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EPA Perspective – Exposure and Effects Prediction and Monitoring

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Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy

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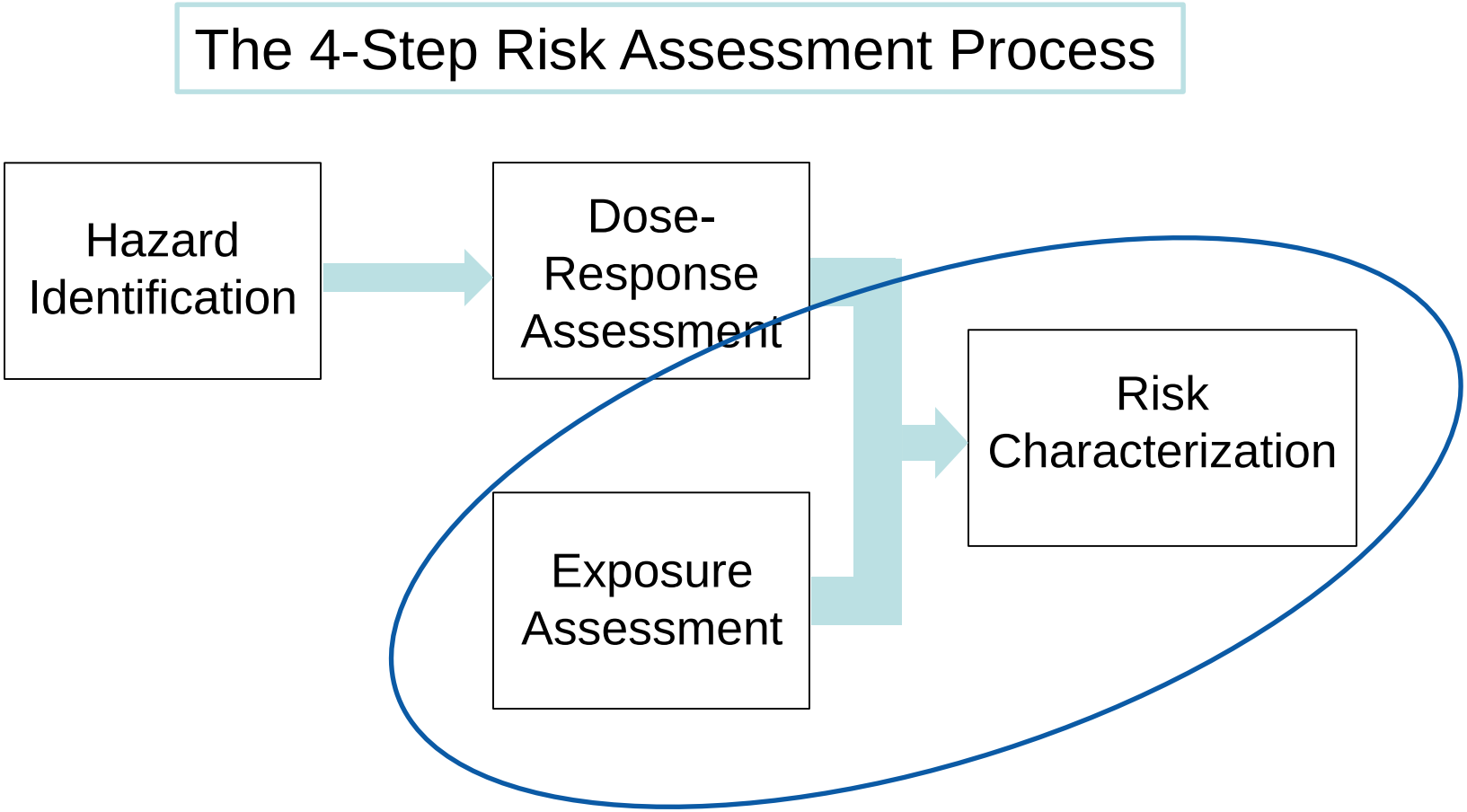
Outline

- Biomarkers as a risk assessment tool
  - exposure assessment & risk characterization
- CDC's NHANES as a source of biomarker data
  - history, goals & available data
- Review of NHANES publications (1999-2013)
  - chemicals, uses, trends & challenges
- NHANES biomarker case study
  - recommendations for future research

Risk assessment paradigm



http://www.epa.gov/risk_assessment/health-risk.htm

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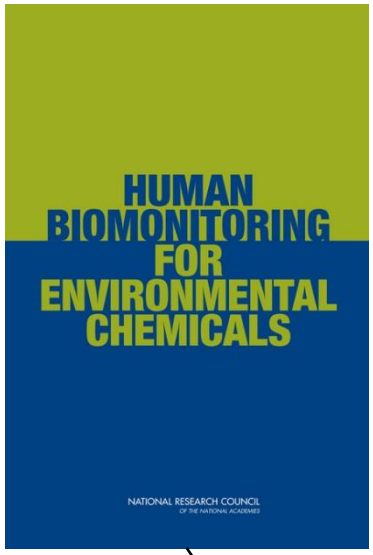
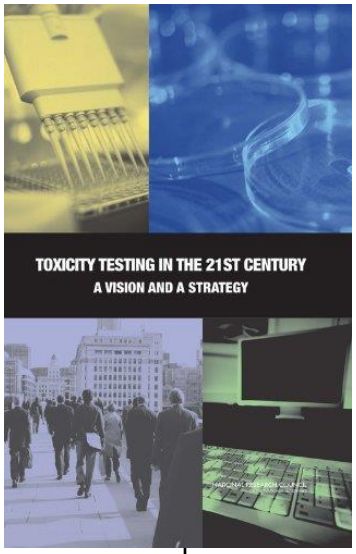
Key research questions

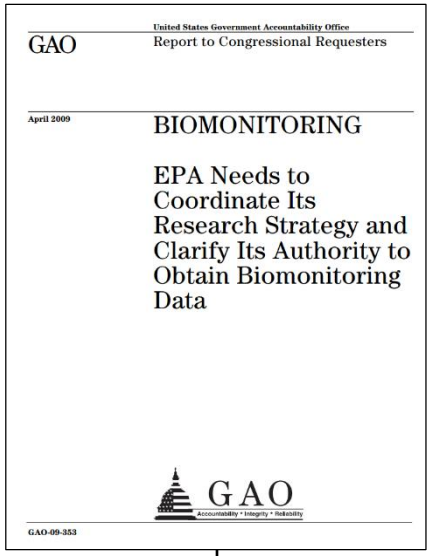
- Exposure assessment:
  - What are the priority stressors?
  - Who is exposed?
  - What are the exposure trends?
  - What are the magnitude and frequency of exposure?
  - What are the exposure sources, routes, and pathways?
- Risk characterization:
  - Which stressors are associated with disease?
  - Do stressor concentrations exceed “acceptable” levels?
  - What are the cumulative effects of stressors?

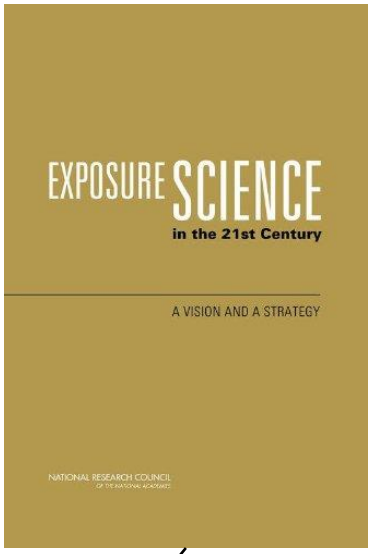
Biomarkers can help provide answers to these questions!

Biomarkers research drivers



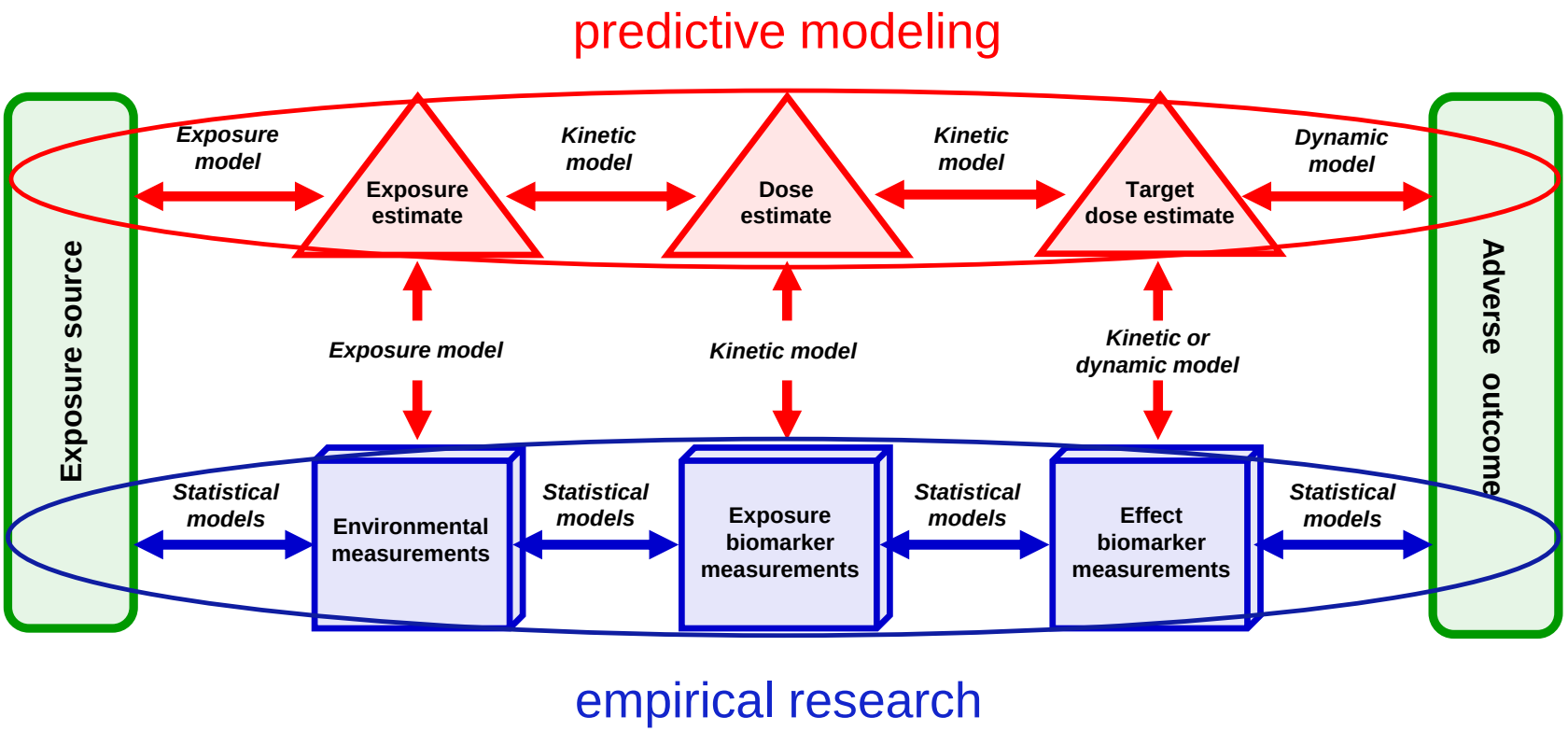






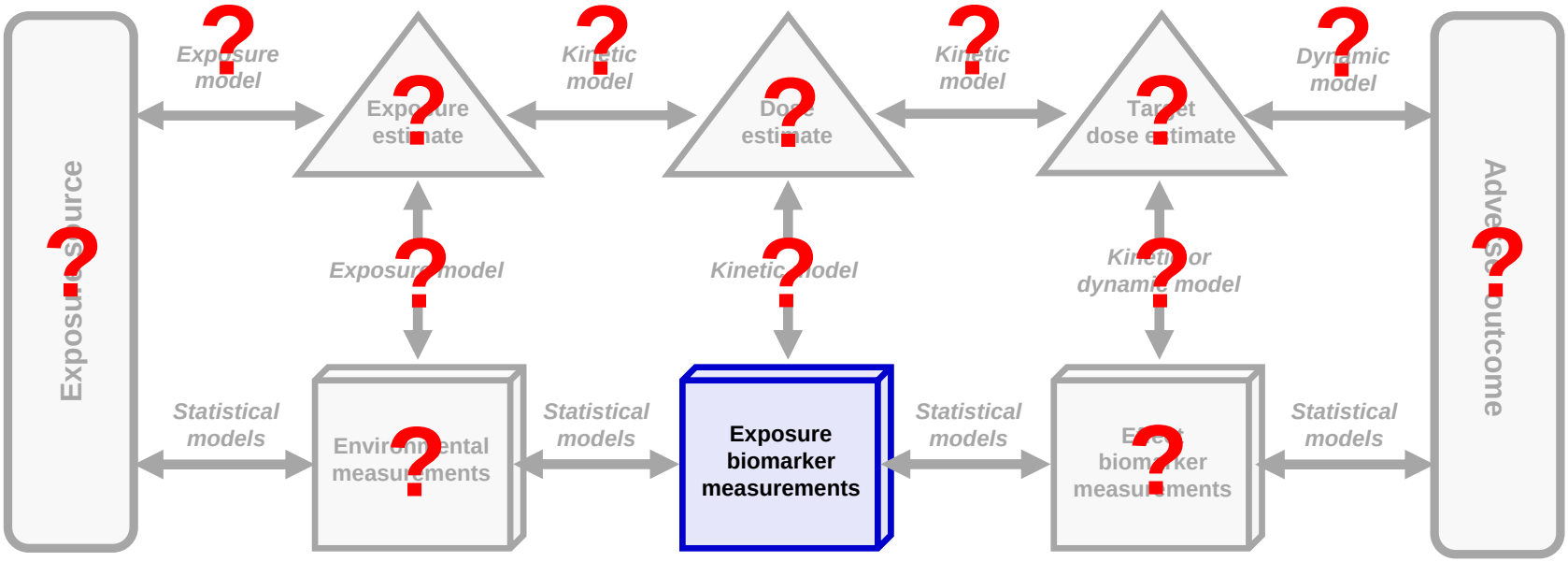
Calls for more biomarker data and increased use of existing data

Biomarkers in the source-to-outcome continuum



Adapted from Sobus *et al.*, Sci Total Environ. 2011 Oct 15;409(22):4875-84.

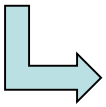
A common scenario: too little data



Which research questions can still be answered?

CDC's National Health and Nutrition Examination Survey (NHANES)

- Origin in the late 1950's
- Continuous survey: 1999 – present
- Data on lifestyle, health, nutrition, biomarkers
- Goals:
  - Establish national baseline for health and nutrition
  - Evaluate disease prevalence
  - Analyze risk factors (e.g., diet) for disease
  - Monitor disease and risk factor trends
  - Explore emerging public health issues
  - Monitor trends in environmental exposures

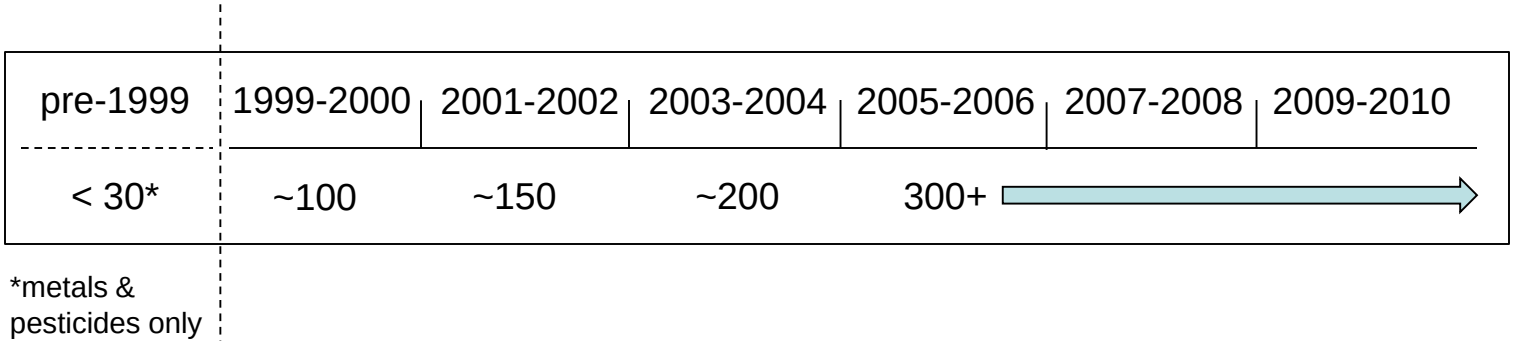


Risk factors for disease?

http://www.cdc.gov/nchs/tutorials/nhanes/surveyorientation/surveyoverview/info1.htm

NHANES biomarkers

- Exposure: metals, dioxins/furans/PCBs, PFCs, pesticides, phthalates, phenols, PAHs, VOCs…



- Health: std. biochemistry profile, blood counts, blood lipids, blood sugars, vitamins and nutrients, hormones, antibodies…

http://wwwn.cdc.gov/nchs/nhanes/search/nhanes_continuous.aspx

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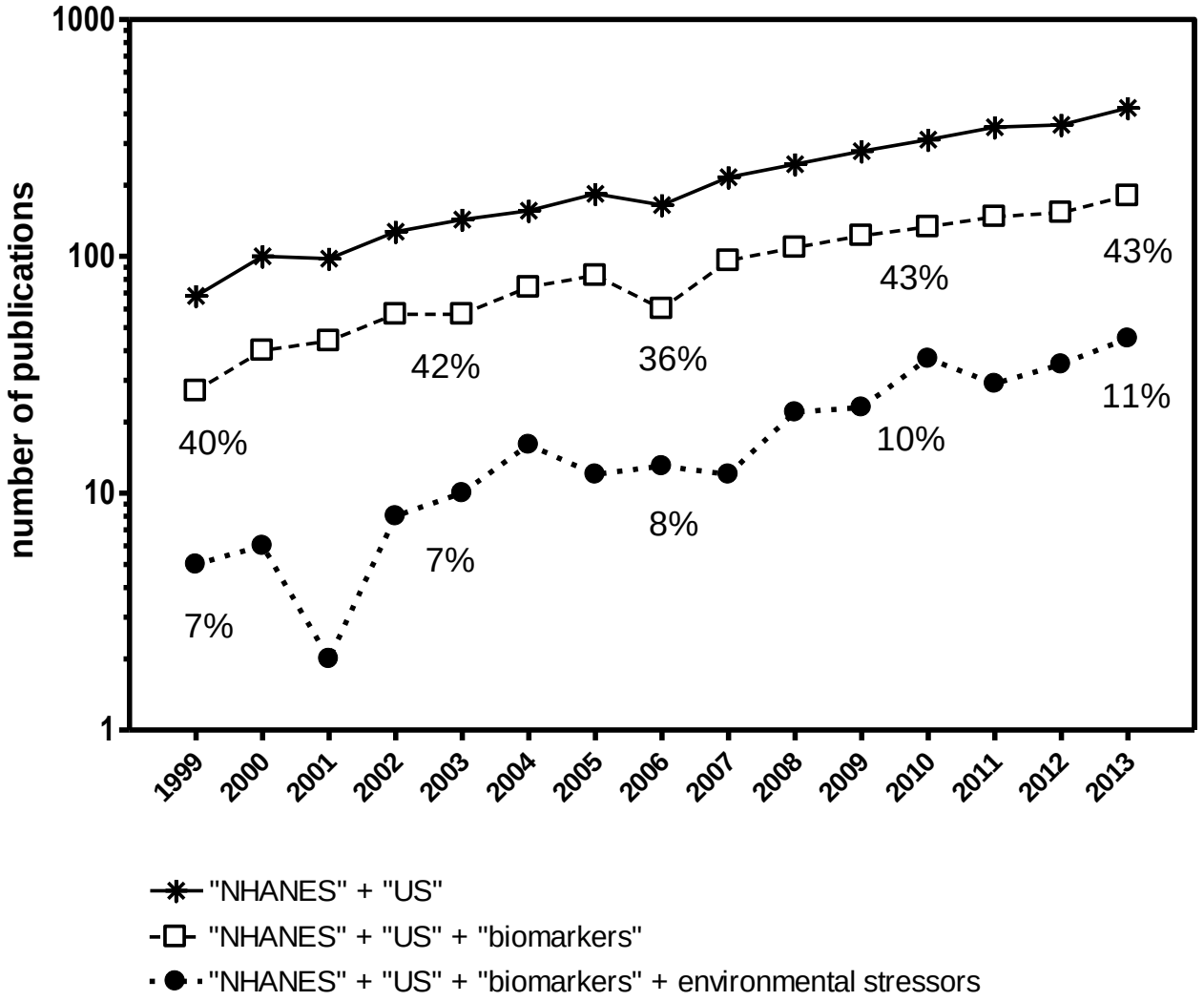
A review of publications using NHANES data

- PubMed search: 1999-2013
- Key Questions:
  - What % of pubs use biomarker data?
  - What % focus on environmental stressors?
  - Which chemicals are being studied?
  - How are biomarker data interpreted?
  - Are there clear publication trends?
  - Are there clear challenges?
  - Are there ways to enhance data interpretation?

NHANES publications (by year)



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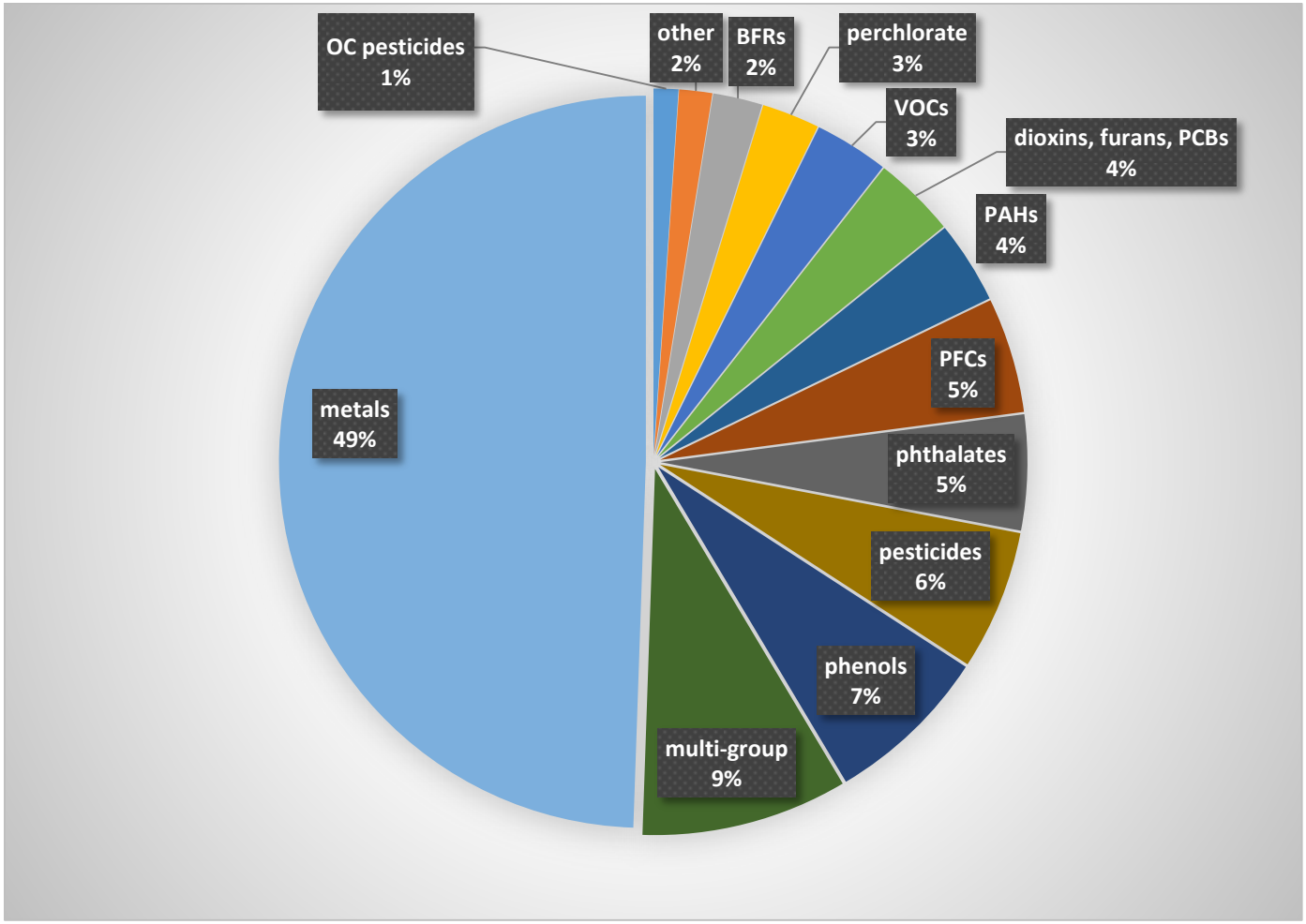
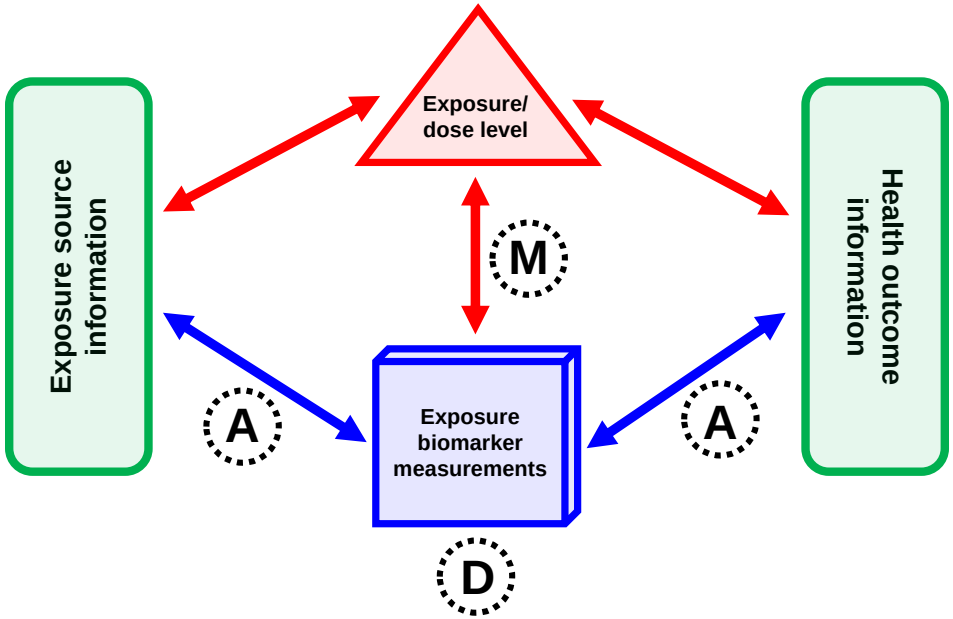
NHANES publications (by chemical class)

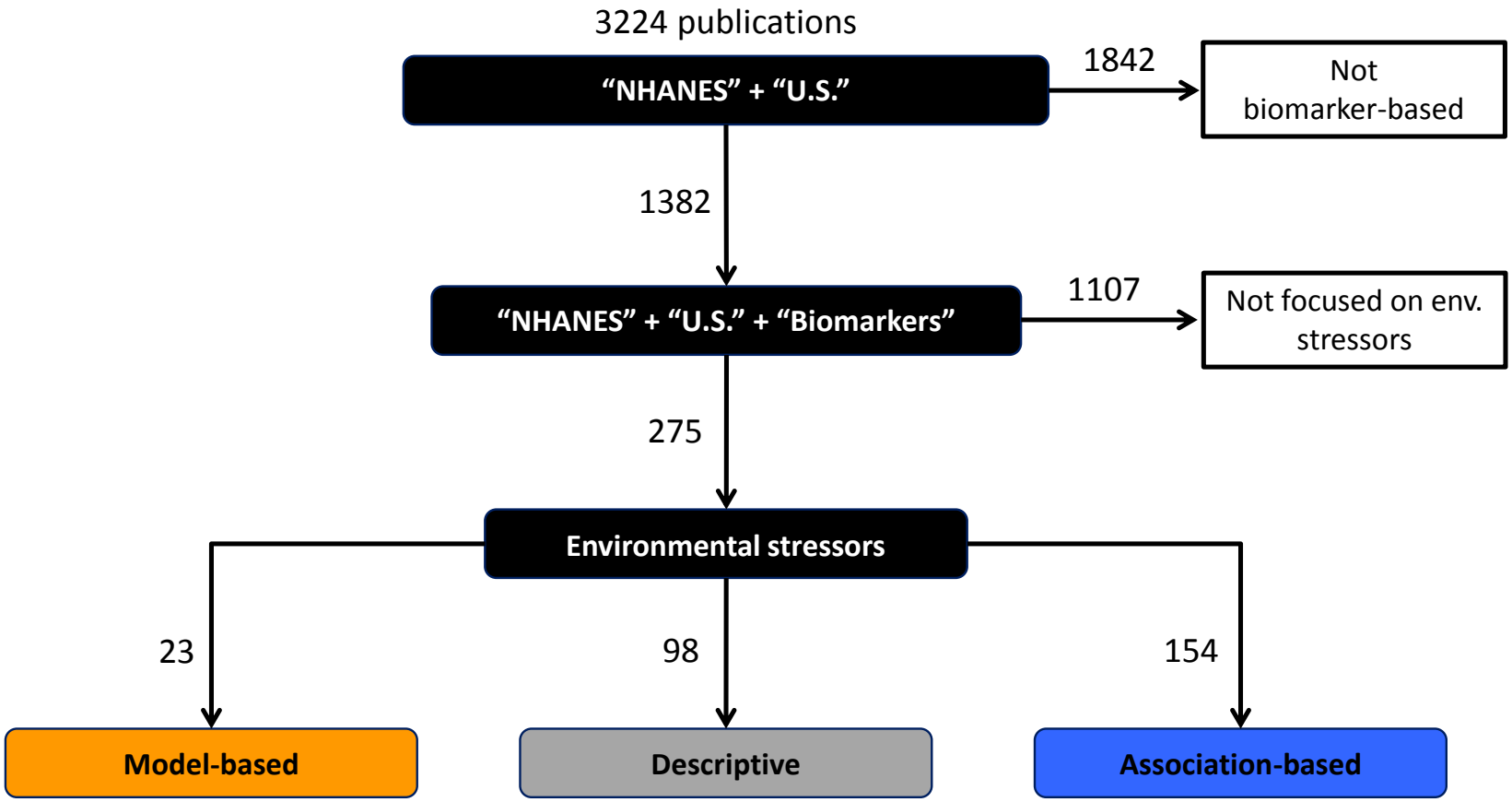


Analysis categories

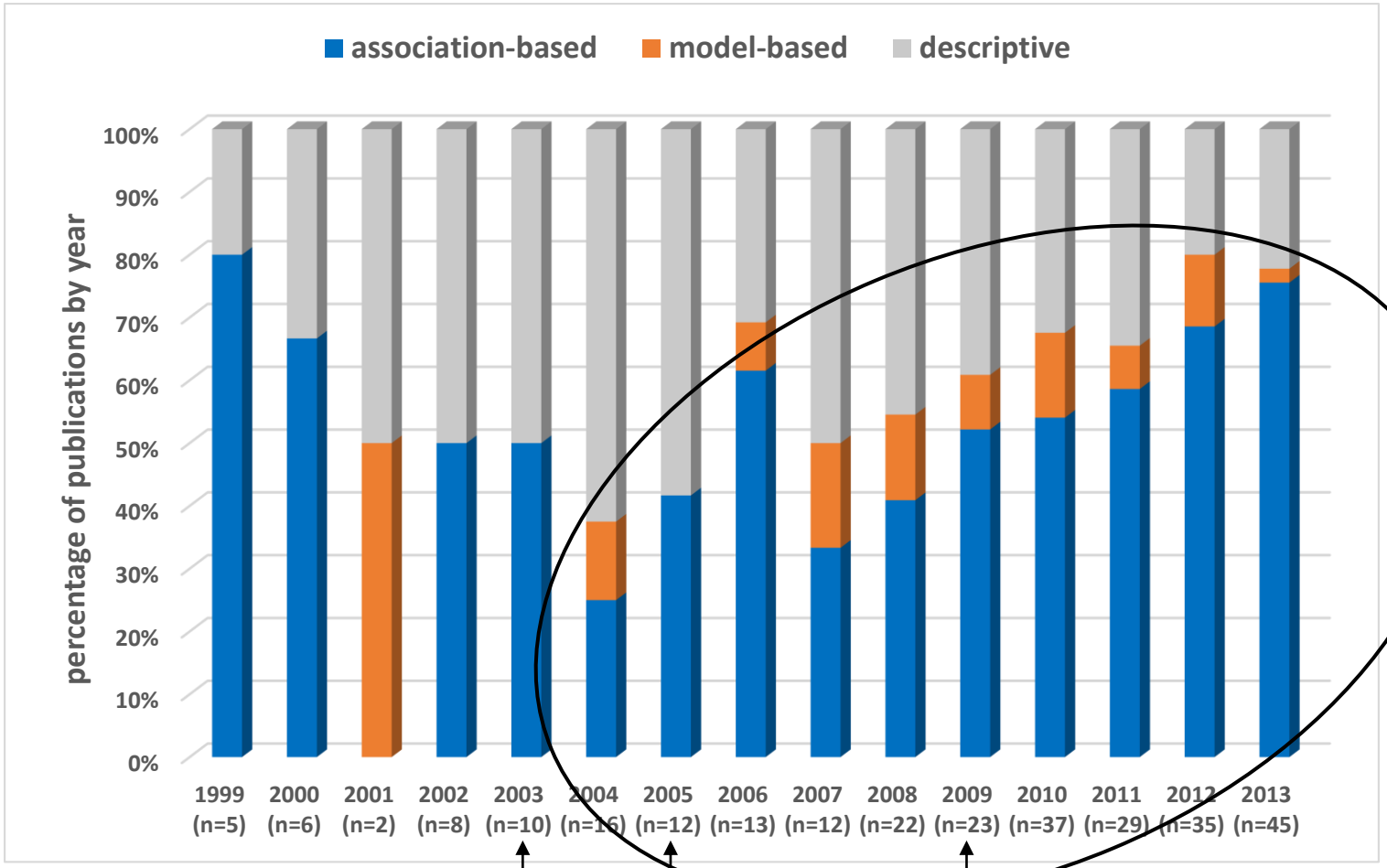


Symbol	Definition
↔	Predictive model (e.g., PK model)
↔	Empirical association (e.g., regression model)
D	Descriptive approach
A	Association-based approach
M	Model-based approach

NHANES publications
(by analysis category)



Trends by analysis category



Trends by biomarker group (association-based studies)

Challenges for association-based studies

- Biomarker selection and measurement:
  - specificity, relevance & method sensitivity
  - sample contamination and stability
  - matrix adjustments
  - variability and misclassification**
- Study design:
  - research rationale (plausibility)
  - data analysis & reporting (multiple testing)
  - cross-sectional design - lack of temporality**

"A proposal for assessing study quality: biomonitoring, environmental epidemiology, and short-lived chemicals (BEES-C) instrument"
Lakind *et al.,* submitted to Environment International

NHANES association case study

- Research questions:
  - Do different exposure metrics yield different associations?
  - Which exposure metrics are preferable?
  - What are the best practices for exposure metric selection?

- Research approach:
  - Evaluate NHANES associations using different metrics
  - Simulate exposures and evaluate using different metrics
  - Compare simulation results to NHANES results

"Changes in epidemiologic associations with different exposure metrics: A case study of phthalate exposure associations with body mass index and waist circumference"
Christensen *et al.,* submitted to Environment International

Results from NHANES 2009-2010

Adjusted regression coefficients for effect of phthalate levels on ln(Body Mass Index). All models adjusted for age, sex, race/ethnicity, height, and PIR. Results presented for models treating phthalate exposures as ln-transformed variables.

	Outcome is ln(Body Mass index)				
Phthalate	nmole/min: β (SE),	nmole/mL: β (SE),	nmole/mL + crt: β (SE),	nmole/g crt: β (SE),	nmole/kg-day: β (SE),
DBP	**0.022 (0.005)****	**0.023 (0.004)*****	**0.014 (0.006)***	0.007 (0.006)	**0.040 (0.006)******
BBzP	**0.019 (0.005)****	**0.021 (0.004)*****	**0.011 (0.005)***	0.006 (0.006)	**0.033 (0.006)*****
DEHP[a]	**0.019 (0.005)****	**0.025 (0.004)*****	**0.017 (0.005)***	0.008 (0.006)	**0.033 (0.005)*****
DiNP	**0.020 (0.004)*****	**0.023 (0.004)******	**0.017 (0.004)****	**0.013 (0.004)***	**0.028 (0.004)******
DiBP	**0.022 (0.005)****	**0.025 (0.005)*****	**0.014 (0.006)***	0.003 (0.007)	**0.045 (0.007)******
DEP	**0.013 (0.004)****	**0.016 (0.003)****	**0.010 (0.004)***	0.005 (0.004)	**0.018 (0.004)****

[a]Represents the molar sum of 4 DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP)

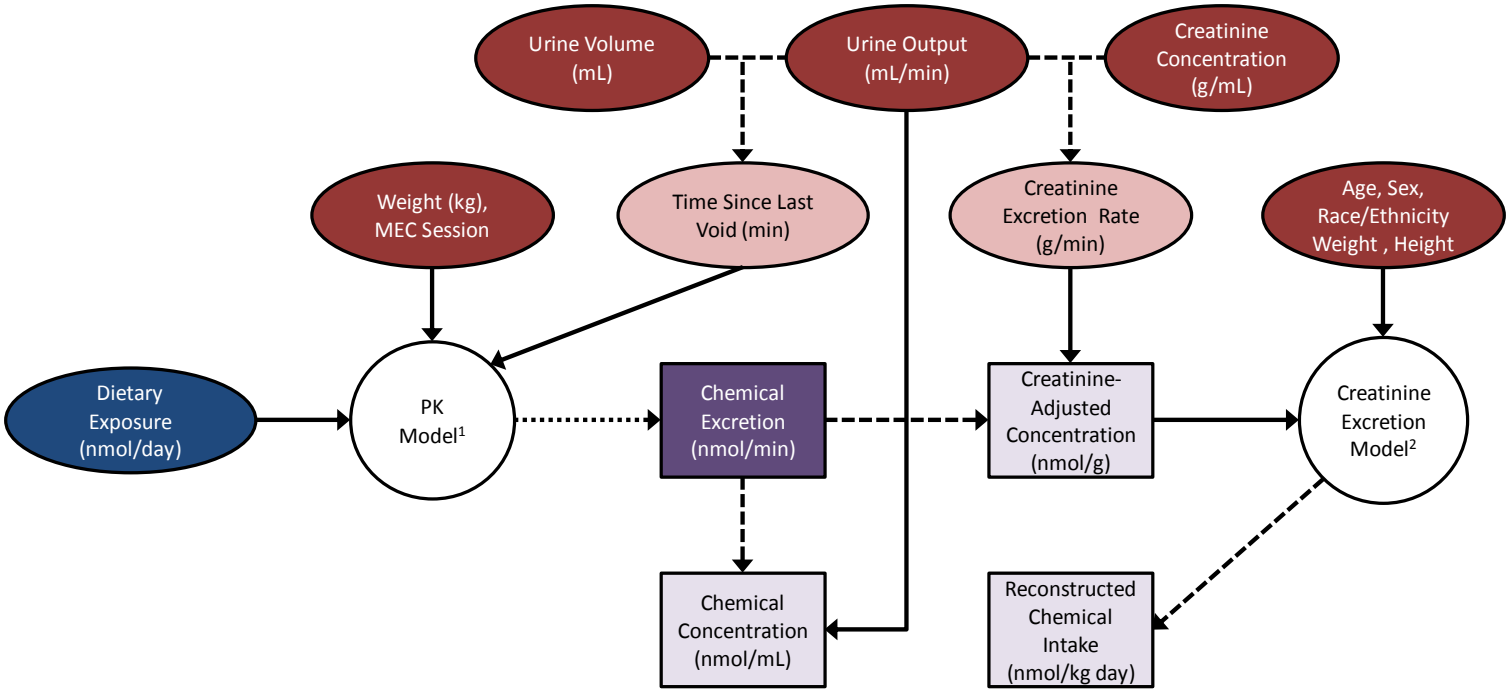
* $p < 0.05$

** $p < 0.001$ (1×10^{-3})

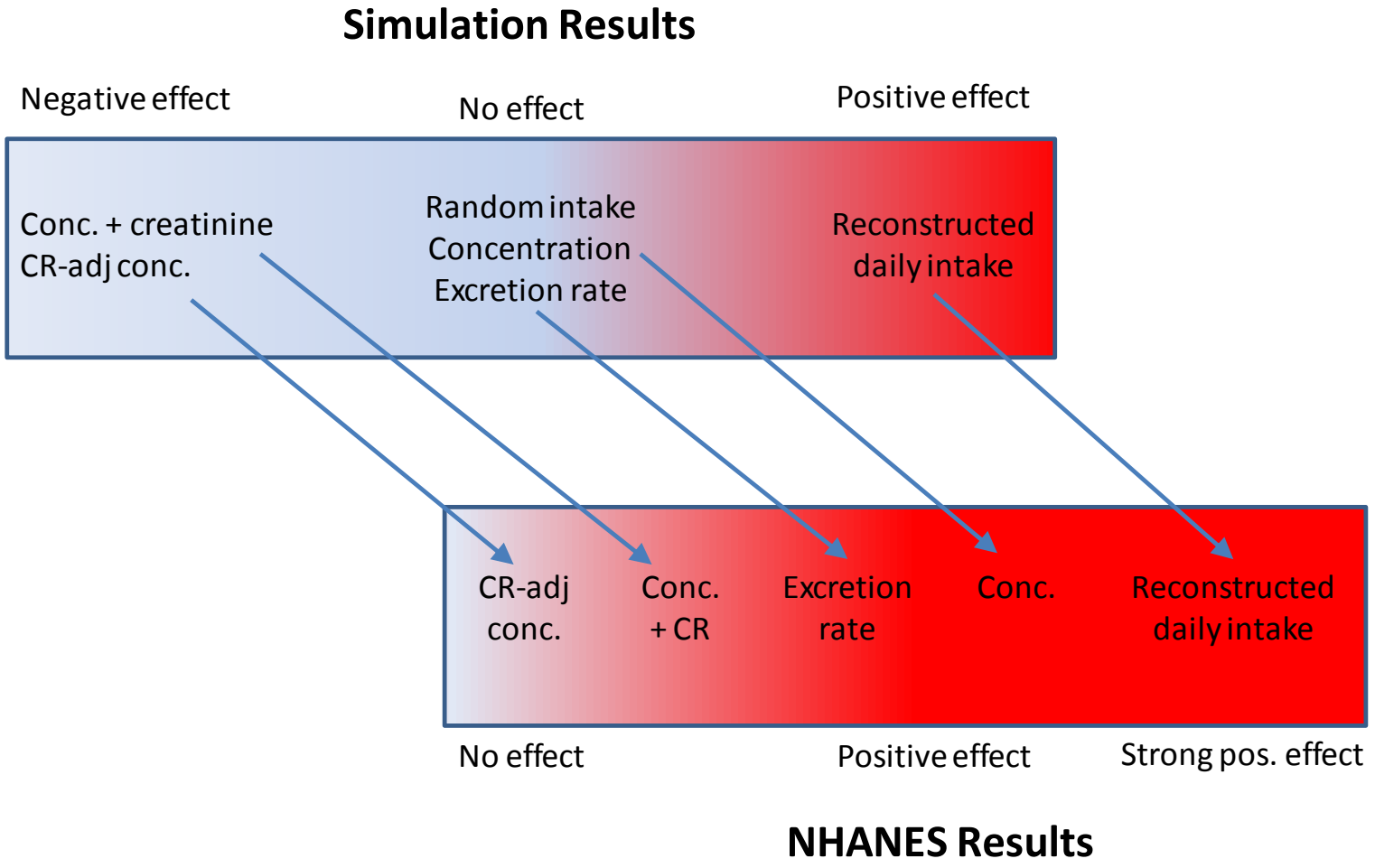
*** $p < 0.000001$ (1×10^{-6})

**** $p < 0.000000001$ (1×10^{-9})

Exposure simulation

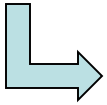


Results comparison



Summary and take-home points

- Increasing use of NHANES biomarker data
- Increasing focus on chemical stressors
- Increasing focus on short-lived chemicals
- Emerging focus on semi-targeted assessments
- Lingering challenges for association-based studies
- Guidance and best practices needed for:
  - Exposure surrogate selection, measurement, and use
  - Outcome surrogate selection, measurement, and use



Inputs from toxicologic pathology:
- Translational biomarkers
- Pathway-based biomarkers
- Early effect biomarkers

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Questions?

EPA campus in Research Triangle Park, NC