

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