

Modeling Cumulative Mixtures Grouped by Common Adverse Outcome

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Overview

“Incorporating novel data streams” ... from a 30,000 foot level...

Two approaches with case studies

- ✧ 1st approach: Estimating the Hazard Index PER SUBJECT in biomonitoring data
 - ✧ 2nd approach: Testing FOR sufficient similarity combining toxicology and exposure/occurrence data
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Dose Addition, Hazard Index and Biomonitoring Data

Case study: Mixtures of phthalates and other antiandrogens

Dose Addition, Hazard Index and Biomonitoring Data

ASSUMPTIONS:

- ✘ Grouping of chemicals is based on assumption that the combination effect of the mixture is approximated by dose addition (DA)
- ✘ Hazard index (HI) is a reasonable quantitative tool for cumulative risk assessment under the assumption of DA
- ✘ Individuals have unique exposures to mixtures of chemicals

OBJECTIVE: to estimate the HI per subject and evaluate its distribution across covariates of interest

Dose Addition, Hazard Index and Biomonitoring Data

For a mixture of c chemicals, the Hazard Index (HI) is

$$HI = \sum_{j=1}^c \frac{DI_j \text{ (mg/kg/day)}}{RfD_j \text{ (mg/kg/day)}}$$

- ✘ RfDs are established from literature values
- ✘ Estimates for daily intake (DI) per chemical are determined per subject from biomonitoring data

Case Study: Mixtures of phthalates and other anti-androgens

- ✘ Phthalates suppress fetal androgen synthesis
 - ✘ More generally, anti-androgens may disrupt the actions of fetal androgens (e.g., blocking androgen action)
 - ✘ Either way, the result is lower testosterone levels in fetal life leading to male reproductive abnormalities
 - ✘ **OBJECTIVE:** risk evaluation of mixtures of phthalates and other anti-androgens in pregnant women
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Dose Addition, Hazard Index and Biomonitoring Data: Case Study

- ✘ For this case study, the RfDs are taken from Kortenkamp and Faust, 2010
 - ✘ Daily intake estimates are calculated using the method described in Koch et al (2007) from David (2000). In short, DI is estimated using
 - ✘ molar urinary excretion of chemical metabolites,
 - ✘ creatinine excretion rate,
 - ✘ published molar fraction constants (linking the amount of the metabolite in the urine and the amount of the parent compound taken up)
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Concentrations measured from biomonitoring per subject



Daily intake estimated from monoester concentrations



Monoesters		Phthalate Diesters	
Mono-n-butyl phthalate	MBP	Di-n-butyl phthalate	DnBP
Mono-benzyl phthalate	MBzP	Butyl benzyl phthalate	BBP
Mono-(2-ethylhexyl) phthalate Mono-(2-ethyl-5-hydroxyhexyl) phthalate Mono-(2-ethyl-5-oxohexyl) phthalate Mono (2-ethyl-5-carboxypentyl) phthalate	MEHP MEHHP MEOHP MECPP	Di (2-ethylhexyl) phthalate	DEHP
Mono-(carboxyisooctyl) phthalate	cx-MiNP	Di-isononyl phthalate	DiNP
Mono-n-octyl phthalate	MOP	Di-n-octyl phthalate	DnOP
Mono-(carboxyisononyl) phthalate	cx-MiDP	Di-isodecyl phthalate	DiDP
Mono-iso-butyl phthalate	MiBP	Di-iso-butyl phthalate	DiBP

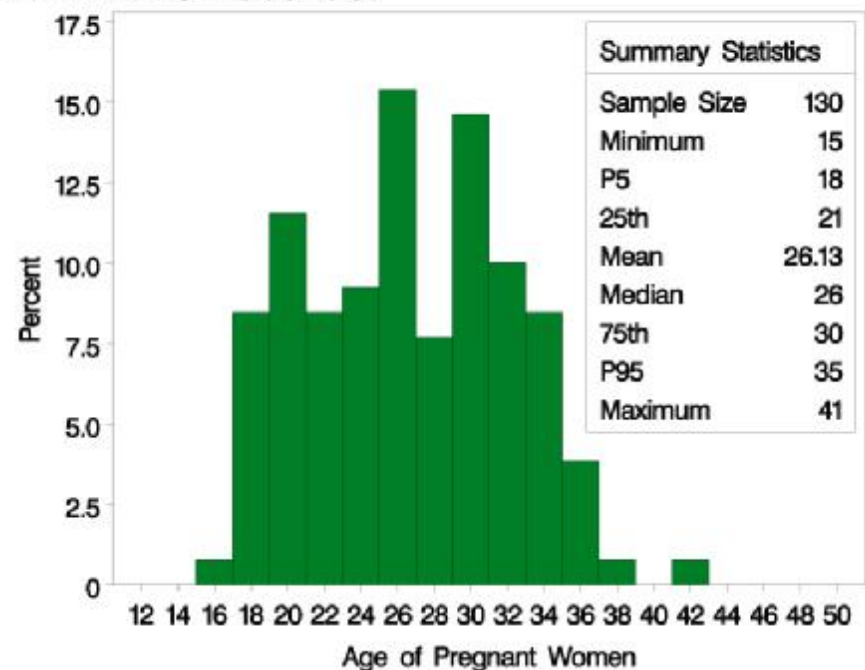
RESULT: Estimated DI of phthalate mixture per subject

Dose Addition, Hazard Index and Biomonitoring Data

DATA: NHANES (2005-06)
pregnant women

- ✧ 382 women coded as pregnant (self-report with pregnancy test)
- ✧ 130 women included in the subsample in which urinary phthalate monoesters were evaluated

Figure 1: Age distribution for pregnant women evaluated for phthalate exposure, NHANES 2005-06.



Case Study: Mixture of Phthalates and other Anti-androgens

NHANES data


✘ Phthalates (plasticizers): DnBP, BBP, DEHP, DiNP, DnOP, DiDP, DiBP

✘ PLUS variety of other anti-androgens:

- Chemical used to make plastic (Bisphenol-A),
- Preservatives in cosmetics and pharmaceuticals (butyl paraben, propyl paraben)
- Fungicides/pesticides (vinclozolin, prochloraz, procymidone, linuron, fenitrothion)
- Persistent DDT (mosquito control) metabolite (p,p'-DDE), and
- Flame retardant (BDE99)

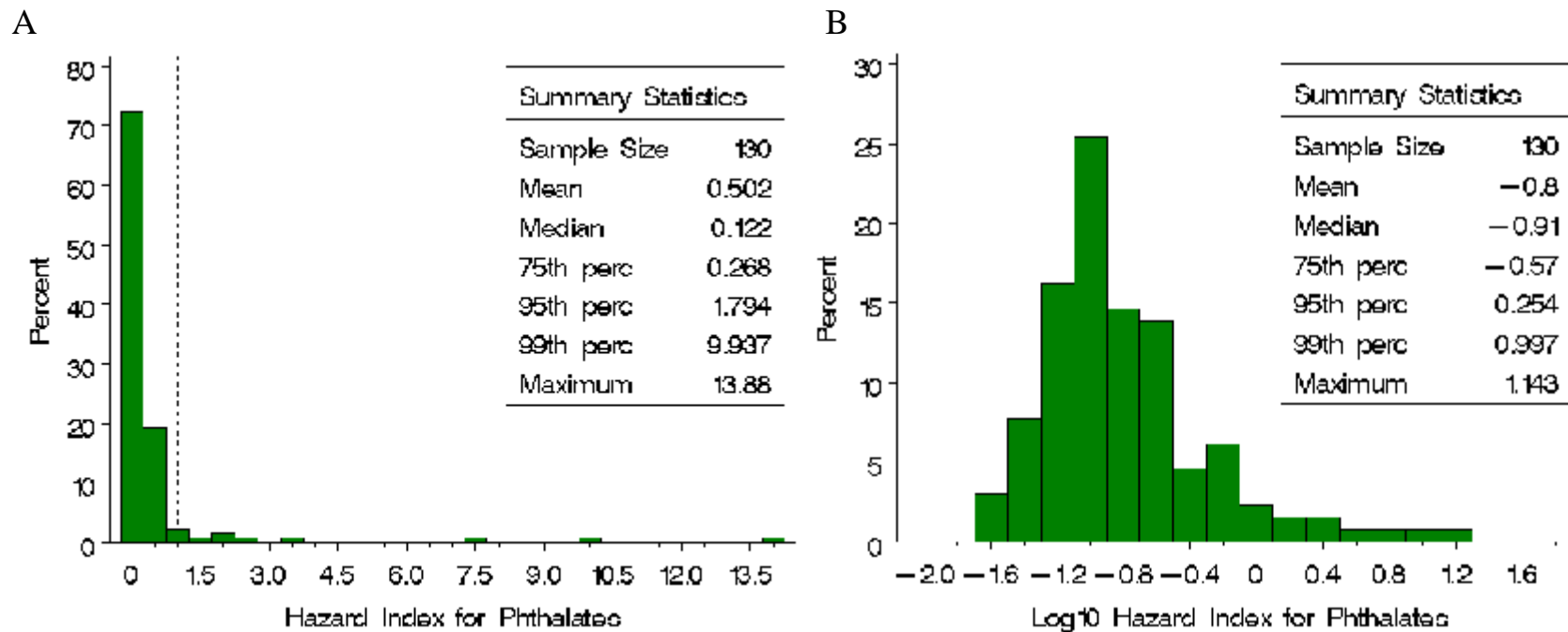
Summary data:
K&F, 2010

Table 3: Summary statistics for the distributions of the percentage of each diester in the sum of diesters per pregnant woman (N=130).



Phthalate Diester	Mean (%)	Standard Deviation	Minimum (%)	Maximum (%)
DBP	0.12	0.10	<0.01	0.57
DiBP	0.04	0.06	<0.01	0.55
BBzP	0.08	0.08	<0.01	0.41
DEHP	0.44	0.20	0.06	0.99
DiNP	0.18	0.15	<0.01	0.84
DnOP	0.05	0.05	<0.01	0.33
DiDP	0.09	0.09	<0.01	0.85

Figure 2: Distribution of the Hazard Index (A,B) for 7 phthalates as estimated in pregnant women using daily intake estimates from urinary metabolite concentrations and Case 1 values for RfDs. Data are from NHANES, 2005-06 for the 7 phthalates.



~15% of pregnant women sampled have HI > 1.0 from 7 phthalates

Modeling mean log(HI)

- ✘ Mean log(HI) from 7 phthalates was modeled as a function of demographic variables per pregnant woman:
 - ✘ BMI, age, race, poverty index, marital status, and triceps skinfold measurement
- ✘ Backward elimination process was used
- ✘ Poverty index, marital status, and skinfold were removed with p values > 0.25
- ✘ Race was removed (p=0.140)
- ✘ FINAL model included BMI (negative, p=0.060) and age (positive, p=0.051)
- ✘ Older women and women with lower BMIs have higher HI values



Table: Hazard index percentiles with approximate percent of sample of pregnant women (N=130) with HI > 1.0 from NHANES (2005-06).



Analysis set	Hazard Index Percentile				~%>1.0
	Median	75 th	95 th	99 th	
7 phthalates	0.12	0.27	1.79	9.94	15%
7 phthalates + (BPA, BPB, PPB)	0.15	0.32	1.81	9.98	16%
7 phthalates + (BPA, BPB, PPB) + median intake of 7 other AAs	0.33	0.49	1.98	10.2	18%
7 phthalates + (BPA, BPB, PPB) + high intake of 7 other AAs	0.75	0.91	2.40	10.6	24%

1st approach conclusions

- ✘ There are an unacceptable percentage of pregnant women with estimated Hazard Index (using the RfDs from K&F) exceeding 1.0 as measured from NHANES data
- ✘ Additional modeling of HI should be undertaken
- ✘ LIMITATIONS:
 - ✘ Temporal evaluation of HI not possible from NHANES
 - ✘ Selection of chemicals used here is somewhat arbitrary (taken from Kortenkamp and Faust, 2010)
- ✘ DATA GAP & RESEARCH NEEDS:
 - ✘ Constants for estimating daily intake from internal biomonitoring data for many chemicals

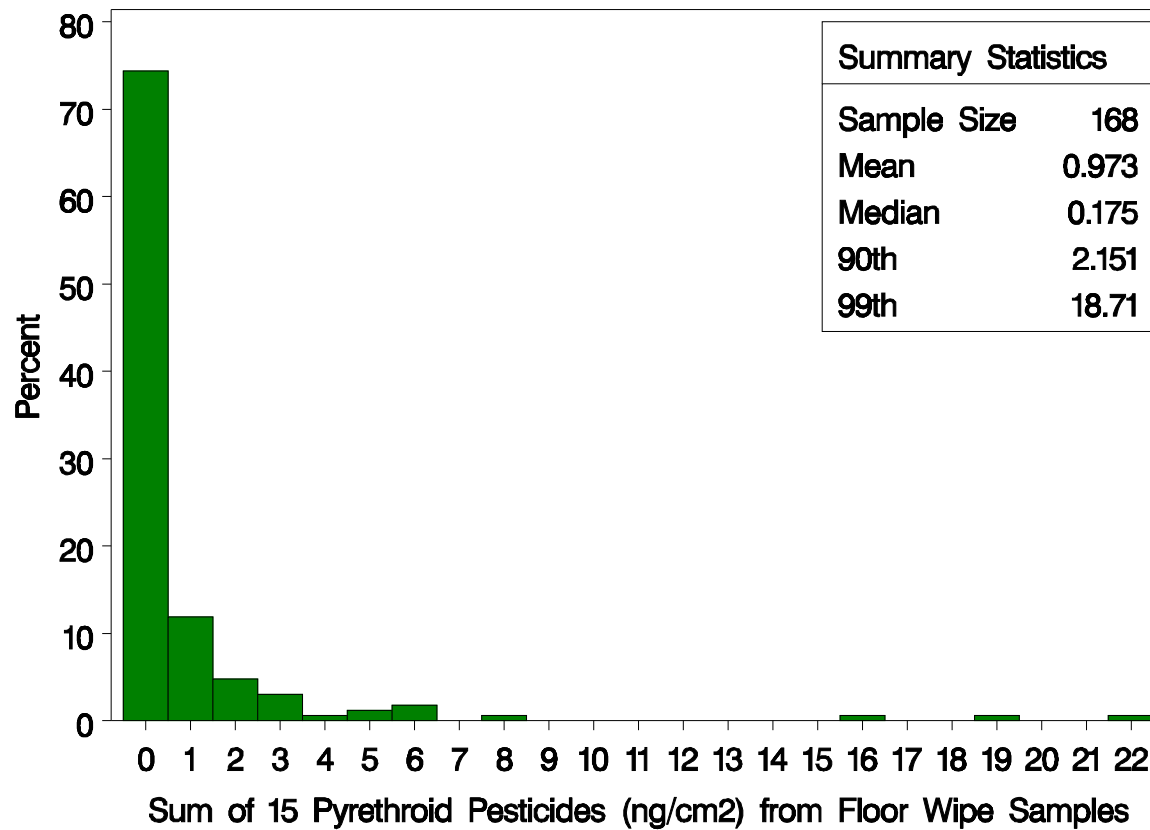
Test for Sufficient Similarity of Chemical Mixtures

Case Study: Mixtures of pyrethroids with exposure data from
national study of child care centers

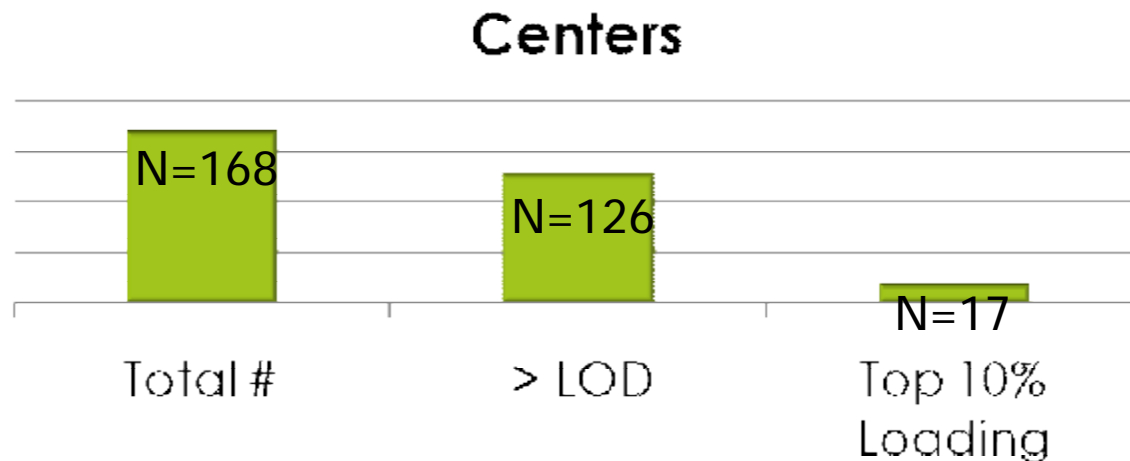
Motivating Case Study (Tulve et al, 2006)

- ✘ The First National Environmental Health Survey of Child Care Centers (CCC Study) was a probability-based national study of child care centers with a focus on aggregate exposure of children to pesticides.
 - ✘ The study included 168 child care centers from 30 sampling units and measured pesticide occurrence.
 - ✘ Samples were collected from July - October 2001 at multiple locations within a center by means of floor, tabletop, and desk swipes.
 - ✘ Here, we consider only floor swipe data for pyrethroid pesticides.
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Figure 1: Histogram of the sum of 15 pyrethroids/pyrethrins measured from floor wipes in 168 child care centers in the CCC Study.



Motivating Case Study (Tulve et al, 2006)



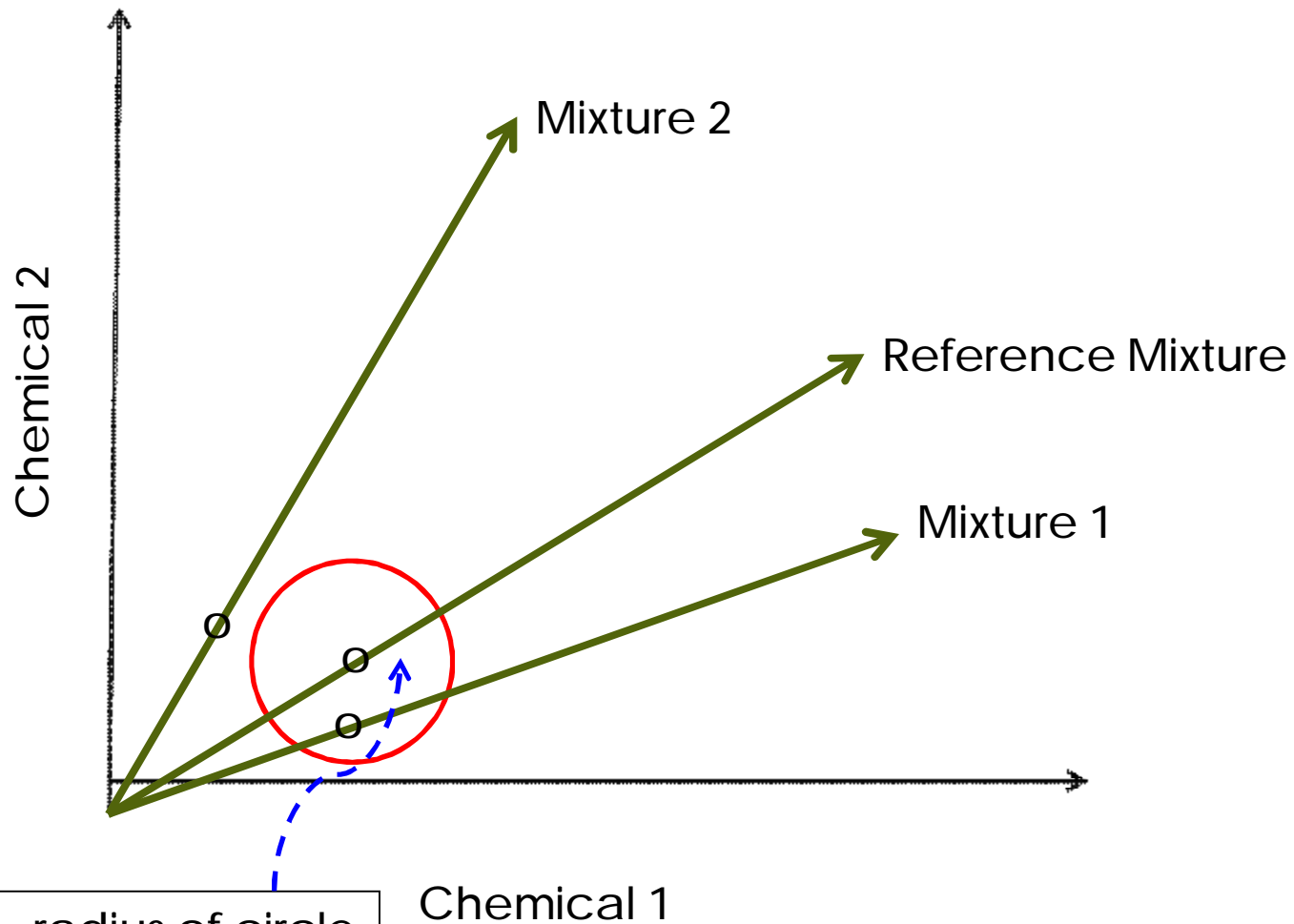
The average residues from the top five chemicals in the 17 “top” centers accounted for 96% of the sum.

This average was the mixing ratio used in a neurotoxicity study of five pyrethroids (Wolansky et al).

Background

- ✘ Whole mixture approaches do not require default assumptions of additivity.
 - ✘ We define sufficient similarity, without assuming additivity, using equivalence testing methodology comparing the distance between benchmark dose estimates for mixtures in both data rich and data poor cases.
 - ✘ 2-dimensional schematics are readily generalizable to higher dimensions
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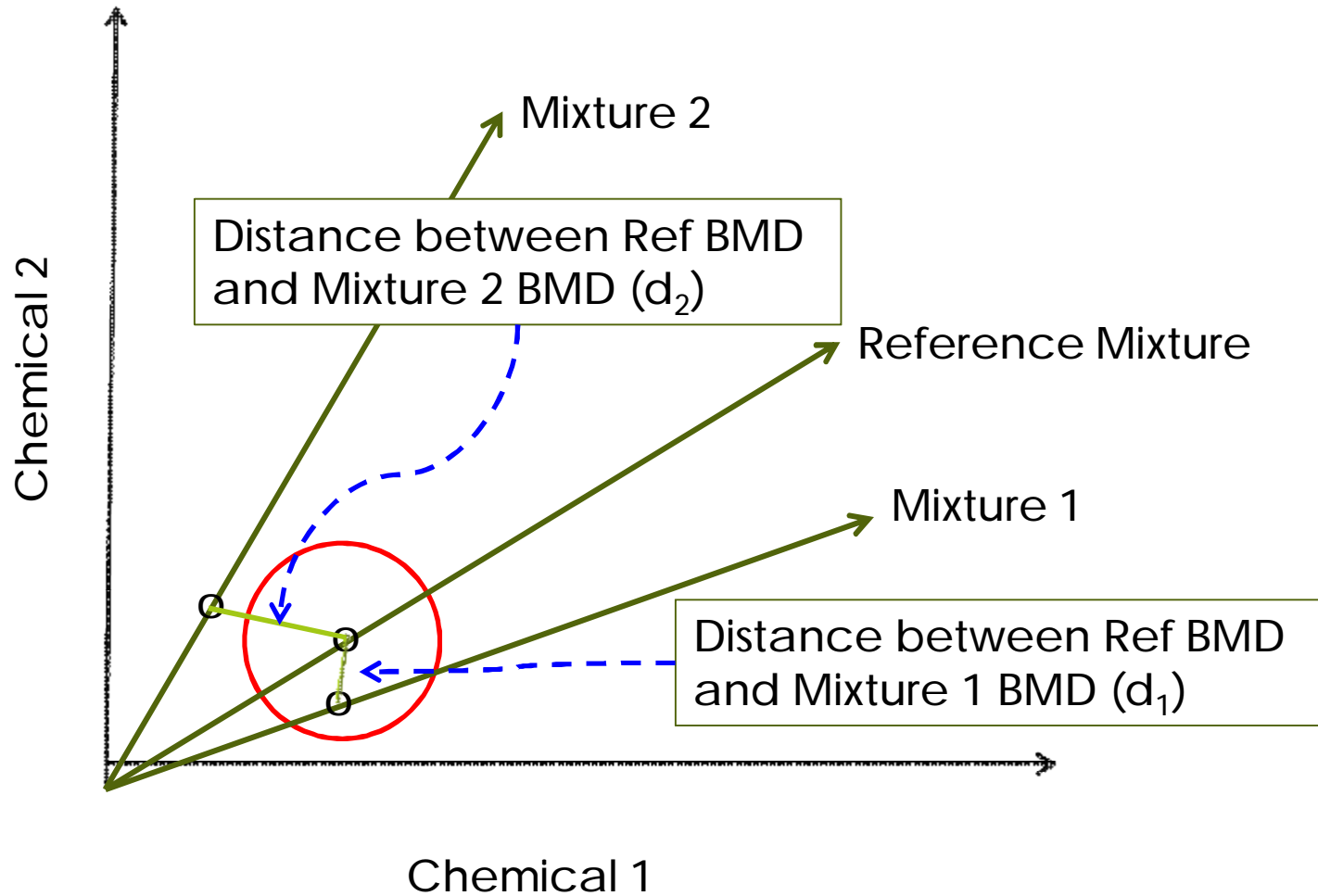
DATA Rich Scenario Schematic



Define R = radius of circle

ϵ depicts BMD
Red circle depicts the Similarity Region

DATA Rich Scenario Schematic



\circ depicts BMD
Red circle depicts the Similarity Region

Test FOR Sufficient Similarity

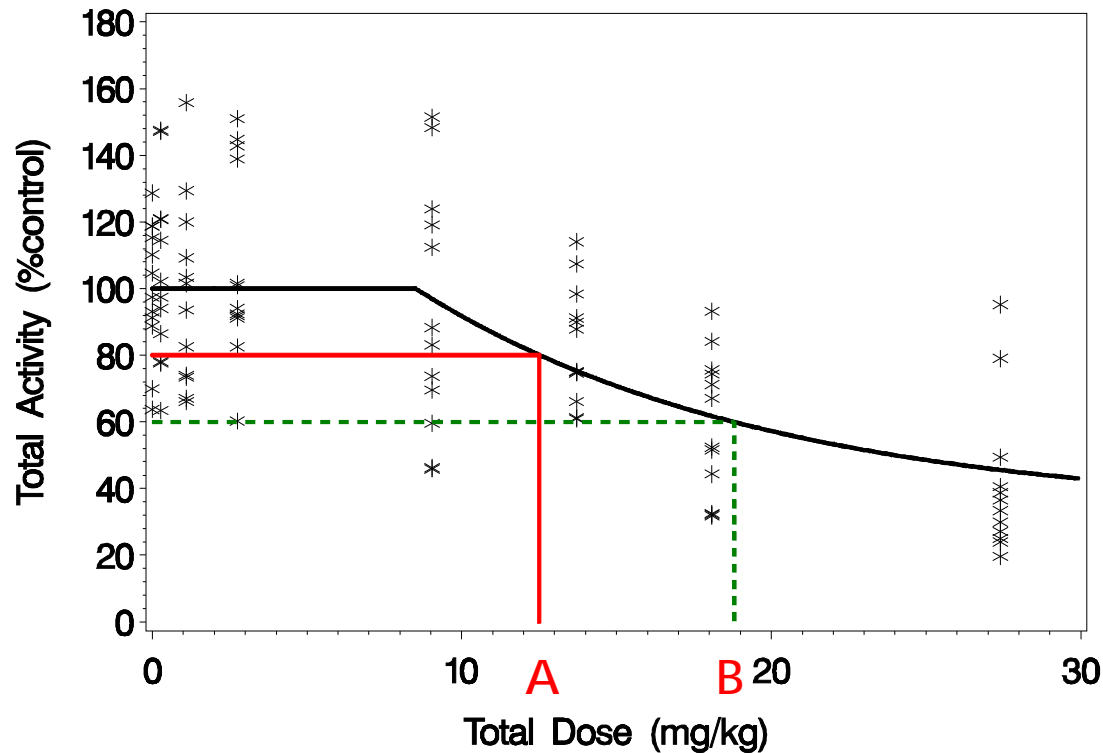
- ✘ Define the radius of the similarity region to be R
- ✘ Define d_j as the distance between the BMD for the reference mixture and the j th candidate mixture (as specified from exposure data).
- ✘ The estimate for d is determined from the estimated BMDs.
- ✘ TEST FOR Sufficient Similarity:

$$H_0: d > R \text{ vs } H_1: d < R$$

- ✘ Reject H_0 if upper confidence limit on $d < R$

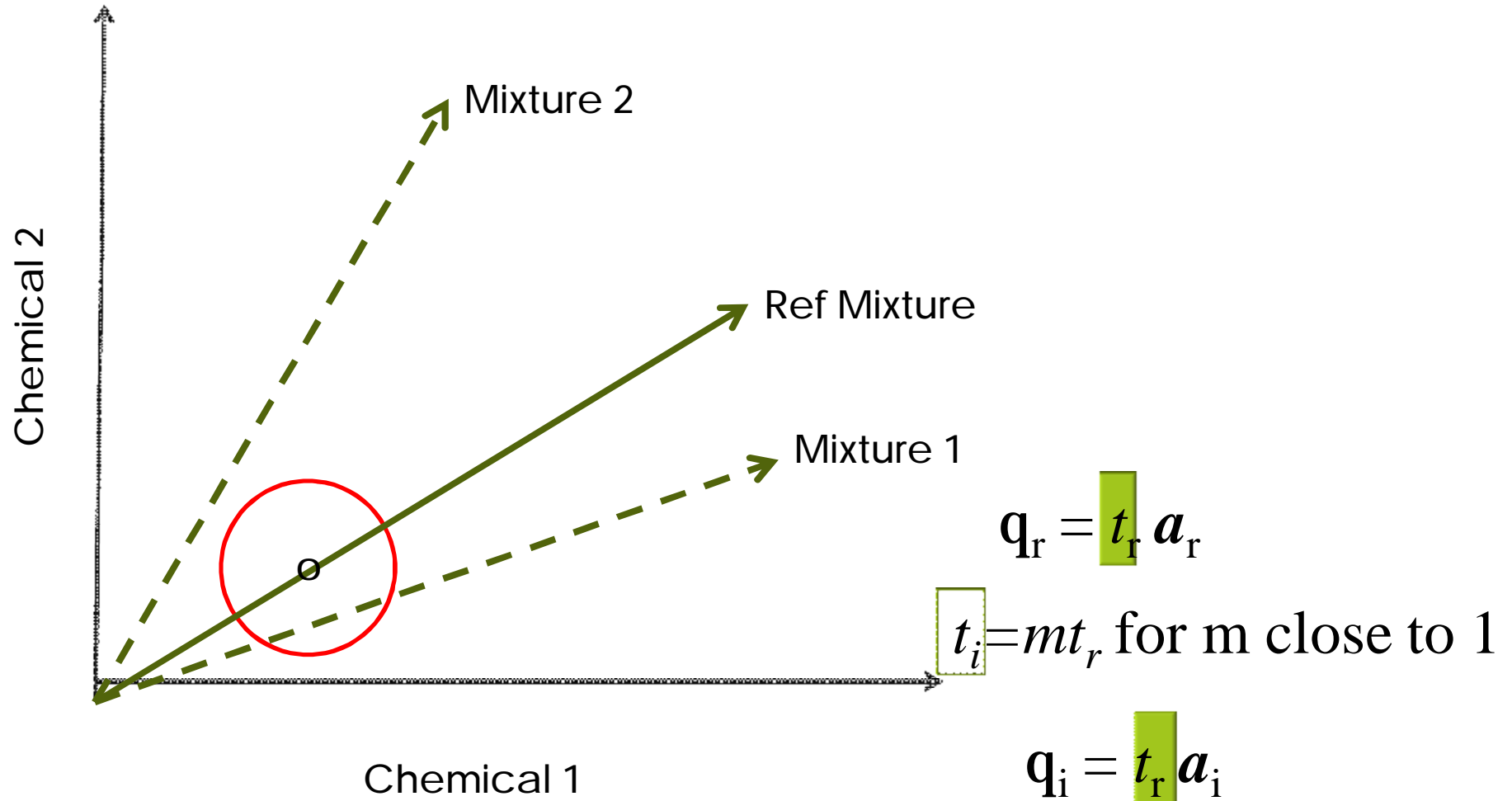
Specifying R using Expert Judgment

Mixture=5 Chemical Mixture

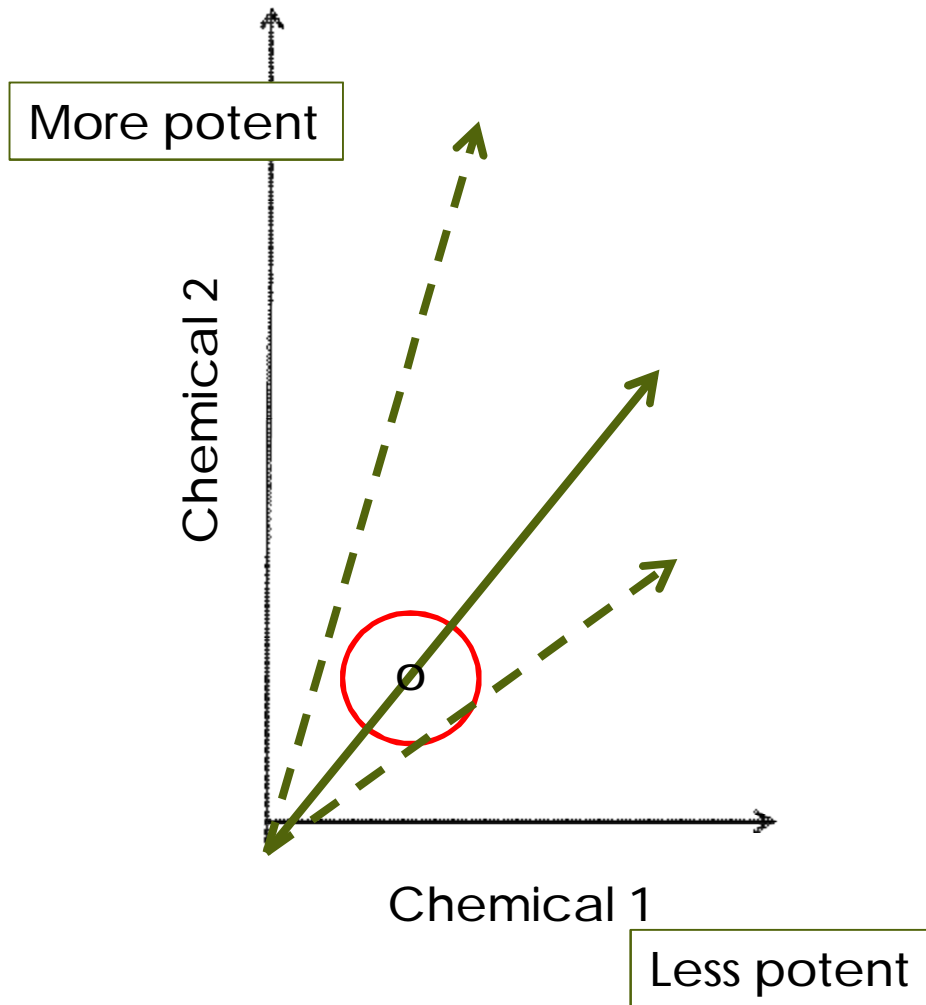


Define R as the distance between A and B

DATA Poor Scenario Schematic



DATA Poor Scenario Schematic adjusted by weights



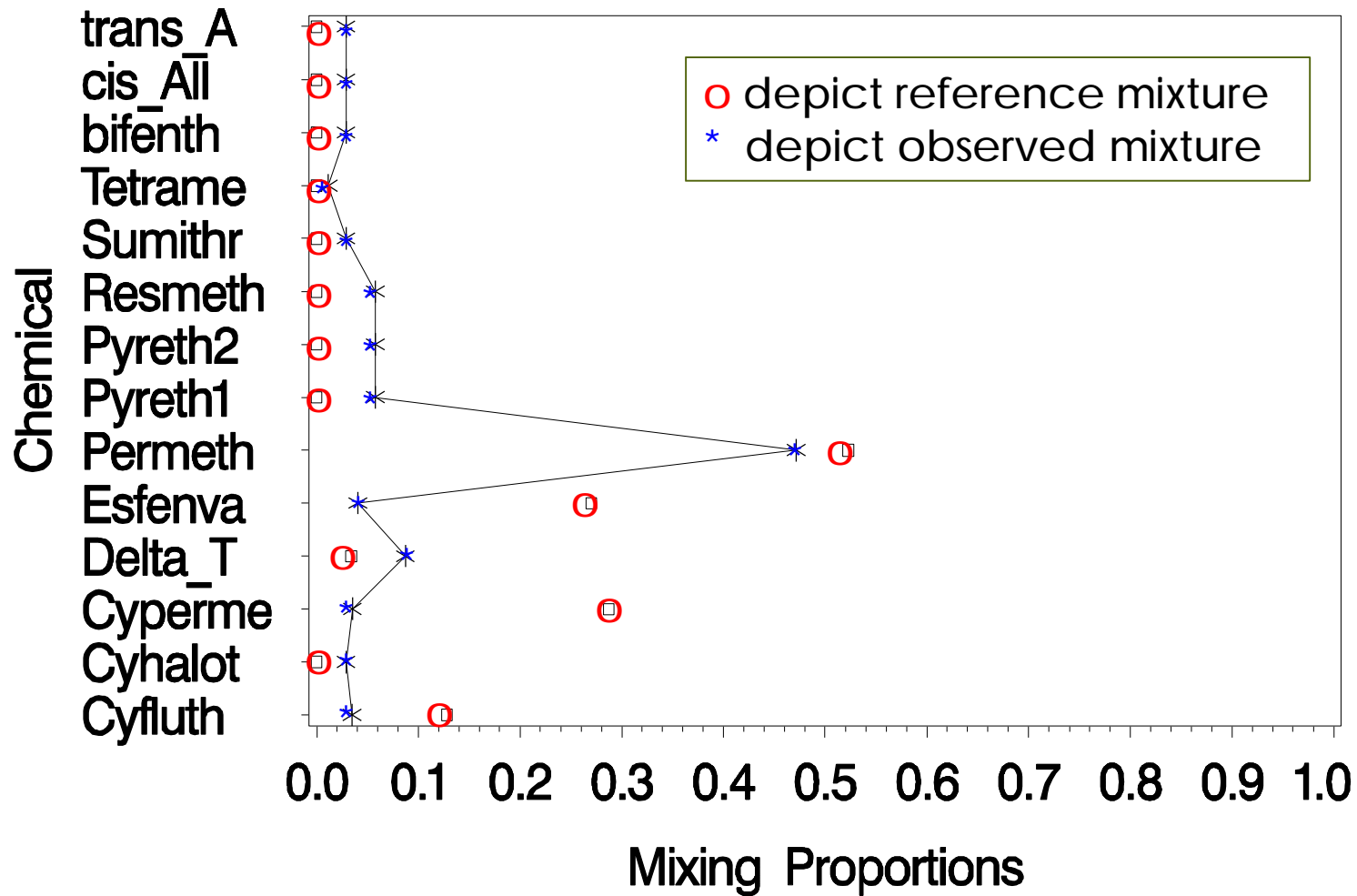
Weights are determined using relative potencies

Table 1: Summary percentage of pyrethroids measured from floor wipes in the CCC Study in the top 10% of the centers (in terms of total loading).

Chemical	Average percent in top 10% of CCC Study Centers	Normalized for top 6 to sum to 100*	Relative Potency Estimates**
Cyfluthrin	12.4	12.8	1.14
Cypermethrin	27.8	28.7	0.24
Delta/tralomethrin	3.2	3.4	1.00
Esfenvalerate	2.6	2.7	2.09
<i>Cis</i> -permethrin	19.1	52.3	0.06
<i>trans</i> -permethrin	31.3		
<i>cis</i> -allothrin	0.6	0	Set at 1.0
<i>trans</i> -allothrin	<1	0	Set at 1.0
Bifenthrin	<1	0	0.78
Cyhalothrin	1.9	0	1.90
Pyrethrin I	<1	0	Set at 1.0
Pyrethrin II	<1	0	Set at 1.0
Resmethrin	<1	0	0.01
Sumimethrin	<1	0	Set at 1.0
Tetramethrin	<1	0	Set at 1.0

* used by Wolansky et al in mixture dose-response study of neurotoxicity;

** Relative potency estimates from Wolansky et al (Wolansky *et al.* 2006; Wolansky *et al.* 2009); chemicals not evaluated by Wolansky et al have relative potency estimates set at 1.0



Upper 95% Conf Int on d = 4.48

Results from Case Study

- ✘ A weighted analysis was performed using relative potency estimates from Wolansky et al
- ✘ There were 114 centers from which the observed mixture is considered sufficiently similar to the reference mixture.
- ✘ That is, the upper confidence limit on the distance between the estimated reference BMD and the estimated BMD from the center's observed mixture was below the similarity boundary of 2.1.
- ✘ 90% of the centers with at least some residue concentrations > LOD (N=126) were determined to be sufficiently similar to the reference mixture identified by the toxicology study.



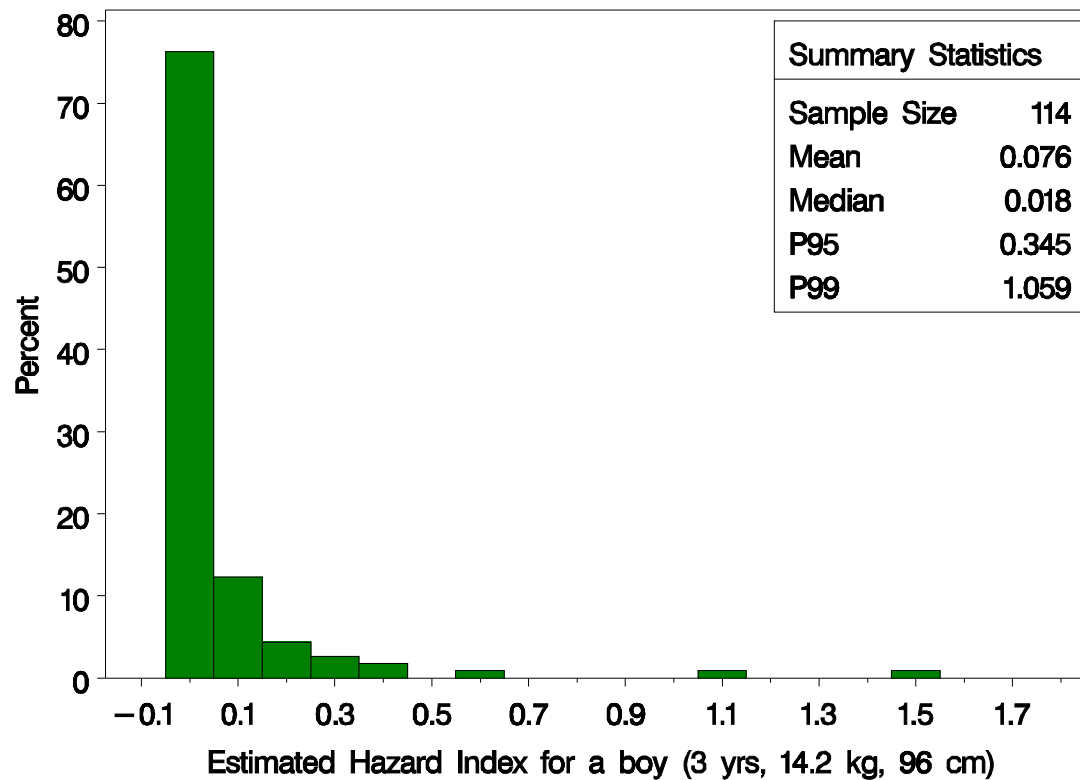
Define a mixture Hazard Index (mHI)

$$\text{mHI} = \sum_{j=1}^c \frac{DI_j \text{ (mg/kg/day)}}{\text{RfD}_j \text{ (mg/kg/day)}}$$

where

- ✧ The RfD_j s are defined from the components of the mixture BMDL
- ✧ The DI_j s are calculated assuming a dermal exposure model (Morgan et al, 2005)

Figure: Histogram for the distribution of the mHI estimates using exposure data considered sufficiently similar to the reference mixture (defined by a weighted distance between the BMDs of less than 2.1 mg/kg).



The index is calculated assuming a 3 year old boy, 14.2 kg and 96 cm tall.

2nd approach Conclusions

- ✘ We have developed an objective approach for defining sufficiently similar mixtures from occurrence data without assuming additivity.
- ✘ The test FOR sufficient similarity has sound statistical properties.
- ✘ LIMITATIONS:
 - ✘ The analysis presented here is limited to include only floor swipe data and one class of pesticides.
- ✘ DATA GAPS & RESEARCH NEEDS:
 - ✘ Objective process for specifying R for general assays needs to be determined.

Acknowledgements

- ✧ Biomonitoring method
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 - ✧ Other members of the CHAP for the US CPSC
 - ✧ Sufficient Similarity
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