Airborne mammary carcinogens and breast cancer risk in the Sister Study

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Hazardous Air Toxics

- 187 pollutants that are known or suspected to be carcinogenic or cause other serious health or environmental effects
- Distinct from criteria air pollutants (PM, O_3, CO, NO_2, Pb, SO_2)
- There are no nationwide ambient air quality standards for air toxics
- Numerous ambient sources:

EPA 2016, EPA 2017

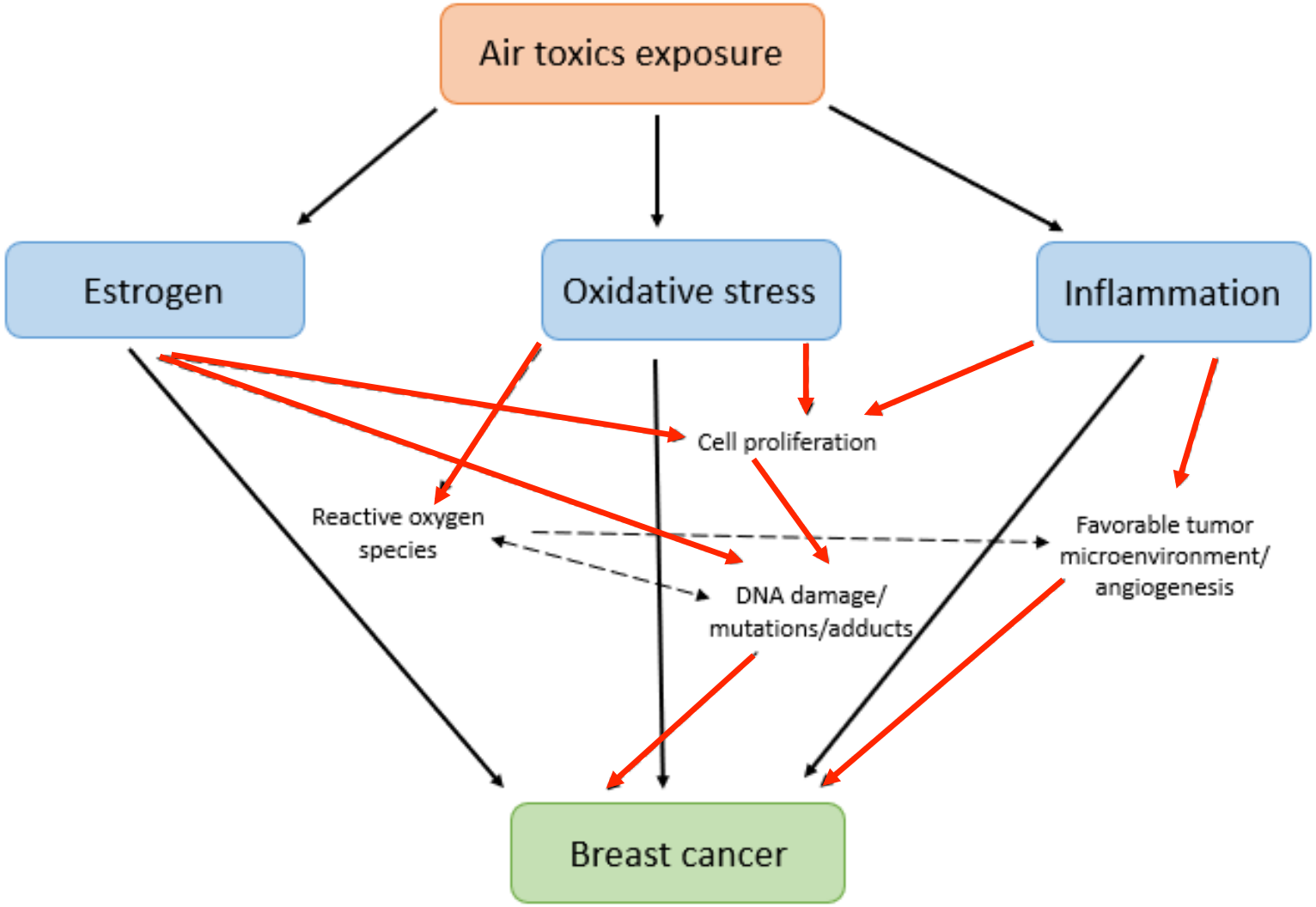
Consideration of Multipollutant Exposures

- Exposure does not occur to single pollutants in isolation
  - ➢Joint effects of multiple pollutants may increase severity
  - ➢Exposures of interest may be correlated
- NIEHS (2011, 2015) and EPA (2016) have called interest to mixtures:

  EPA: *"multi-pollutant control programs can save money and time, and achieve significant health, environmental and economic benefits, while reducing costs and burdens on sources of air pollution"*
- There are a variety of methods available- it's important to specify what question you are interested in evaluating

EPA 2016, Dominici 2010, NIEHS 2011, NIEHS 2015

Biological Mechanisms: Air toxics and breast cancer



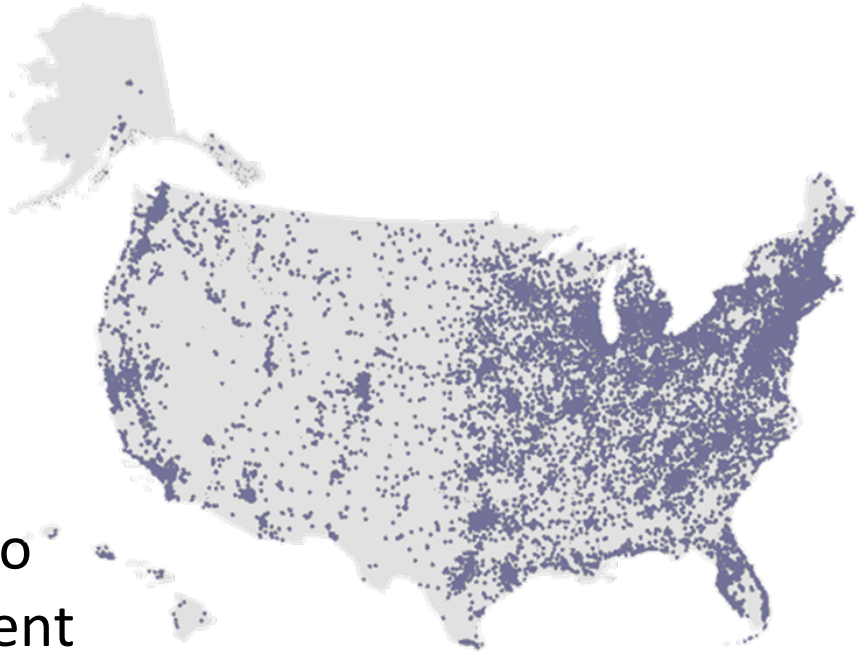
Carcinogenic Air Toxics

- Published review identified 216 chemicals associated with mammary gland tumors in at least one animal study
  - ➢ 29 are air toxics and available in the most complete nationwide data source of modeled concentrations, the National Air Toxics Assessment (NATA)

1,2-Dibromo-3-chloropropane	Carbon tetrachloride	Polycyclic organic matter
1,3-butadiene	Chloroprene	Propylene dichloride
1,4-dioxane	Ethylbenzene	Propylene oxide
2,4-dinitrotoluene	Ethylene dibromide	Styrene
2,4-toluene diisocyanate	Ethylene oxide	Toluene
2-chloroacetophenone	Ethylidene dichloride	Vinyl chloride
Acrylamide	Hydrazine	Vinylidene chloride
Acrylonitrile	Methylene chloride	Xylenes
Benzene	Nitrobenzene	
Benzidine	o-Toluidine	

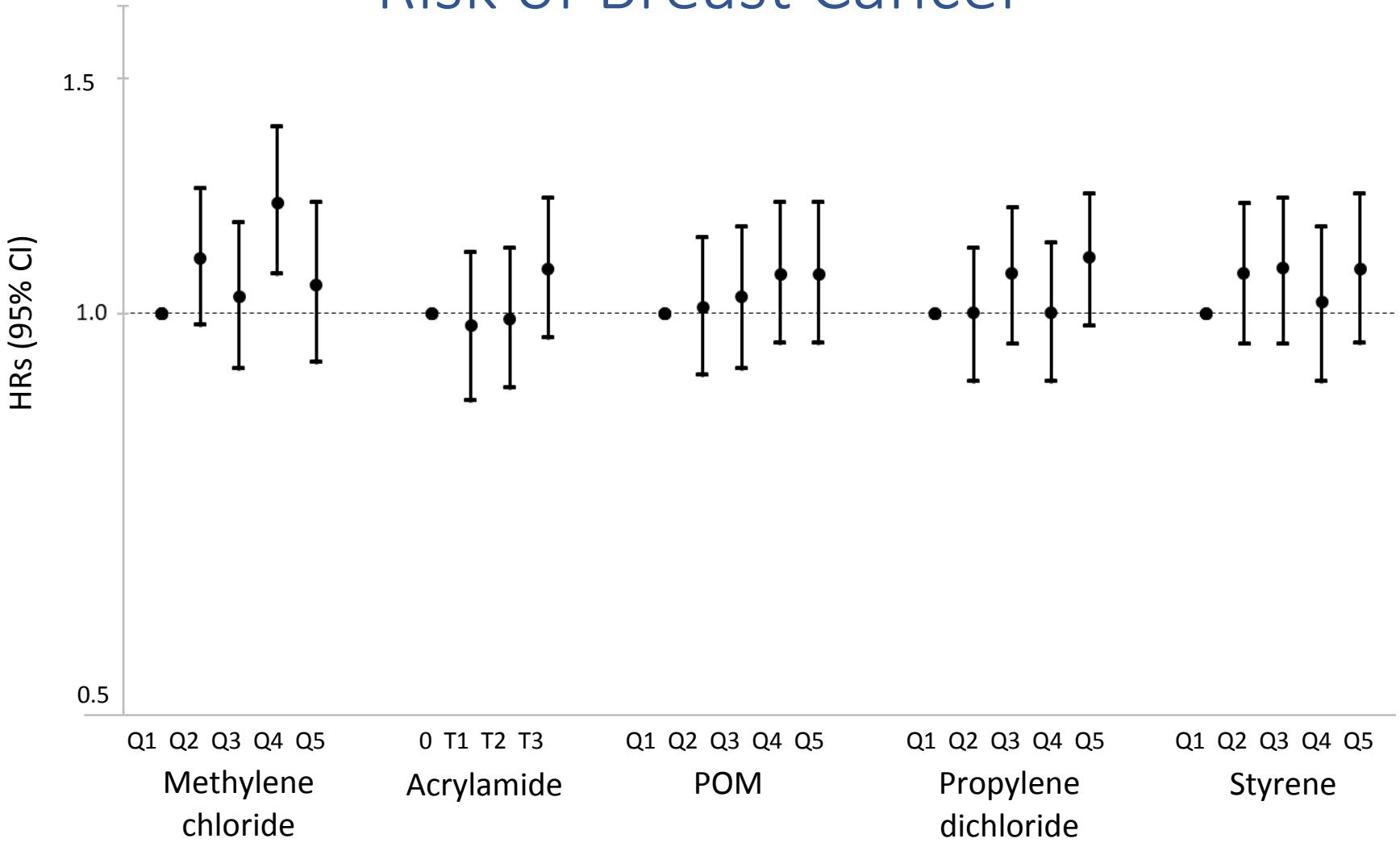
Rudel 2007

The Sister Study



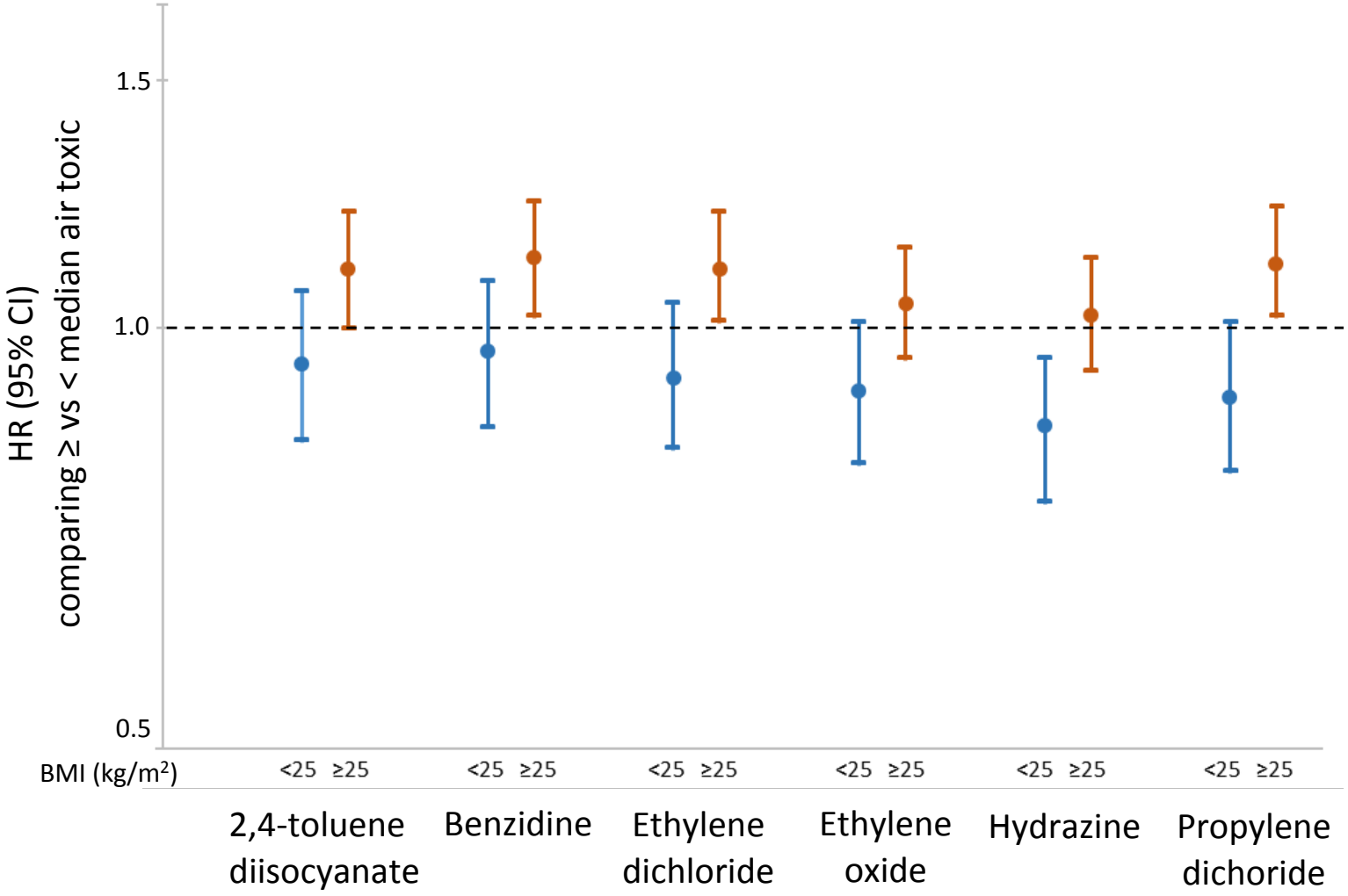
- Prospective observational cohort
  - 50,884 women, recruited from 2003-2009
  - Ages 35-74 at enrollment
  - Sister had been diagnosed with breast cancer, but no prior breast cancer diagnosis themselves at enrollment
- Excluded women without baseline address geocoded at census tract-level for linkage to exposure data and women with breast cancer diagnosis before enrollment was complete → n=49,718 included
- 2,975 breast cancer events (invasive or ductal carcinoma *in situ*) through September 2016 (an average of 8.4 years after enrollment)

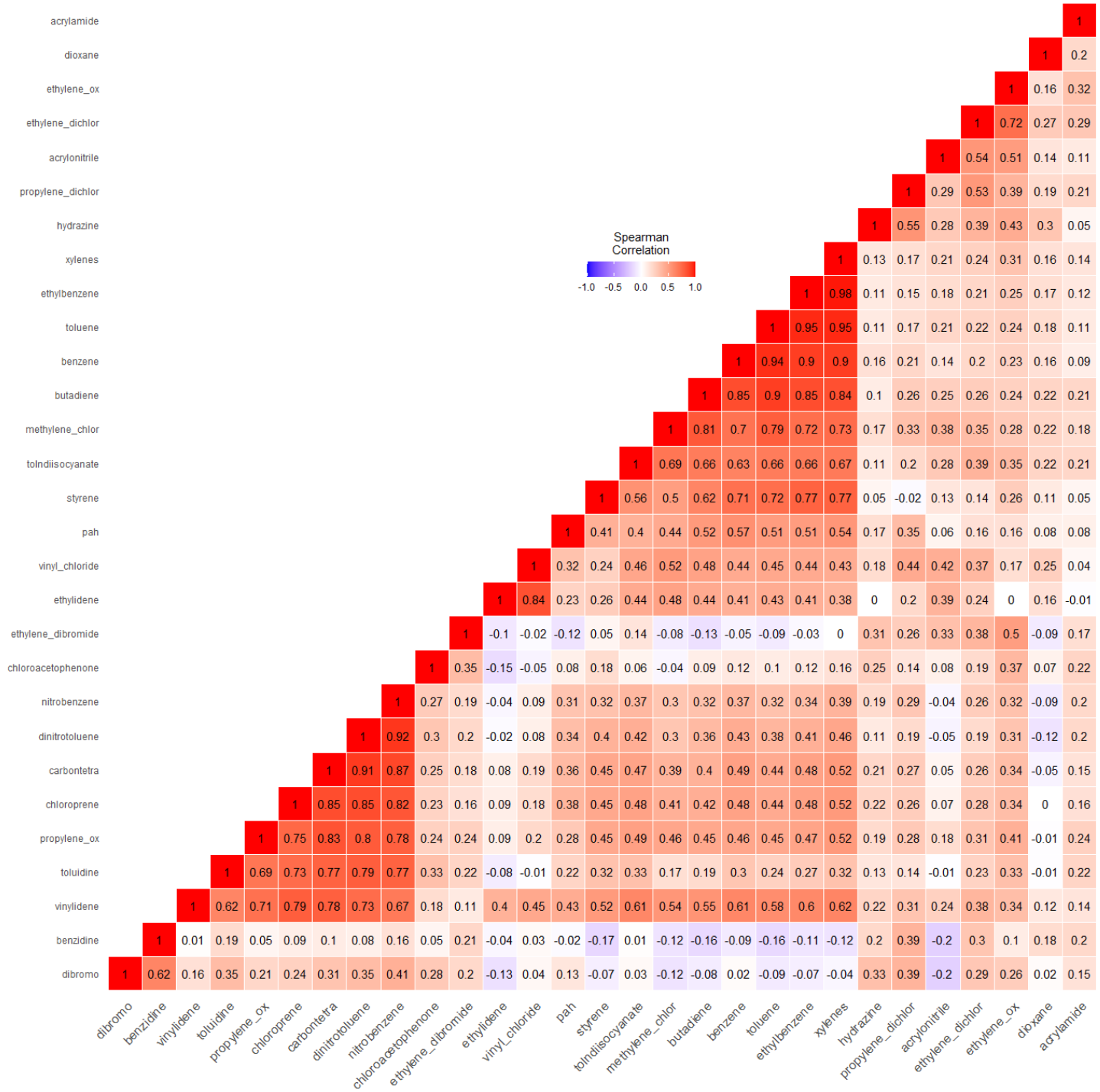
Certain Air Toxics were Associated with an Increased Risk of Breast Cancer



From a Cox proportional hazards model adjusted for age, race, residence type (urban/suburban/small town/rural), education, smoking

The Relationship Between Air Toxics and Breast Cancer was Stronger Among Overweight or Obese Individuals





10% of correlations >0.7

18% of correlations >0.5

Strongest: Ethylbenzene & xylenes (r=0.98)

Weakest: Ethylene dibromide & xylenes (0.001)

Considering Air Toxics in Multipollutant Groups

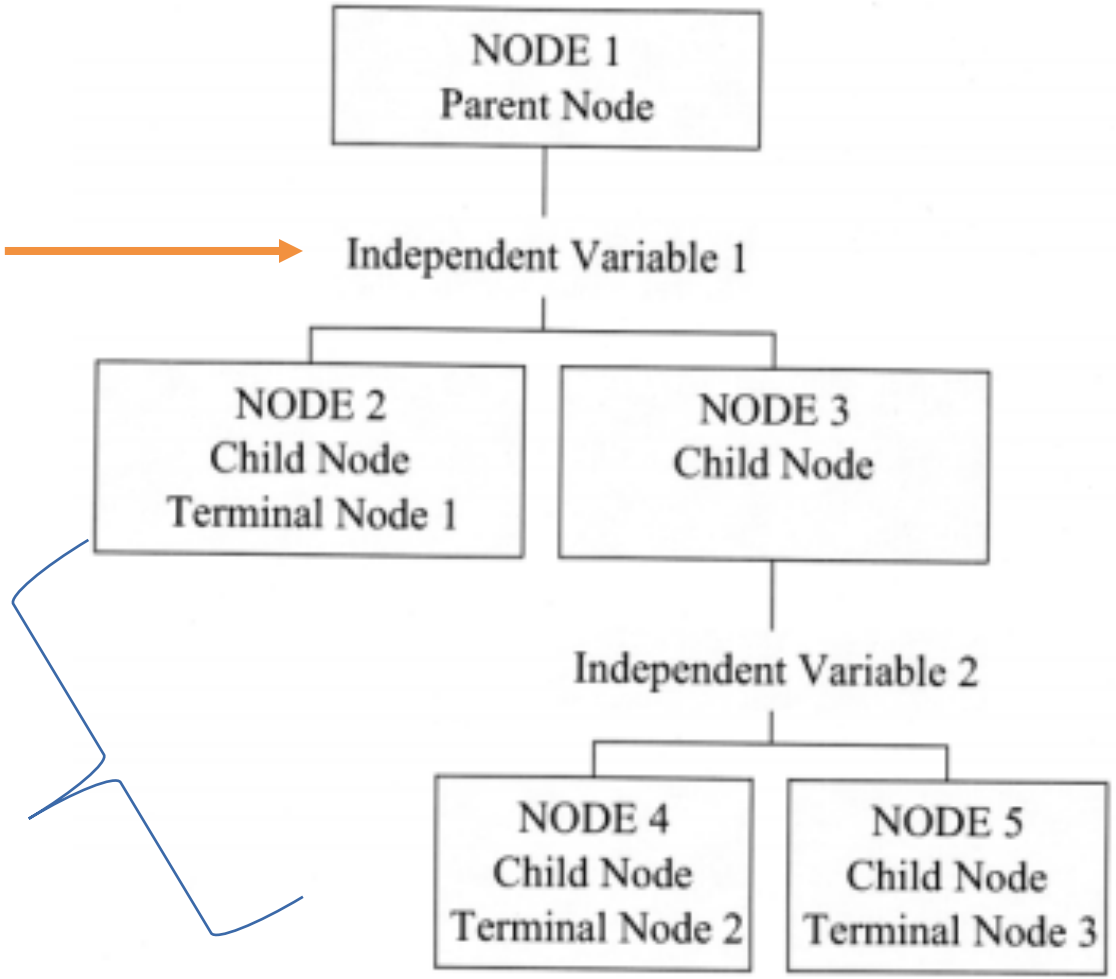
- Goal: Examine whether there are combinations of pollutants that may be more are less harmful for breast cancer than would be expected based on exposure to a single pollutant

- Classification and Regression Trees (CART)
  - Classification trees: used for discrete outcomes (i.e. breast cancer)
  - Regression trees: used for continuous outcomes
  - A forward-selection, recursive partitioning approach

Gini Index:

- Based on impurity functions
- Selects the variable resulting in binary groups that are most different with respect to the outcome

Splitting Criteria

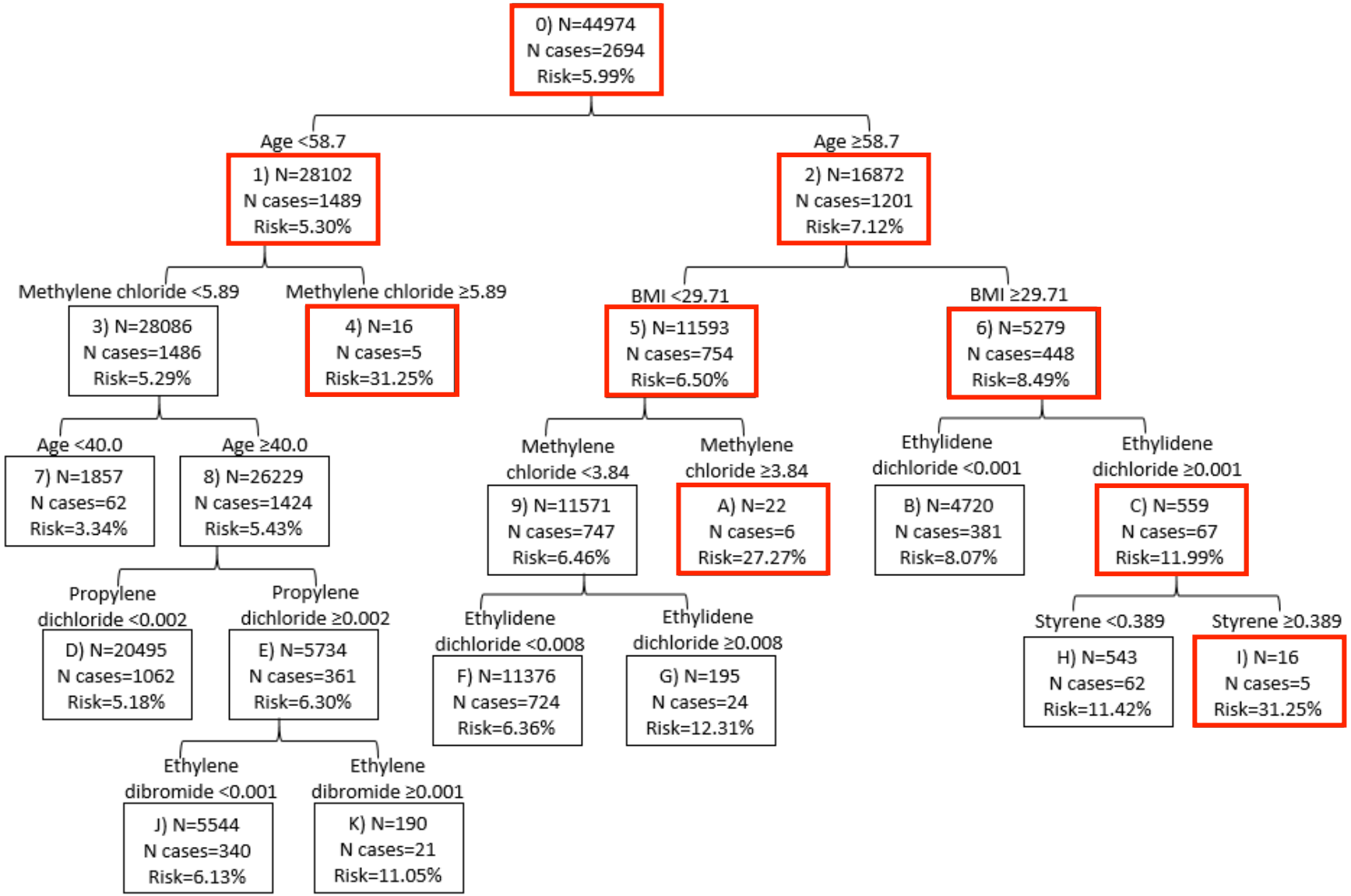


Stopping Criteria

- Minimum # of cases in a node = 5
- Maximum number of levels on a branch = 5
- Total number of terminal nodes = 11

Lemon 2003, Loh 2011, Yohannes 1999

Multipollutant Classification Tree



Conclusions

- Certain air toxics were associated with a higher risk of breast cancer
  - Methylene chloride, POM, propylene dichloride, and styrene
  - Biologically plausible: IARC group 1 or 2A; chromosomal instability, DNA damage, oxidative stress and inflammation, estrogenic
- These air toxics, with the exception of POM, were part of multipollutant groups that were identified in the classification tree
  - Methylene chloride was the highest on the tree
- Single pollutant analyses were stronger among those who were overweight or obese
  - BMI was used in the formation of branches with certain air toxics on the classification tree

IARC, Schlosser 2015, Ohyama 2001, Toyooka 2017, IARC 2017, Zhang 2016, Santodonato 1997

Impact

- Ambient air toxic exposure is widespread
  - Regulation of air toxics on a national scale is currently non-existent
  - Estimation of air toxic concentrations has limitations
- Breast cancer is the most common cancer among women
- CART easily handles non-linear and non-additive associations
  - Informed cut-points that may have been missed with traditional regression
  - Identified high levels that may be important, but may impact a small number of women
  - Investigator-driven parameters
- The findings from the classification tree may reflect harmful co-exposures for breast cancer of interest for future evaluation

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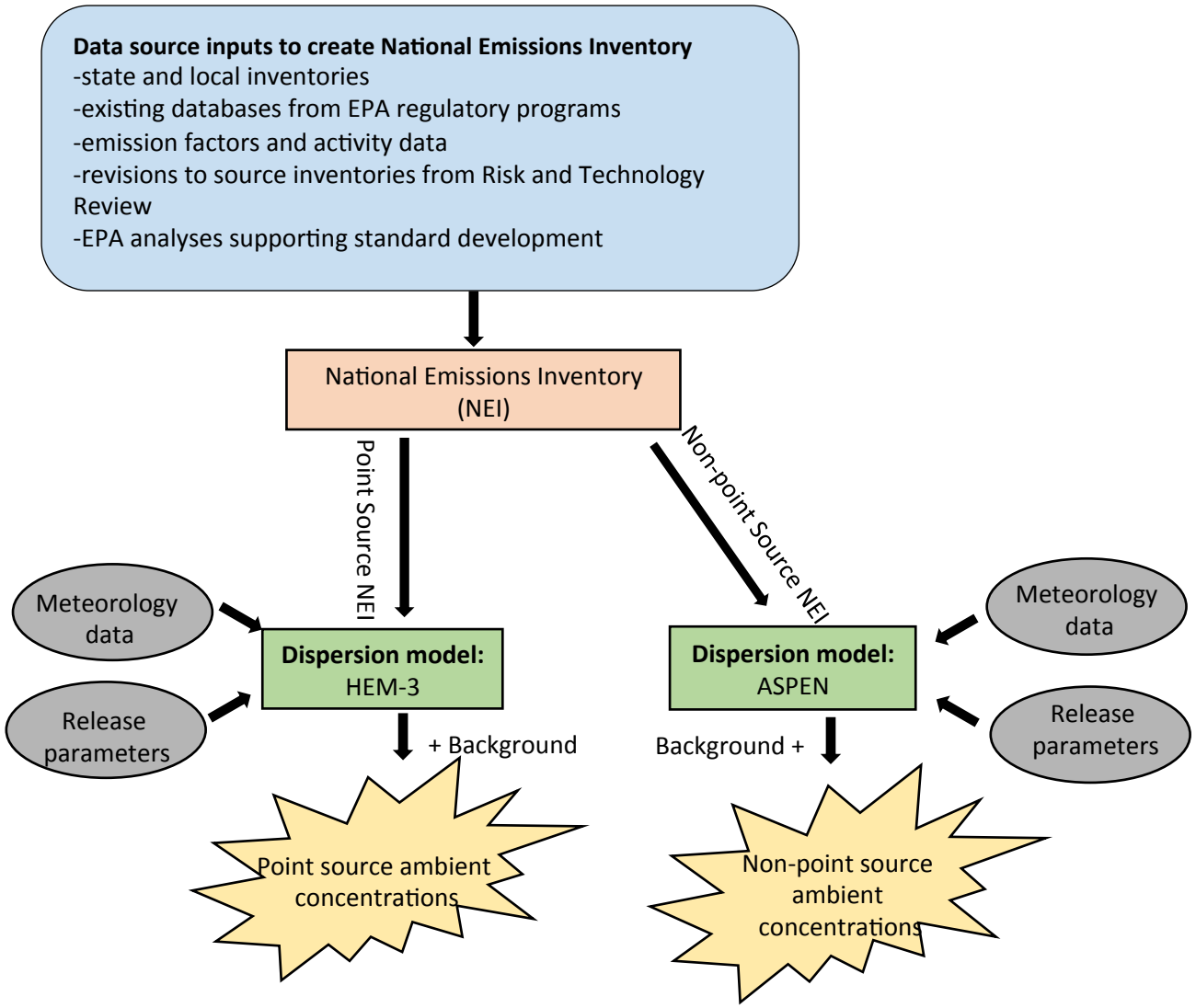
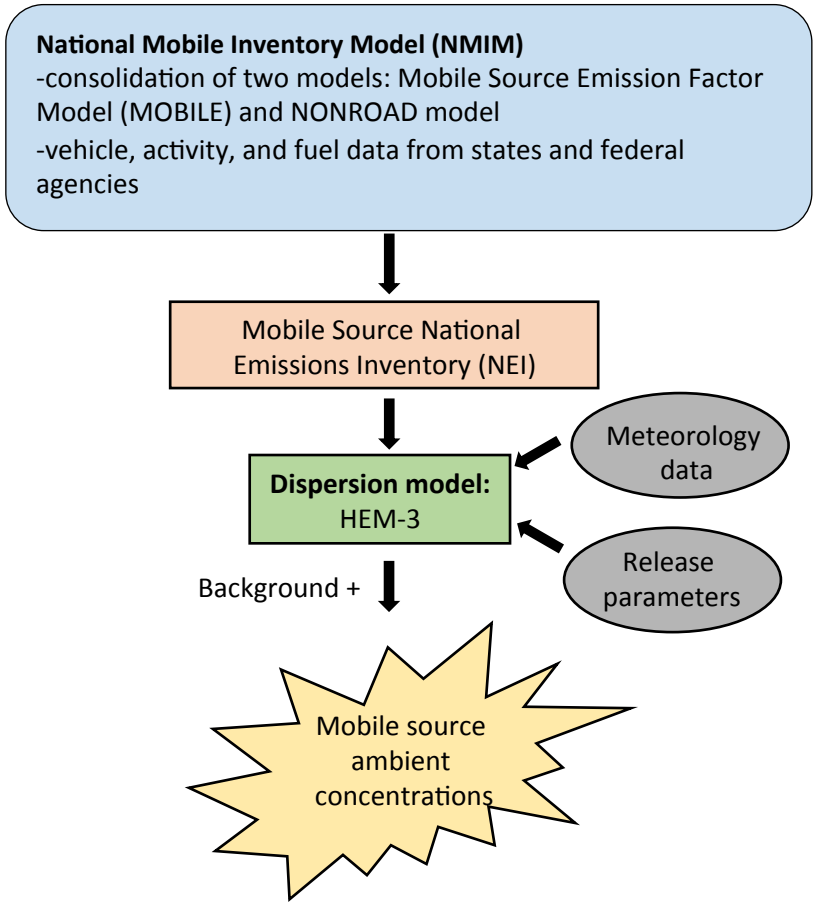
Exposure Assessment: National Air Toxics Assessment

- NATA is the only nationwide data source for air toxics
- 2005 version of the NATA was used in this dissertation
  - In the middle of the enrollment period for the Sister Study
  - Incorporates important assessment changes compared to previous years
- Source categories:
  - Point (e.g. large factories, waste incinerators, airports)
  - Non-point (e.g. prescribed burns, dry cleaners, small manufacturers)
  - On-road mobile (e.g. cars, trucks, buses)
  - Non-road mobile (e.g. airport ground support, trains, boats)
  - Background and secondary formation

EPA NATA TMD 2011

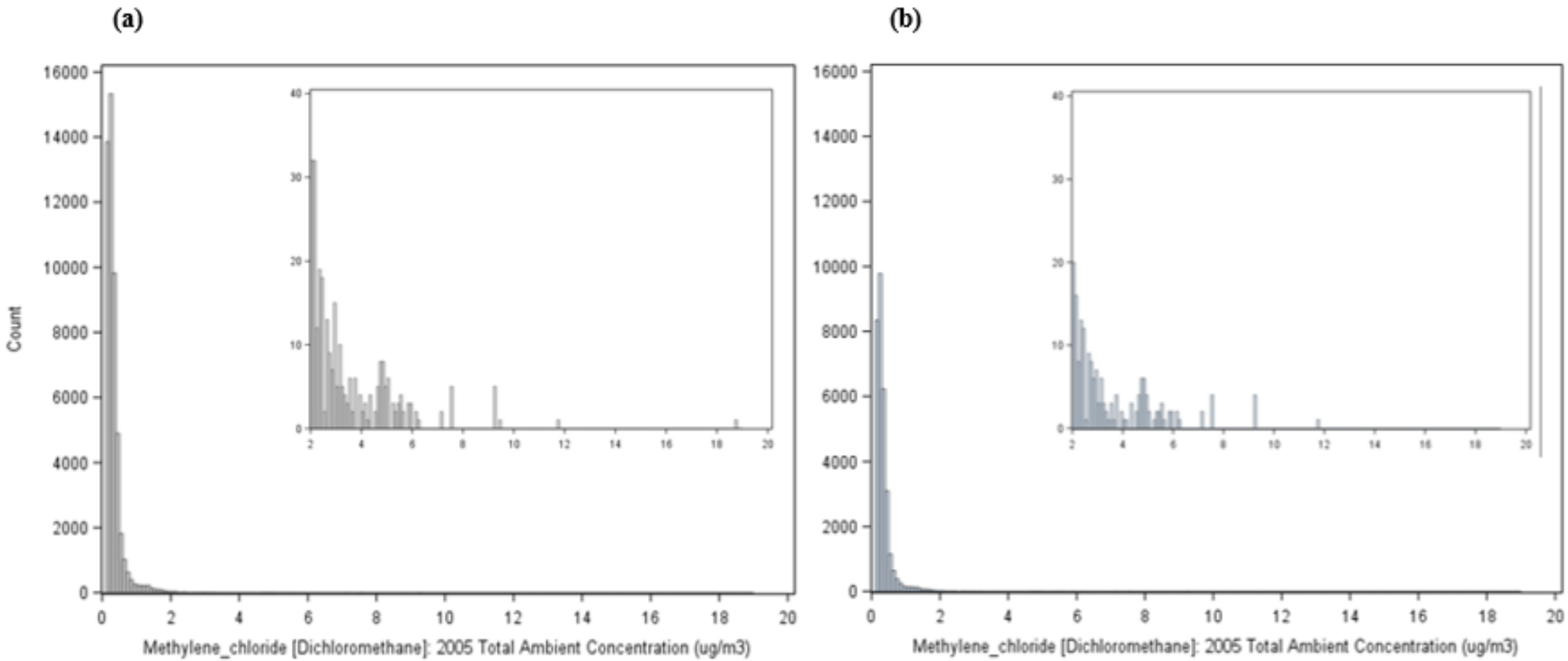

Data source inputs to create National Emissions Inventory
-state and local inventories
-existing databases from EPA regulatory programs
-emission factors and activity data
-revisions to source inventories from Risk and Technology Review
-EPA analyses supporting standard development
National Emissions Inventory (NEI)
Point Source NEI
Non-point Source NEI
Meteorology data
Release parameters
Dispersion model: HEM-3
+ Background
Point source ambient concentrations
Meteorology data
Release parameters
Dispersion model: ASPEN
Background +
Non-point source ambient concentrations


National Mobile Inventory Model (NMIM)
-consolidation of two models: Mobile Source Emission Factor Model (MOBILE) and NONROAD model
-vehicle, activity, and fuel data from states and federal agencies
Mobile Source National Emissions Inventory (NEI)
Meteorology data
Dispersion model: HEM-3
Release parameters
Background +
Mobile source ambient concentrations

CART Splitting Criteria

- Gini improvement measure
  1. Gini diversity index is calculated as $2p_{ijl}(1-p_{ilj})$ for the parent node and two child nodes
  2. Weighted diversity index of the two child nodes based on the proportion of the observations that end up in each node from the parent node
  3. Gini improvement measure= (parent node diversity index) – (weighted diversity index)
  - ➢ All exposure variables are examined and the one (and its cut-point) that leads to the highest value of the Gini improvement measure is selected as the splitting point

Lemon 2003, Loh 2011, Yohannes 1999


(a)
(b)
Count
Methylene_chloride [Dichloromethane]: 2005 Total Ambient Concentration (ug/m3)
Methylene_chloride [Dichloromethane]: 2005 Total Ambient Concentration (ug/m3)