An Overview of Methods to Address Distinct Research Questions on Environmental Mixtures: An Application to Persistent Organic Pollutants and Leukocyte Telomere Length

Yanelli Nunez, PhD Candidate

yanellinunez.github.io

2019 ISEE Annual Conference
Utrecht, Netherlands
08.26.2019

Why mixtures?

- We are exposed to hundreds (thousands) of stressors at any single time point
- The combination of exposures likely induces different responses

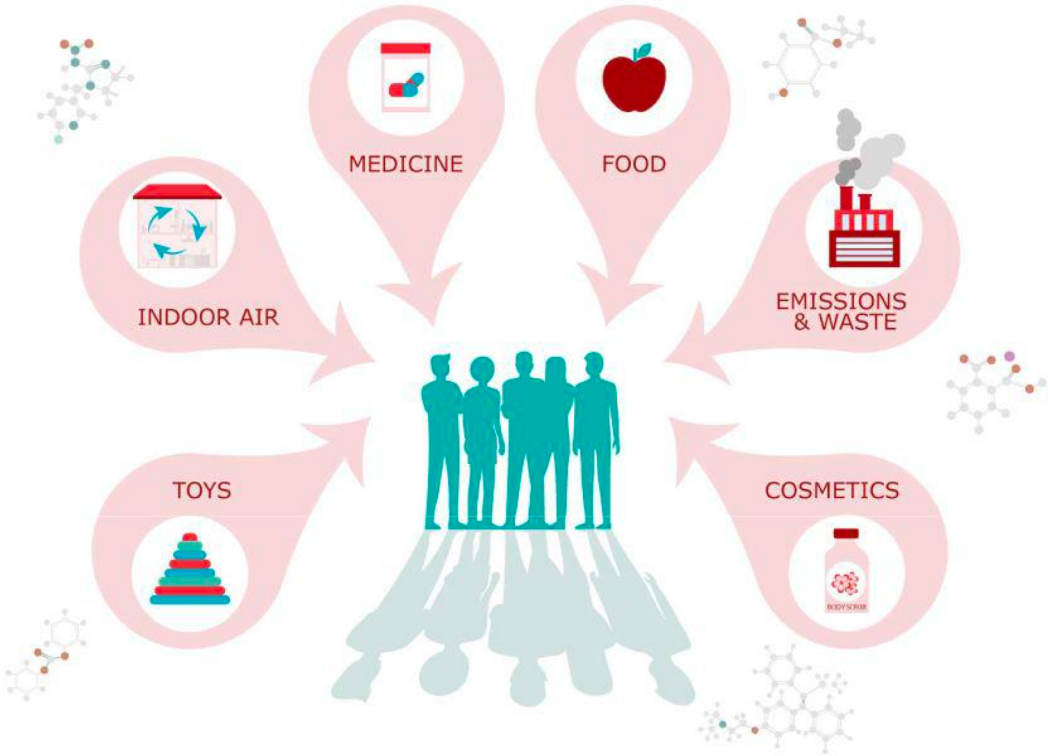


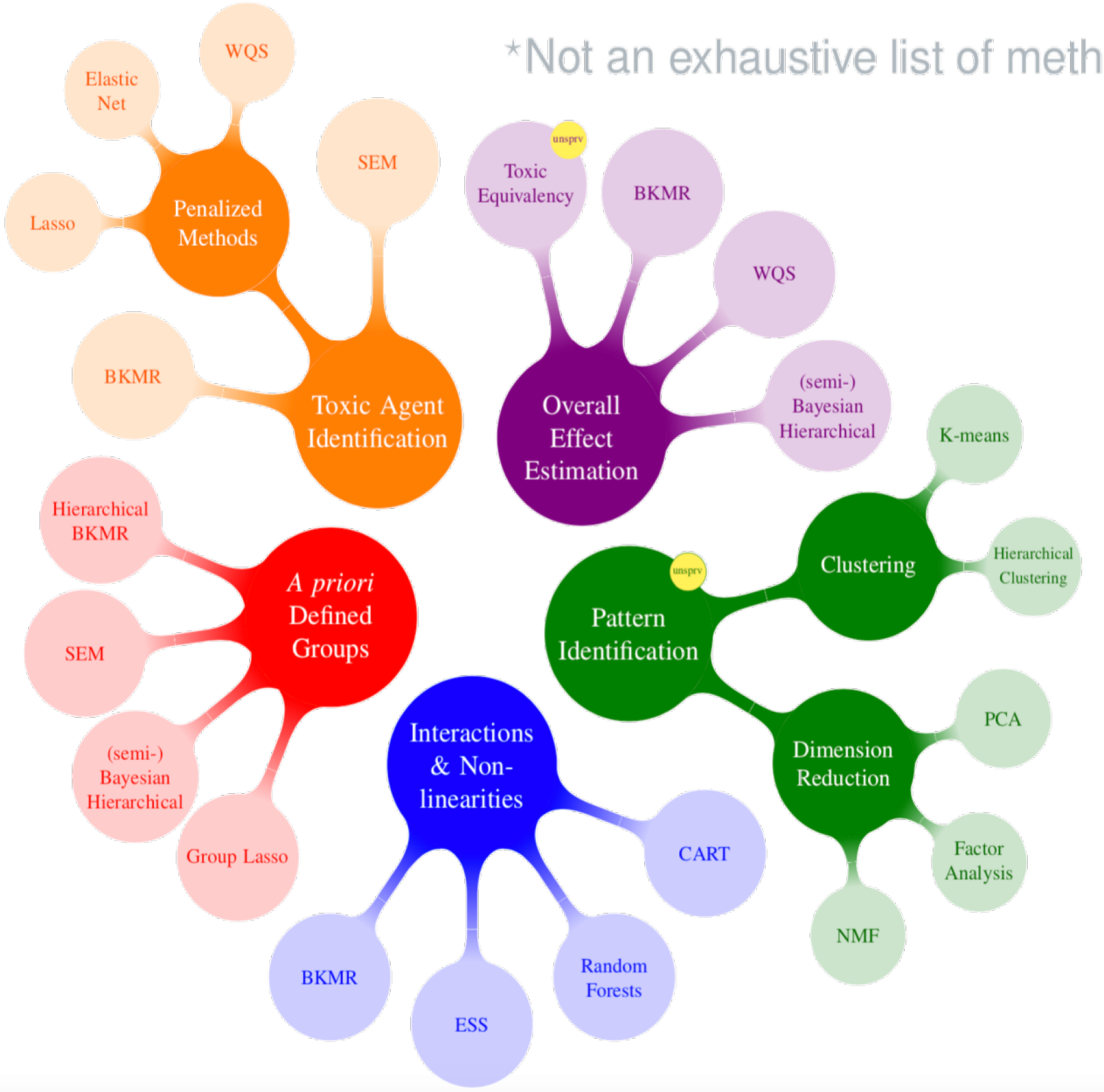
Image from: ec.europa.eu

What is a mixture?

- Indicates exposure to multiple "stressors" simultaneously
  - Chemical
  - Non-chemical (e.g. socioeconomic status)

- New statistical methods are being adapted and developed for this task

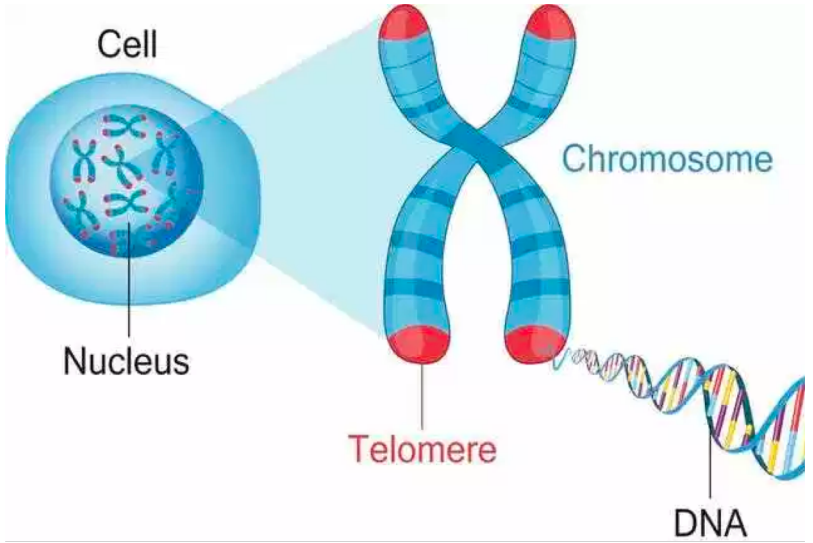
- Different methods answer different questions
- Based on our primary research question, different methods are appropriate
- No single method outperforms all others for all potential questions



Objective

- Contribute to a better understanding of appropriate uses of mixture methods based on the research questions each method best answers

- Illustration of example methods geared toward distinct research questions
  - persistent organic pollutants (POPs) as a mixture
  - leukocyte telomere length (LTL) as outcome



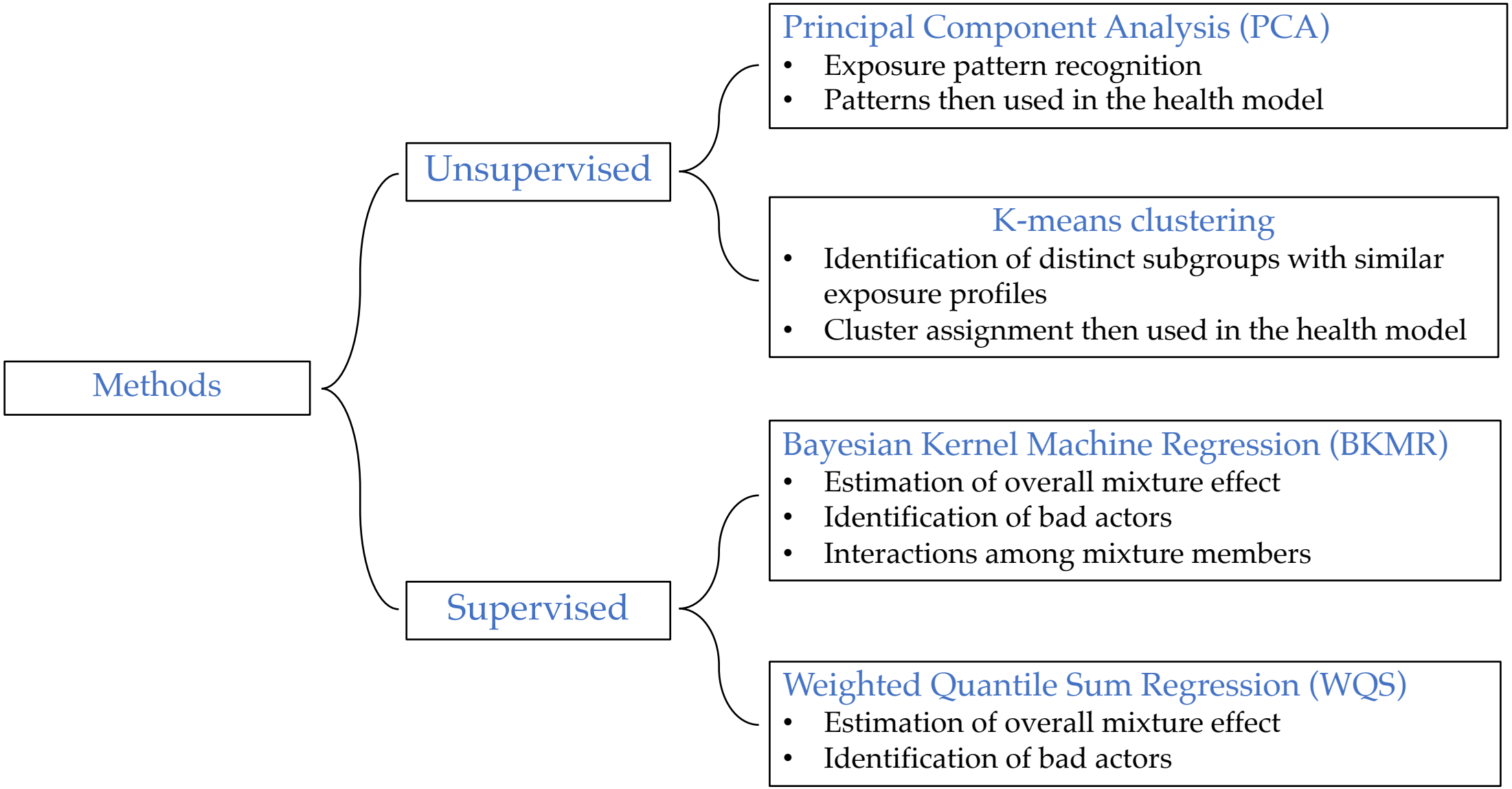
Environmental Health Perspectives, Vol. 124, No. 5 | Research

Cross-sectional Associations between Exposure to Persistent Organic Pollutants and Leukocyte Telomere Length among U.S. Adults in NHANES, 2001–2002

Susanna D. Mitro, Linda S. Birnbaum, Belinda L. Needham, and Ami R. Zota

- Evaluates the association between POPs and LTL
- Gain insight into a potential mechanism underlying poly-chlorinated biphenyl- (PCB-) and dioxin-related carcinogenesis
- Used potency-weighted sums

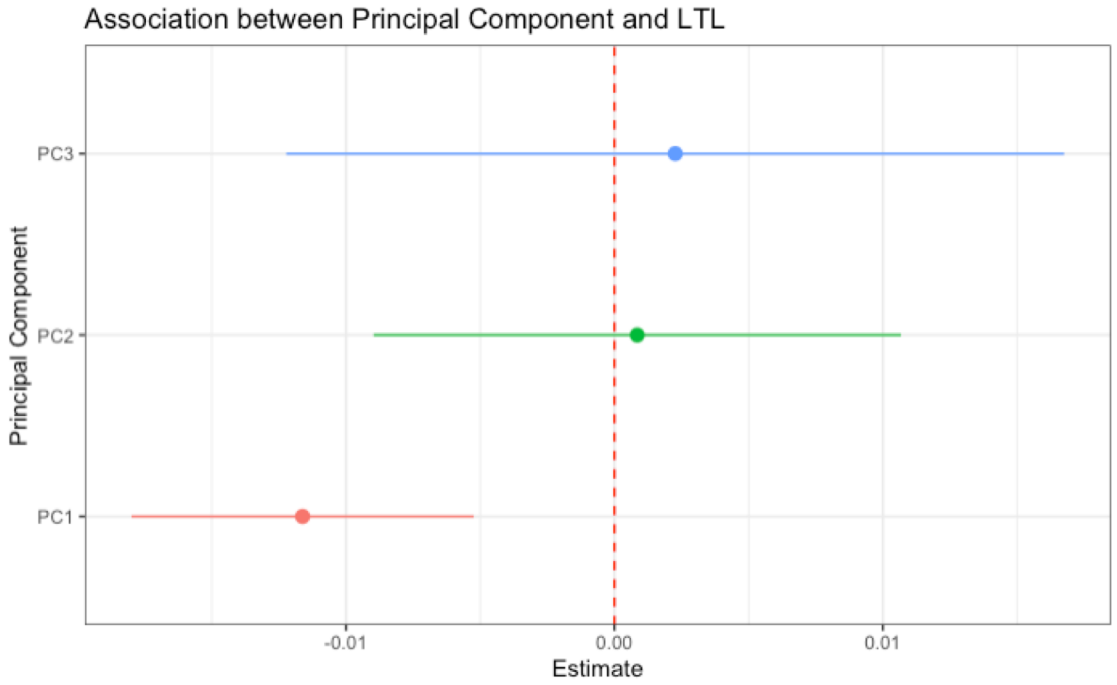
- **Study Population:**
  - NHANES 2001 – 2002 (N = 1003 US adults)
- **Outcome:**
  - Leukocyte telomere length (LTL); log-transformed in all analyses
- **Exposure Assessment:**
  - 8 non-dioxin like PCBs; 2 non-ortho substituted PCBs; 1 mono-ortho substituted PCB; 3 chlorinated dibenzo-p-dioxins; 4 dibenzo-furans (p =18)
  - Detected at > 60% of the samples
  - All log-transformed
  - Values < LOD → LOD/√ 2
- **Potential Confounders**
  - Age, age^2, sex, race/ethnicity, educational attainment, BMI, serum cotinine, and blood cell count and distribution

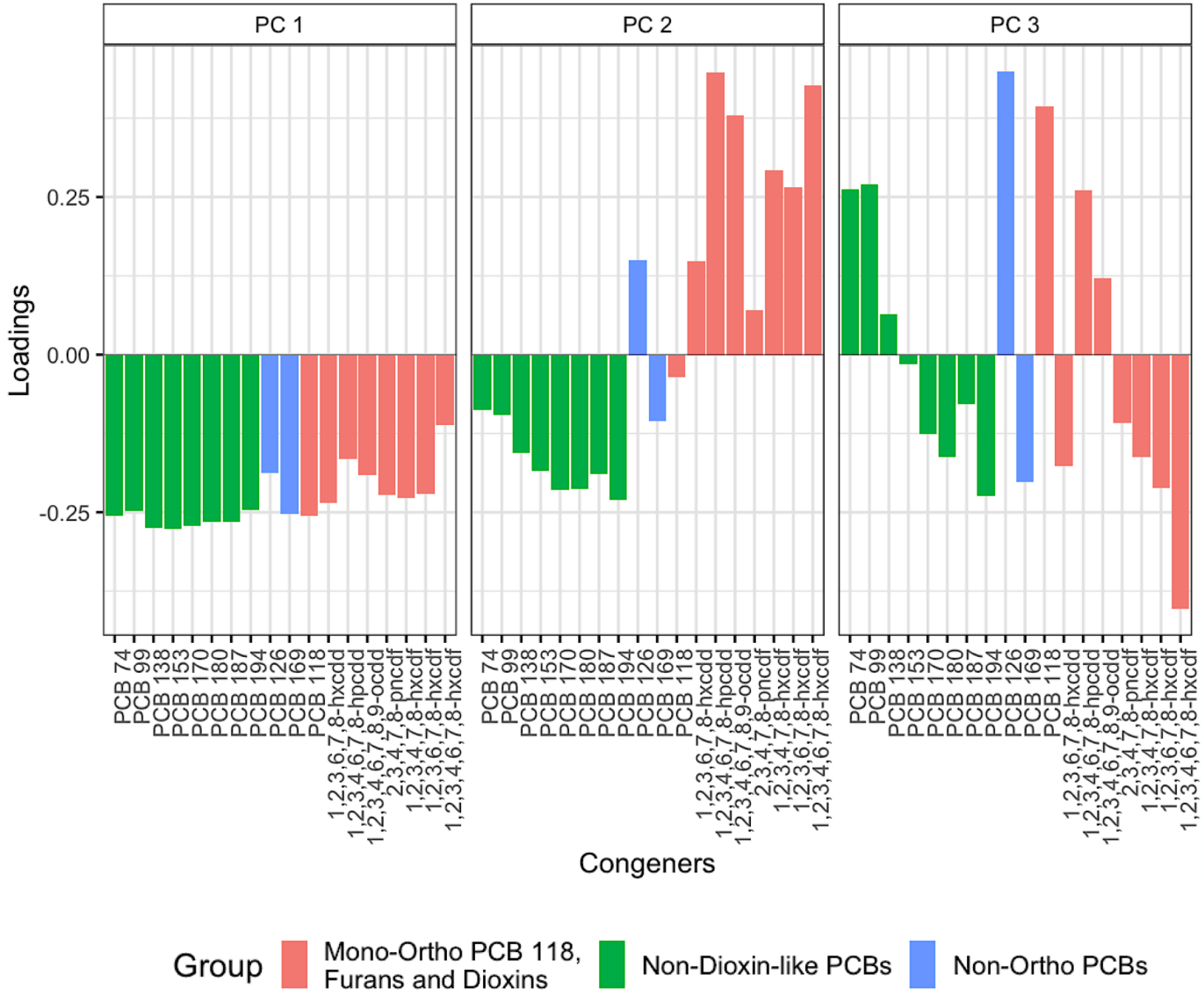

Methods
Unsupervised
Supervised
Principal Component Analysis (PCA)
• Exposure pattern recognition
• Patterns then used in the health model
K-means clustering
• Identification of distinct subgroups with similar exposure profiles
• Cluster assignment then used in the health model
Bayesian Kernel Machine Regression (BKMR)
• Estimation of overall mixture effect
• Identification of bad actors
• Interactions among mixture members
Weighted Quantile Sum Regression (WQS)
• Estimation of overall mixture effect
• Identification of bad actors

PCA

Are there specific patterns in POP exposure?

- Three patterns of exposure identified
- Exposure to all POPs (PC1) was associated with longer log-LTL

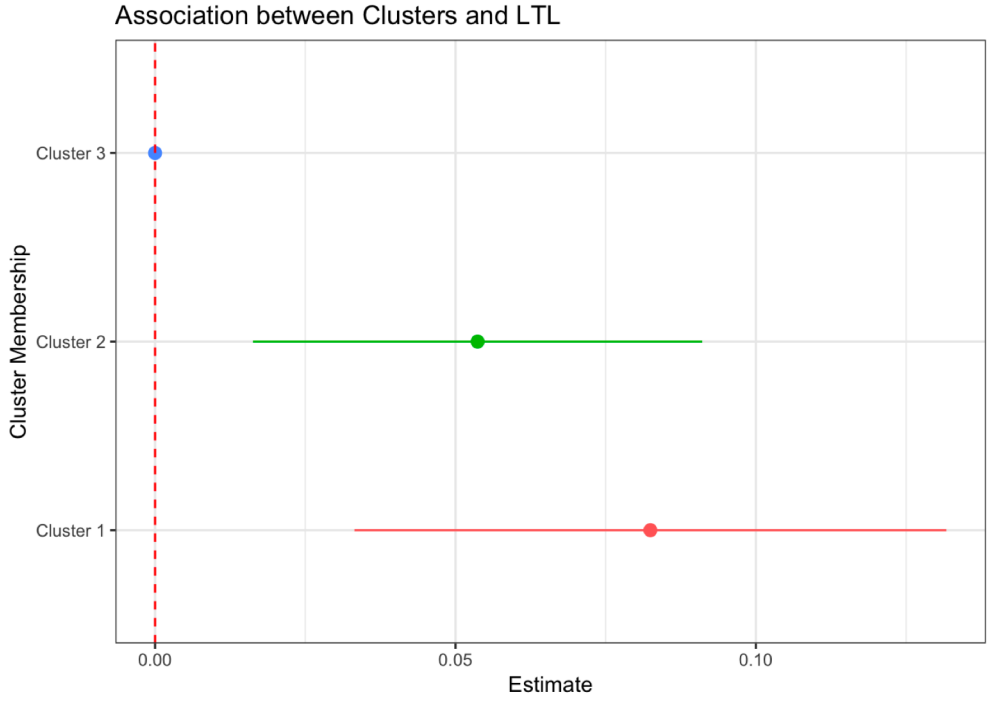


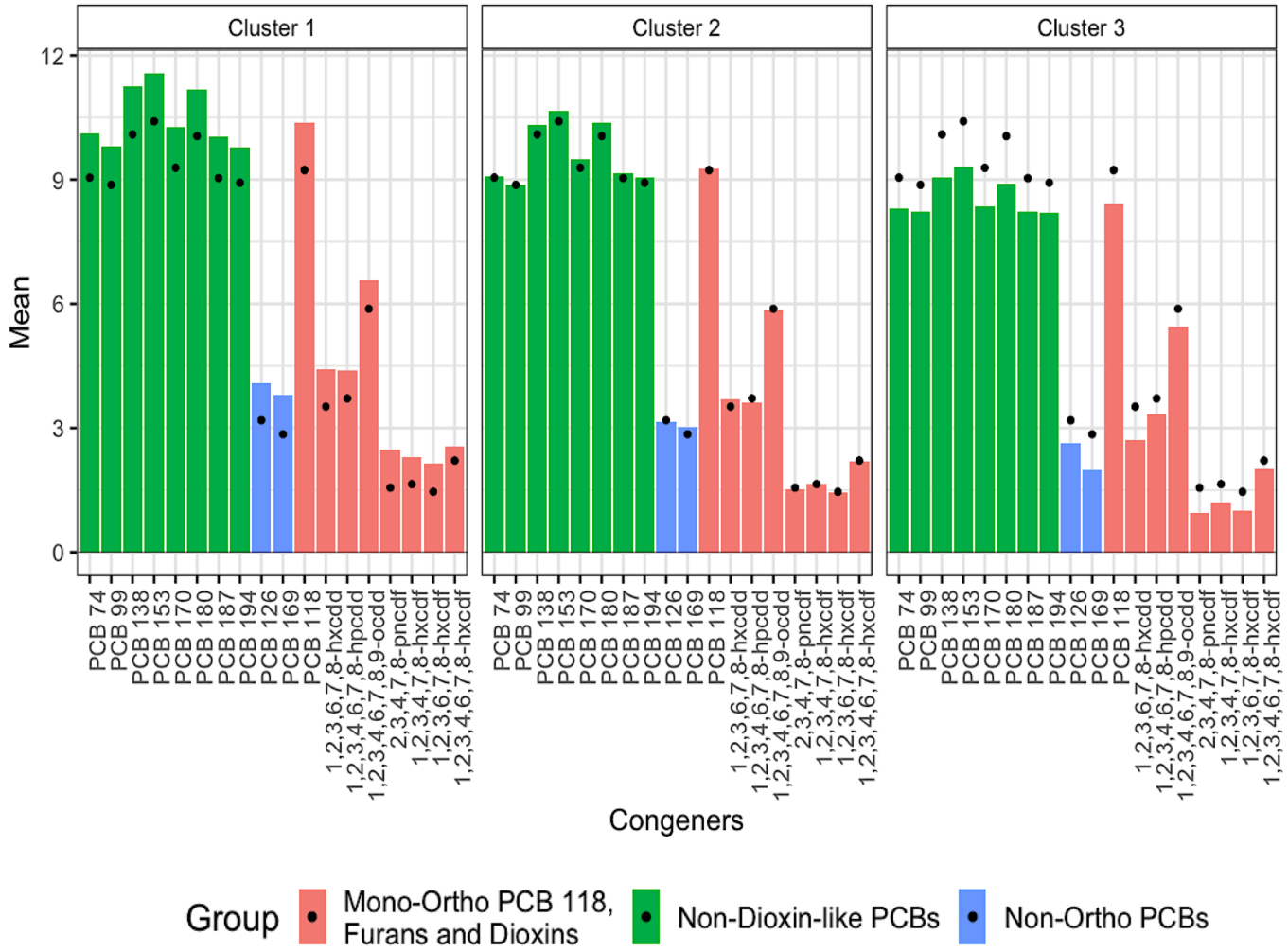


K-means clustering

Are there population subgroups that share similar exposure profiles?

- The study population was clustered by level of exposure: high, average, and low
- Higher exposure was associated with longer log-LTL



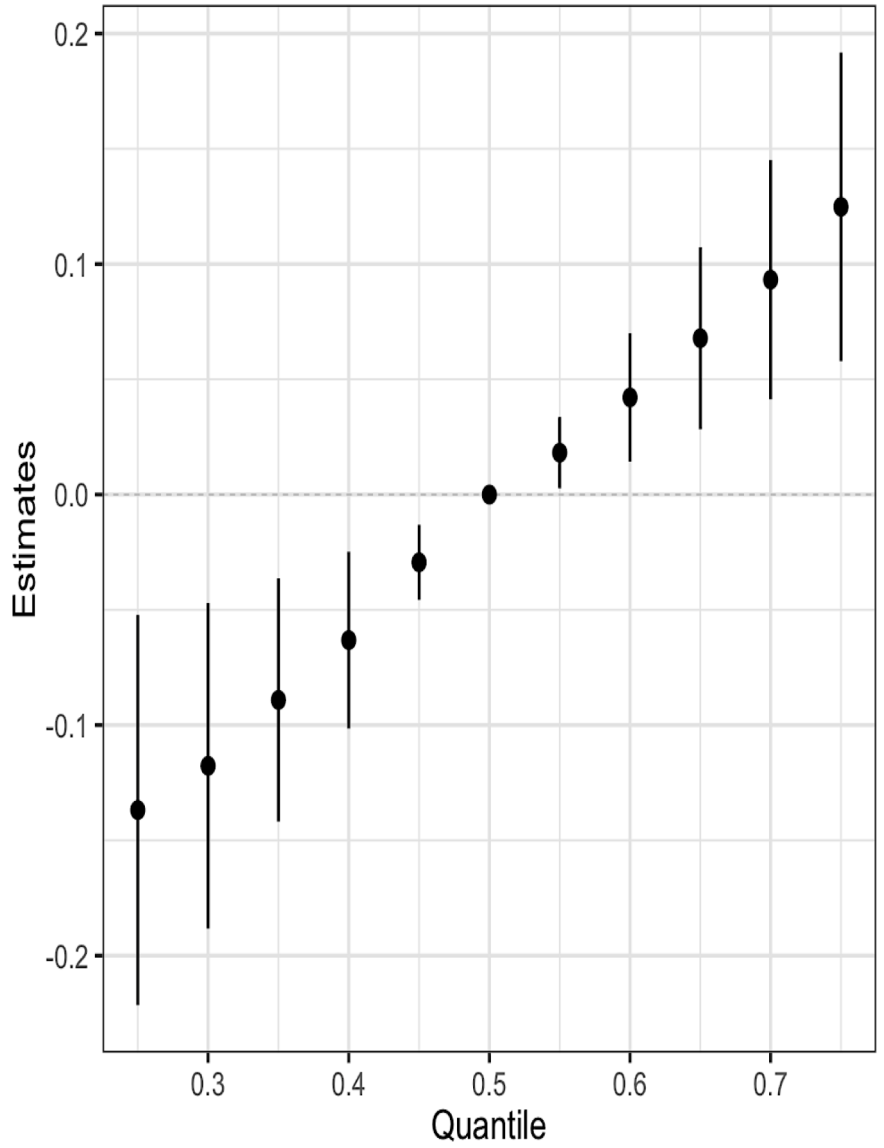


*Points indicate population means

BKMR

Is there an overall POP mixture effect on log-LTL?

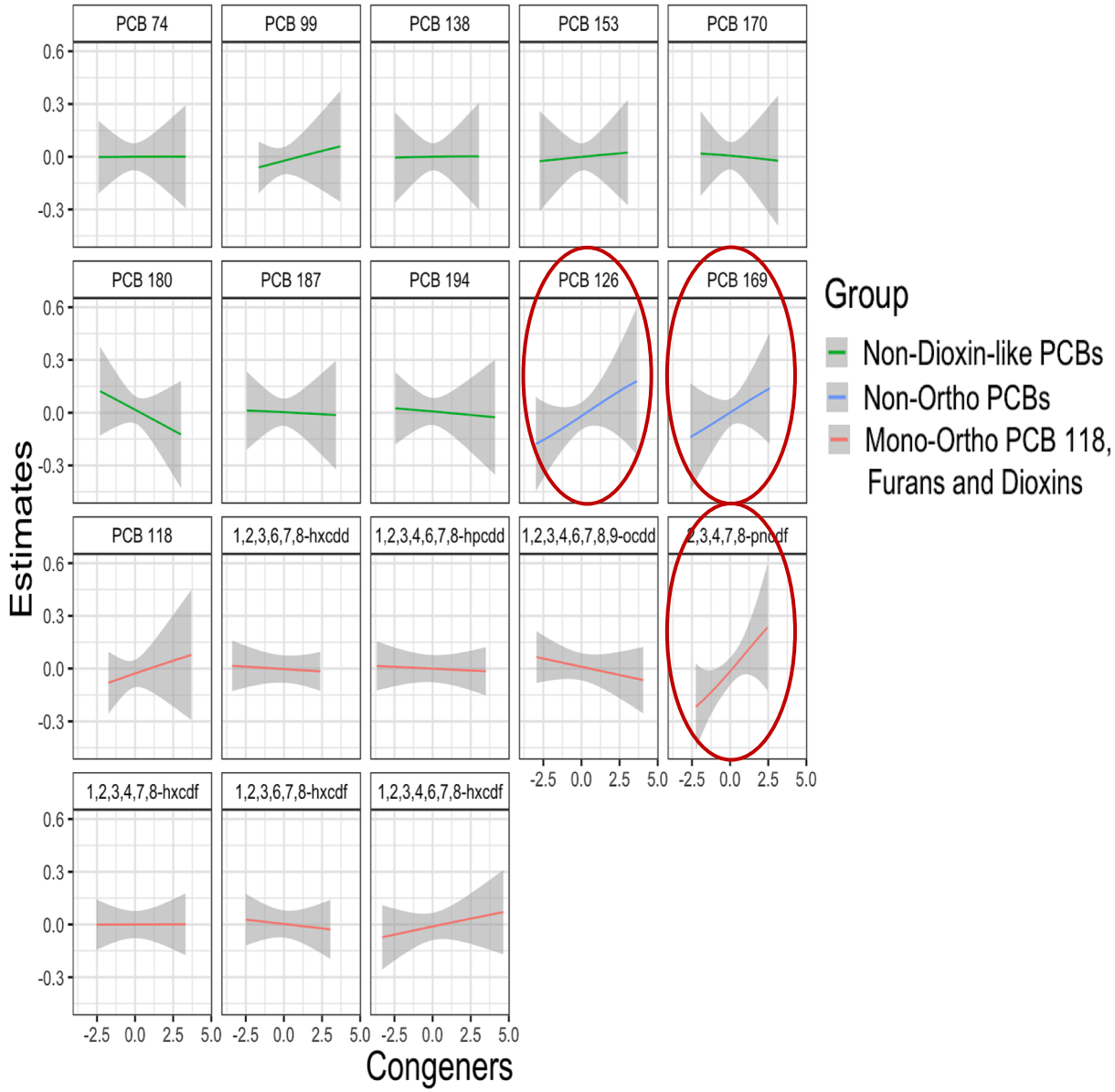
- Higher overall mixture exposure was associated with longer log-LTL



BKMR (cont'd)

What is the exposure-response relationship between each POP and log-LTL? Are there any interactions?

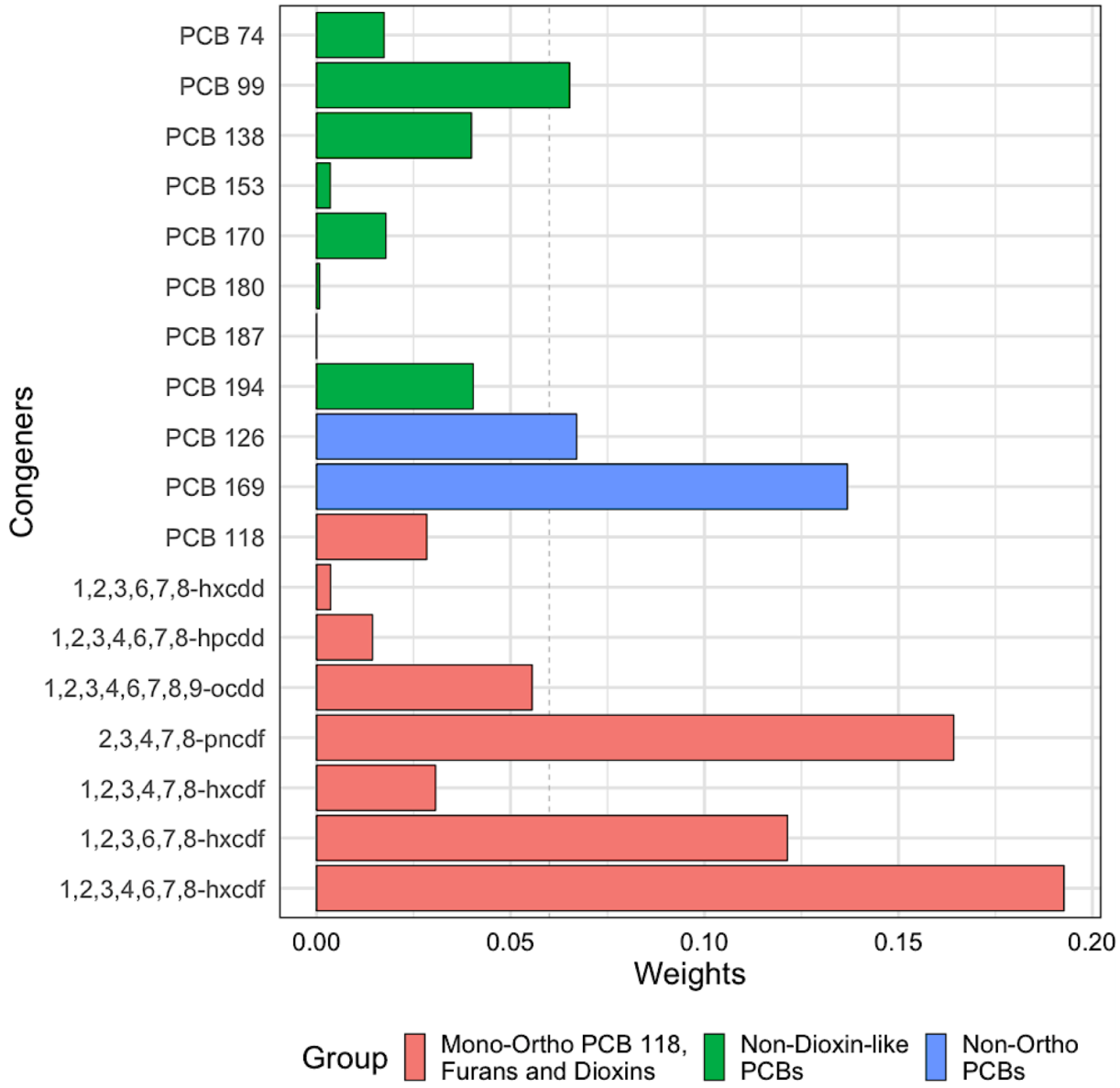
- Furan 2,3,4,7,8-pncdf, PCB 126, and PCB 169 are independently associated with longer log-LTL
- No evidence of interactions between POP



WQS

What is the overall effect of the mixture on log-LTL?
What POPs are most important?

- The mixture index was associated with longer log-LTL
  - $\beta_{WQS} = 0.02$ (95%CI: 0.01, 0.03)
- Three furans, both non-ortho PCBs, and one non-dioxin-like PCB are important mixture members



Discussion/Conclusion

- Using a single publicly available dataset, we applied **different methods to answer distinct research questions**
- In this example similar conclusions can be drawn from unsupervised and supervised approaches
  - Likely due to linear associations with no evidence of interactions
- **Results across methods aren't always comparable but can be complementary**
  - Each method addresses a difference research question
  - Importance of *a priori* defining the research question
  - Expert knowledge is required to interpret solution
- Sensitivity analyses to assess robustness
- To-date no single method exists to answer all mixtures related questions

Acknowledgments

- Marianthi-Anna Kioumourtzoglou
- Lizzy Gibson
- Ahlam Abuawad
- Stefano Renzetti
- Katrina Devick
- Brent Coull
- Chris Gennings
- Jeff Goldsmith
- Ami Zota
- Abby Welbourn

Funding:

- NIEHS PRIME R01(ES028805; ES028811; ES028800)
- NIEHS Centers (P30 ES009089; P30 ES000002; P30 ES023515; U2C ES026555)
- T32 ES007322
- T32 ES007142
- F31 ES030263
- R25 GM062454

https://yanellinunez.github.io/publications.html