



EPA IRIS Bimonthly Public Science Meeting

PCBs: Effects Other Than Cancer

June 17-18, 2015 Arlington, VA

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Professor and Head,

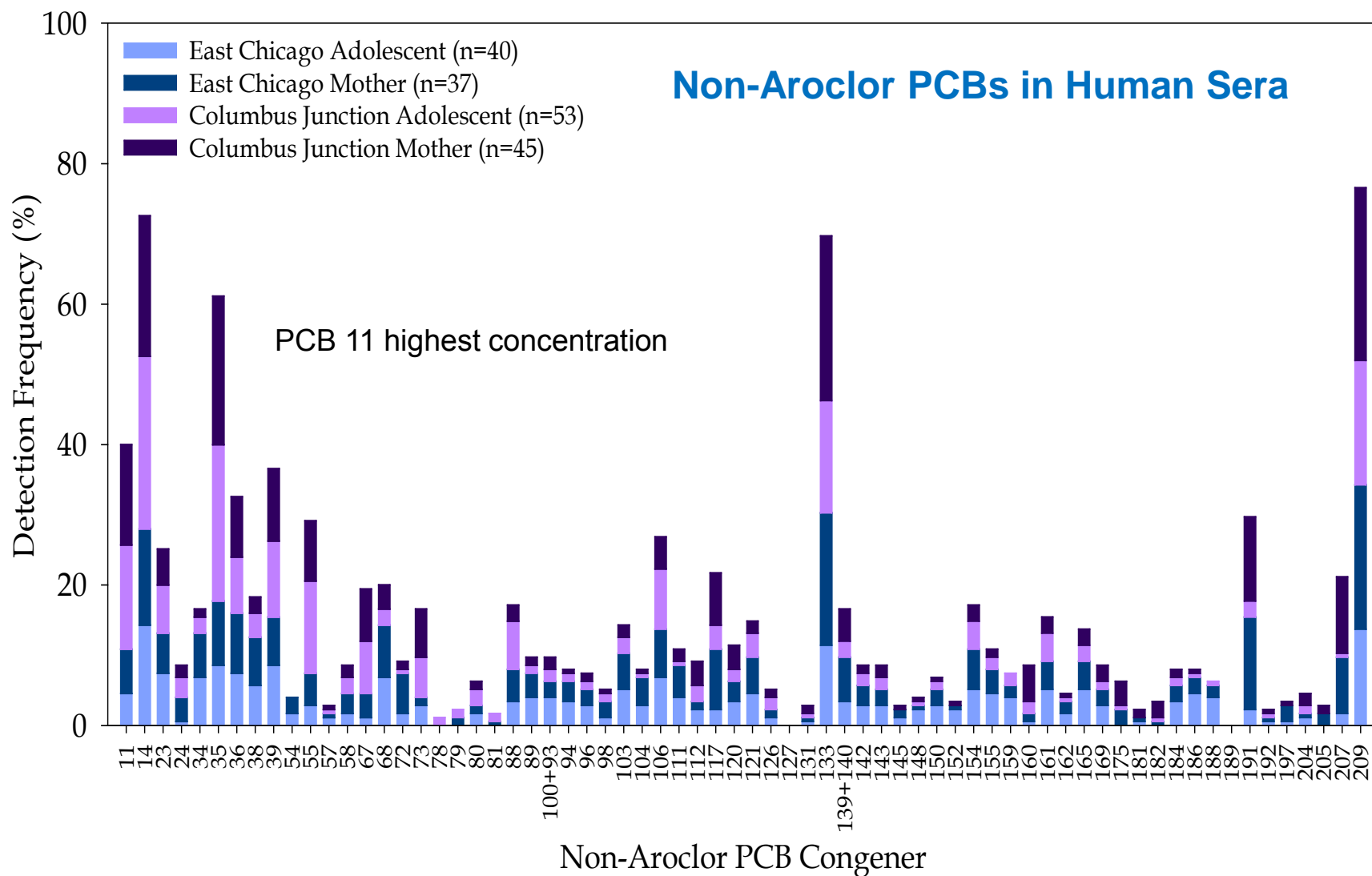
Department of Occupational and Environmental Health

Director, Environmental Health Sciences Research Center



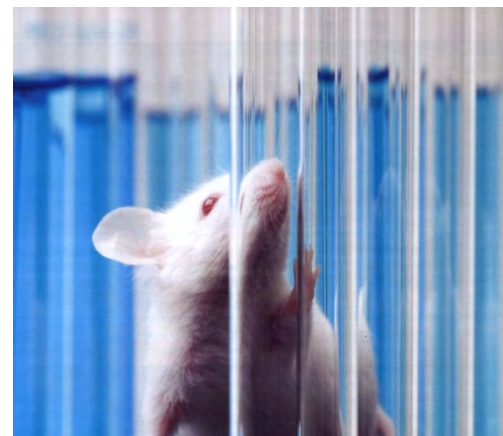
Science Topic 1

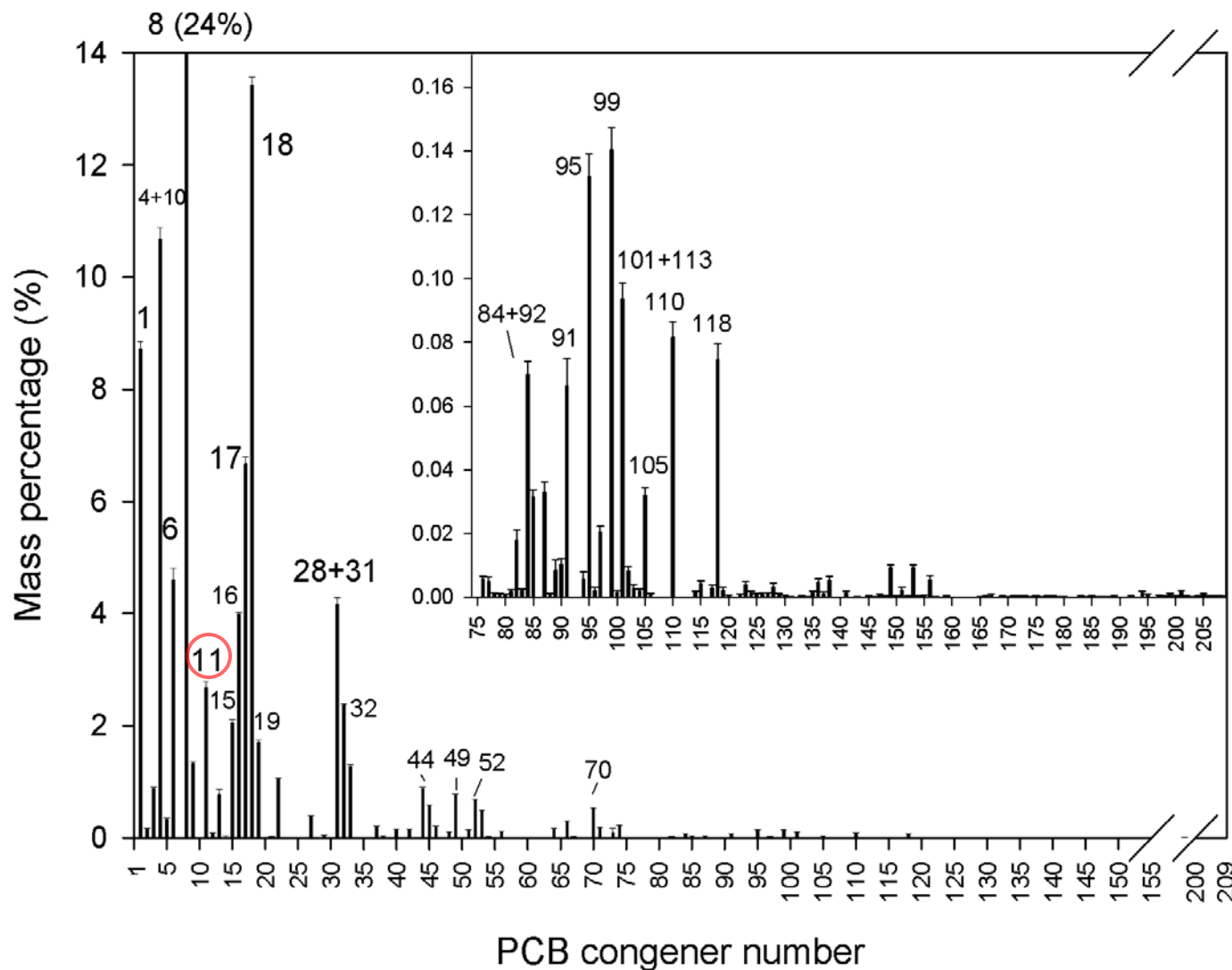
Impact of Congener Profile on the Toxicity
of PCB Mixtures



- Frequency of detection of 70 non-Aroclor congeners in AESOP Study participants
- PCB 11,14, 35, 209 were the most dominating congeners

- We have conducted 6 inhalation studies in rodents
 - Aroclor 1242
 - Chicago Air Mixture (CAM)
 - PCB 11
 - PCB 3
 - ^{14}C -PCB 11
 - CAM+ (CAM supplemented with PCB 11)
- Studies include acute, subacute, subchronic
- Nose-only and whole body exposures

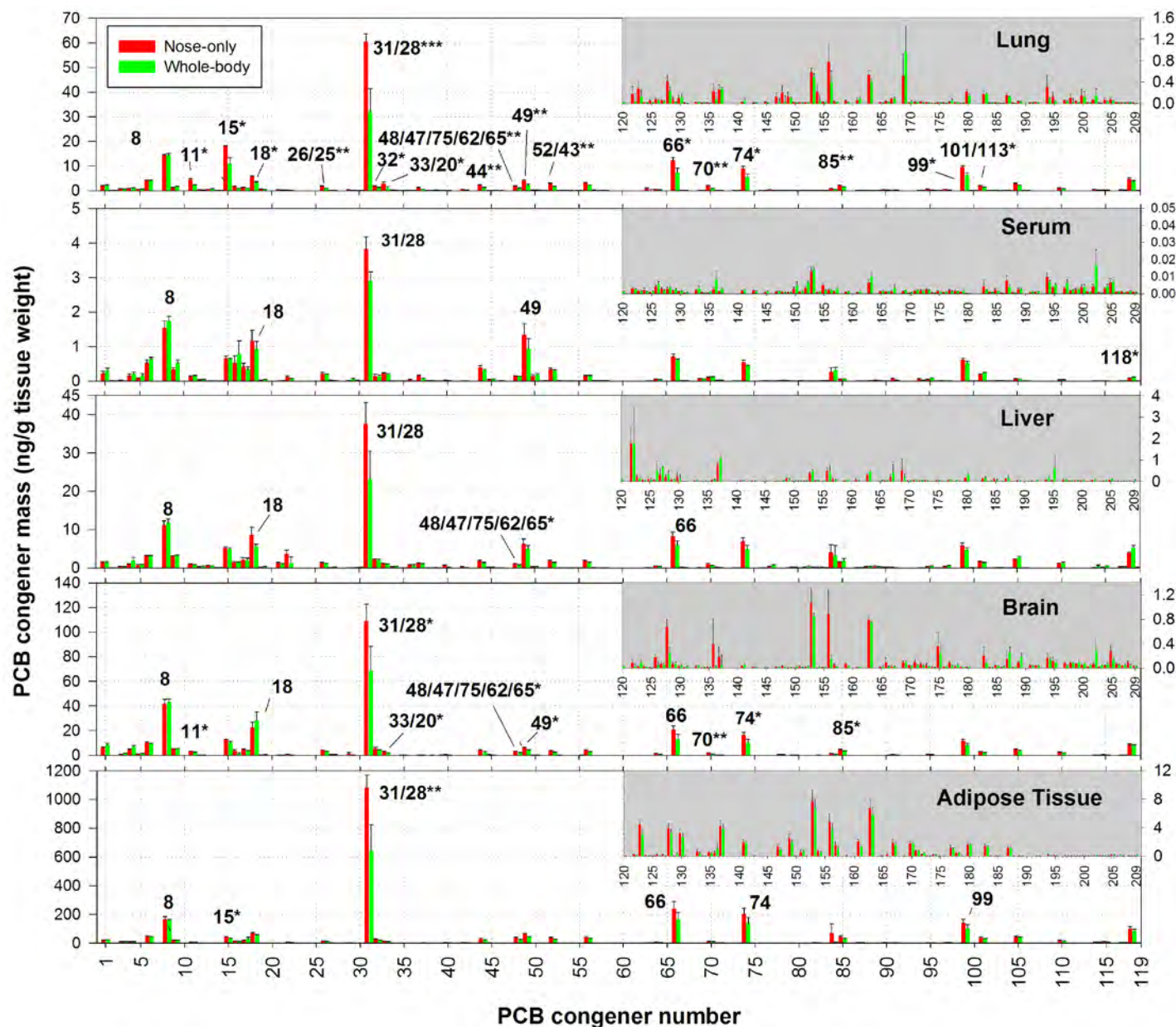




CAM+

PCB vapor generated from a PCB cocktail solution or PCB-coated glass beads held at 25°C. Exposures quantified from XAD collection of chamber outflow.

- Average congener mass % in generated CAM+ vapor for inhalation studies. CAM+ is the vapor from A1242 + A1254 + PCB 11 (64.0%; 34.5%; 1.5% w/w)



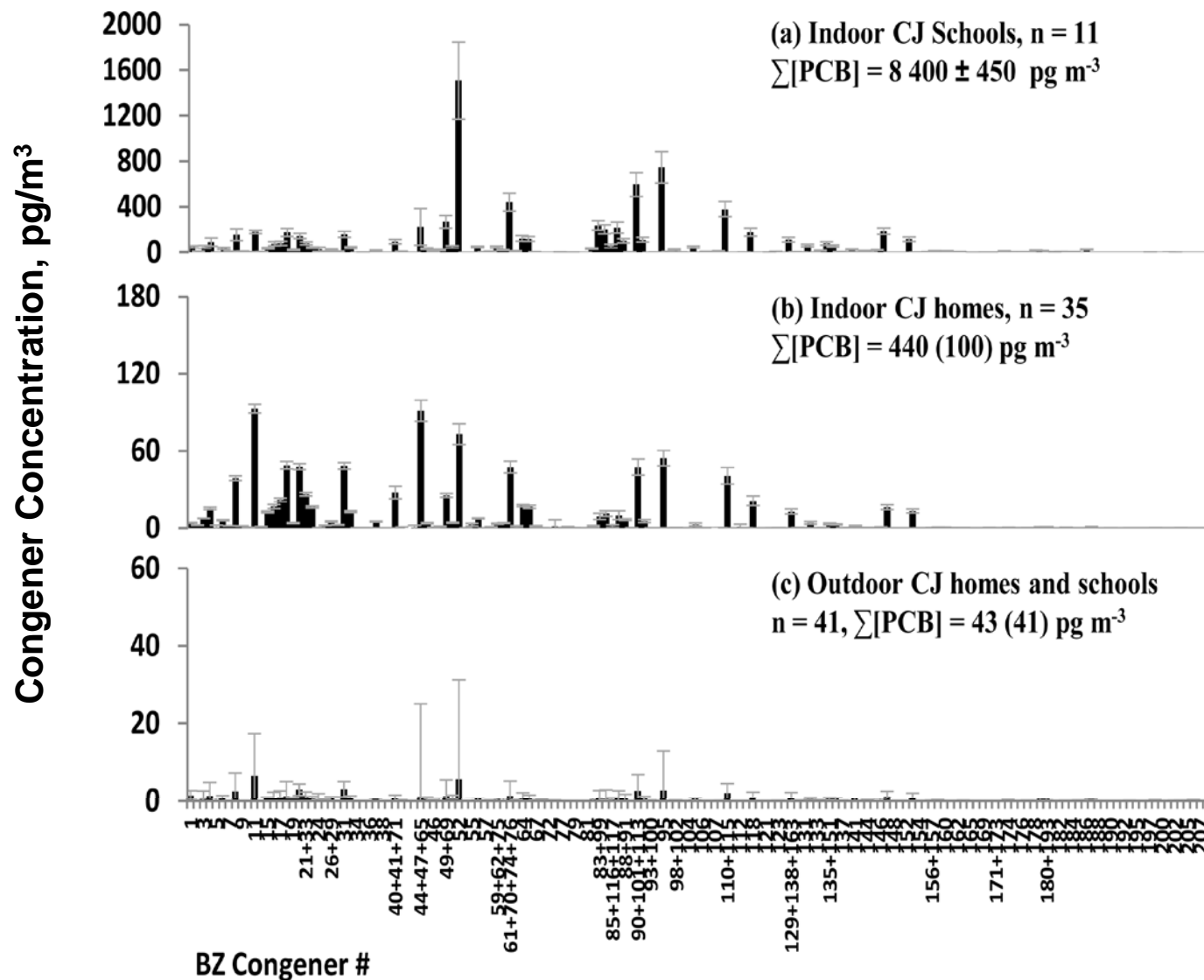
PCB mass by congener after 4-wk inhalation exposure to CAM+ in nose-only and whole body exposure systems.

Inset plot shows PCBs 120-209.

Method quantifies 209 congeners in 162 discrete peaks.

Science Topic 2

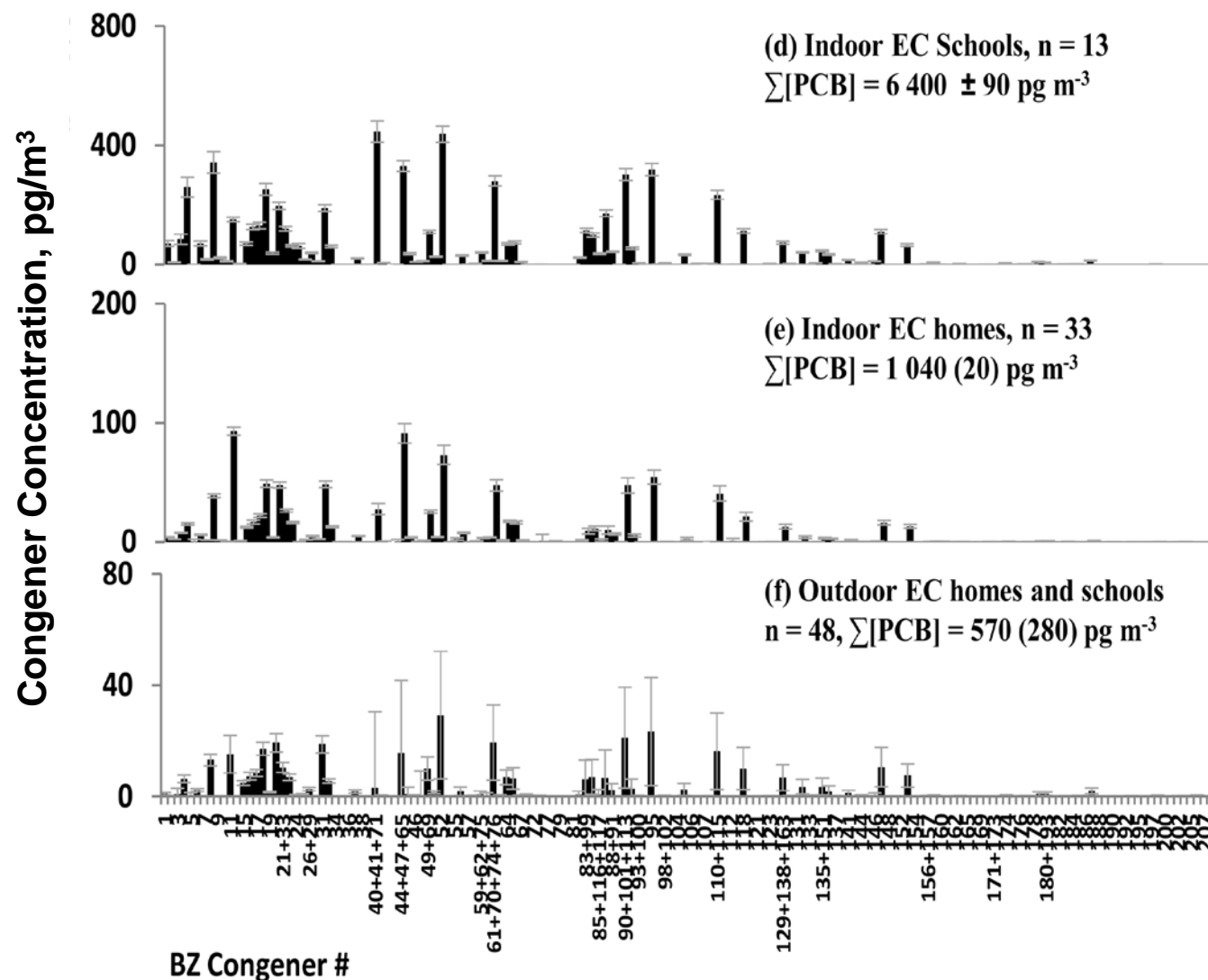
Evaluation of Epidemiological Studies for
PCB Dose-Response Assessment



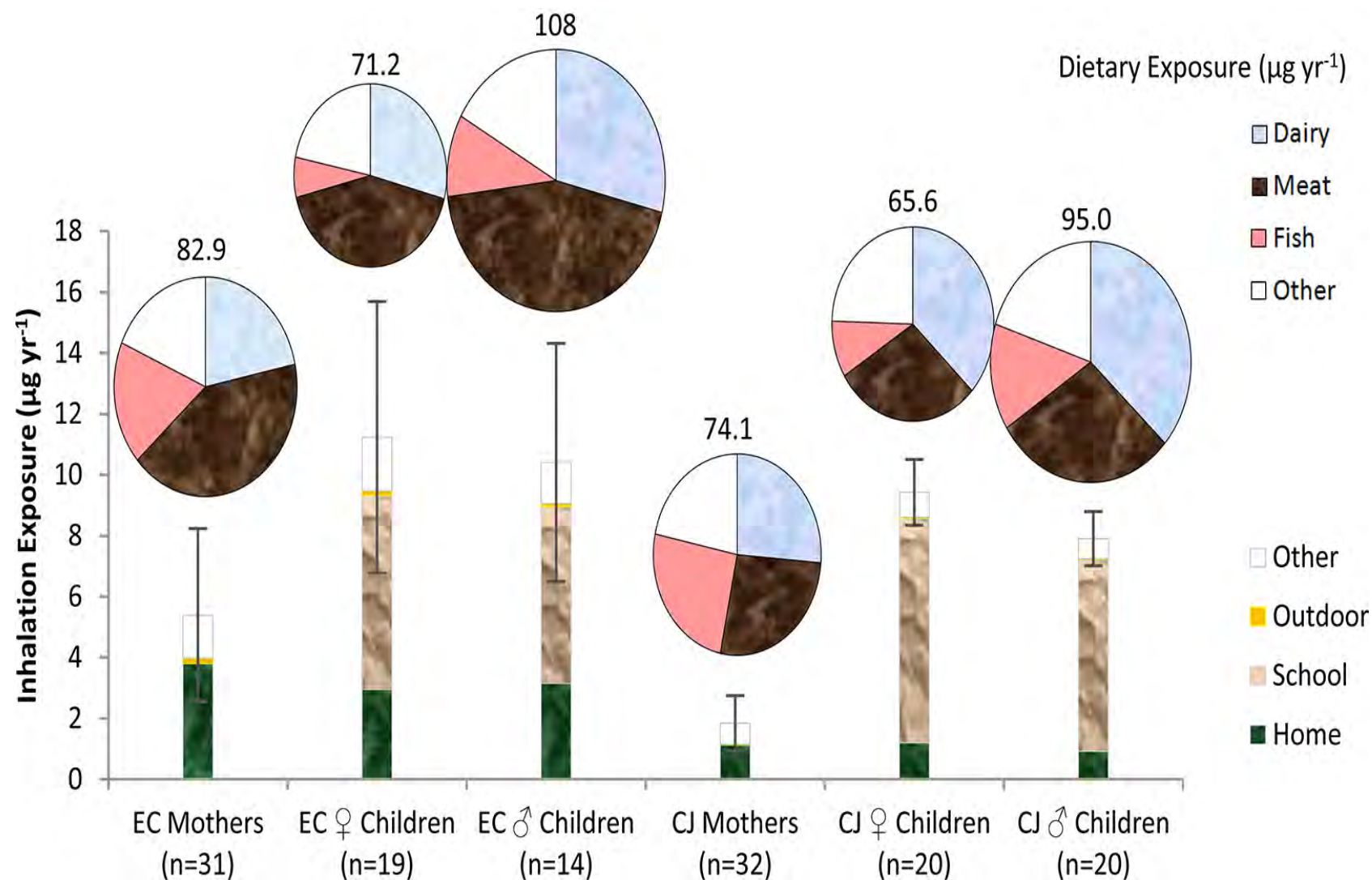
Airborne PCBs in homes and schools of the AESOP rural community. Schools are far higher than homes. Non-Aroclor congeners are apparent in homes.

Science Topic 2:

Evaluation of Epidemiological Studies for PCB Dose-Response Assessment



Airborne PCBs in homes and schools of the AESOP urban community. Schools are higher than homes. Non-Aroclor congeners are apparent in homes.



Inhalation (bars) and dietary (pies) exposure by location and food group for participants in the AESOP Study.

Profiles of children are different than their mothers due to inhalation at school

Most frequently detected congeners (**red**=100% detection)

East Chicago		Columbus Junction	
Children	Mothers	Children	Mothers
153+168	153+168	153+168	153+168
138+163+129	138+163+129	138+163+129	193+180
193+180	193+180	193+180	203
11	203	15	170
15	187	3	146
8	202	2	137
3	137	11	138+163+129
2	167	14	198+199
28+20	118	146	156+157

Children
are
Enriched
with Lower
chlorinated
PCBs

Other Points

- Repeated annual serum sampling and analysis of 209 congeners and 64 OH-PCBs
- Large variability in serum levels year to year
- -87% to +557% (5th-95th percentile)

Science Topic 3

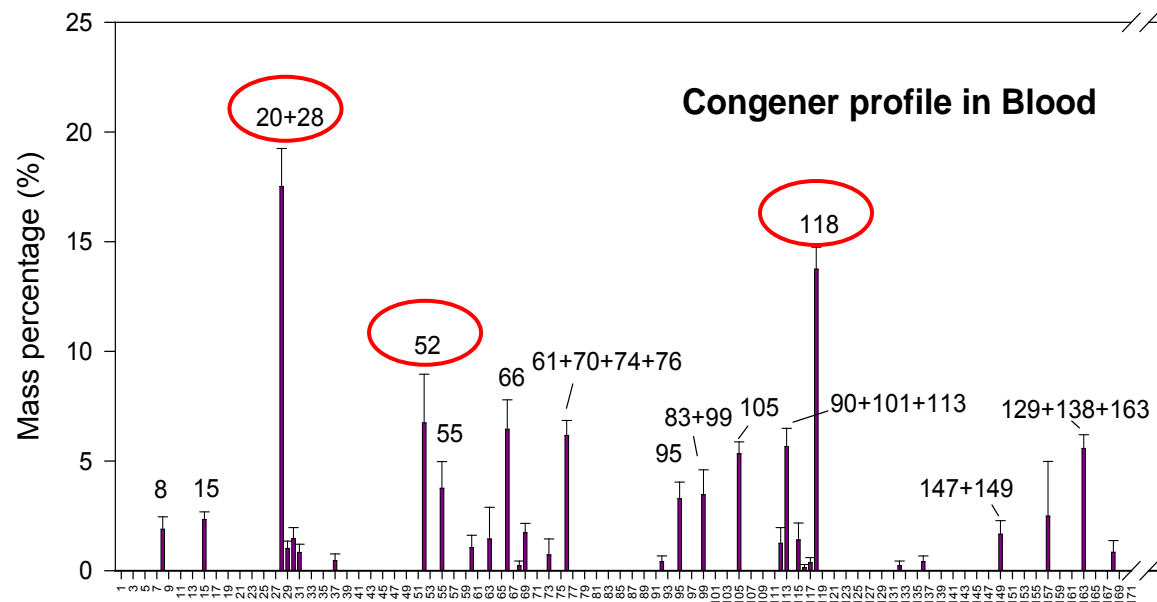
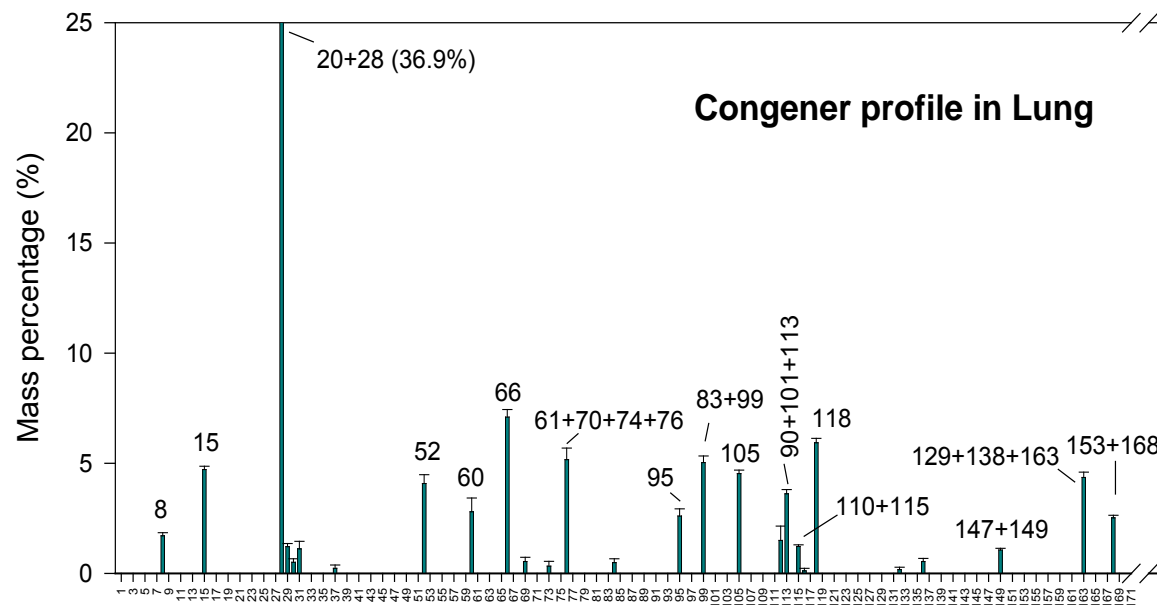
Potential for Hazard Identification and
Dose-Response Assessment for PCB
Exposure via Inhalation

Our rodent studies show rapid distribution and metabolism of inhaled PCB congeners

- **Aroclor 1242 Acute and Subacute Inhalation study in rats**
- $t_{1/2}$ = liver: 5.6 h; lung: 8.2 h; brain: 8.5 h; blood: 9.7 h
- Lung, liver, adipose tissue levels higher than brain or blood
- 10 d exposure → 6.6 µg/g lipid weight in lung & liver
- Minimal toxicity at 1400 µg (5.6 mg/kg)
- **CAM Subchronic Inhalation Study**
- Inhalation exposure → body burden of mostly tri- to hexa-CBs
- Similar congener spectrum in lung, serum, liver, brain, adipose
- Accumulation of neurotoxic PCBs in brain: PCB28, 105 and 118
- GSSG/GSH increased in the blood, minimal toxicity observed

CAM Subchronic Inhalation Study

- A distinct **profile of ~25 accumulated congeners** in tissue



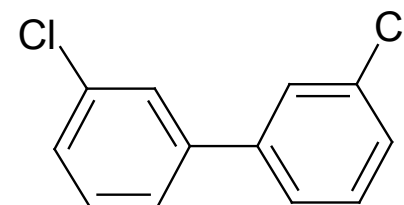
Science Topic 4

Suitability of Available Toxicokinetic Models
for Reliable Route-to-Route, Interspecies,
and/or Intraspecies Extrapolation

Science Topic 4:

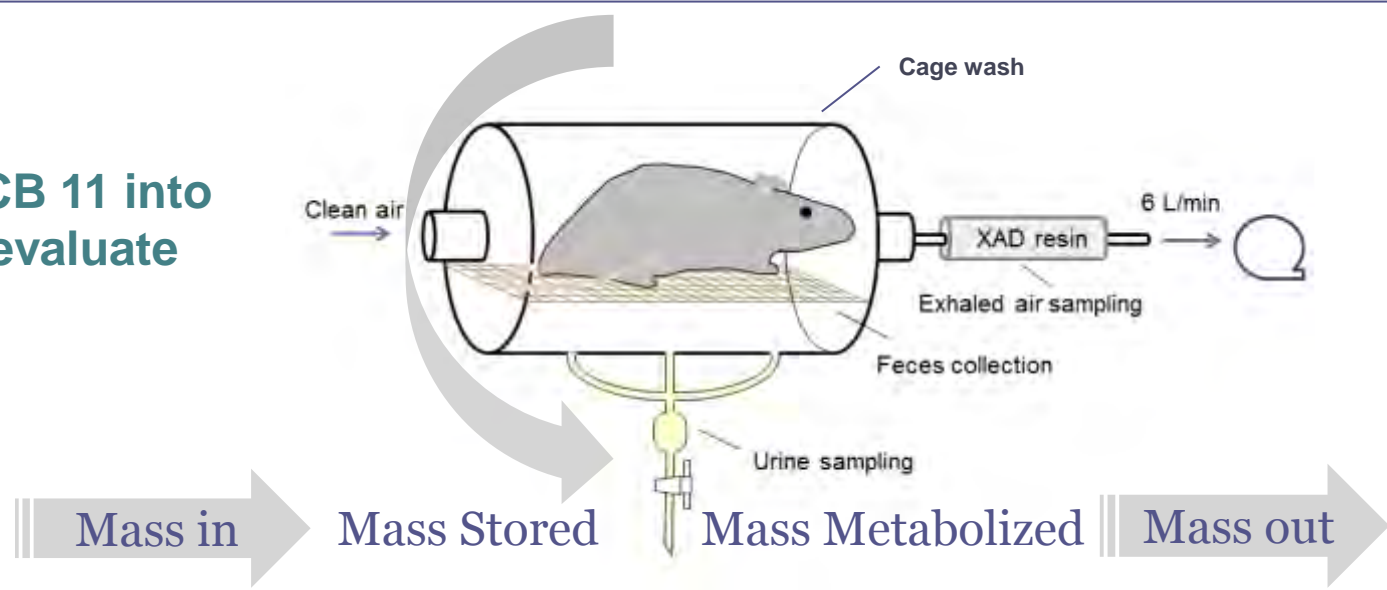
[^{14}C]-PCB11 Study

3,3'-Dichlorobiphenyl

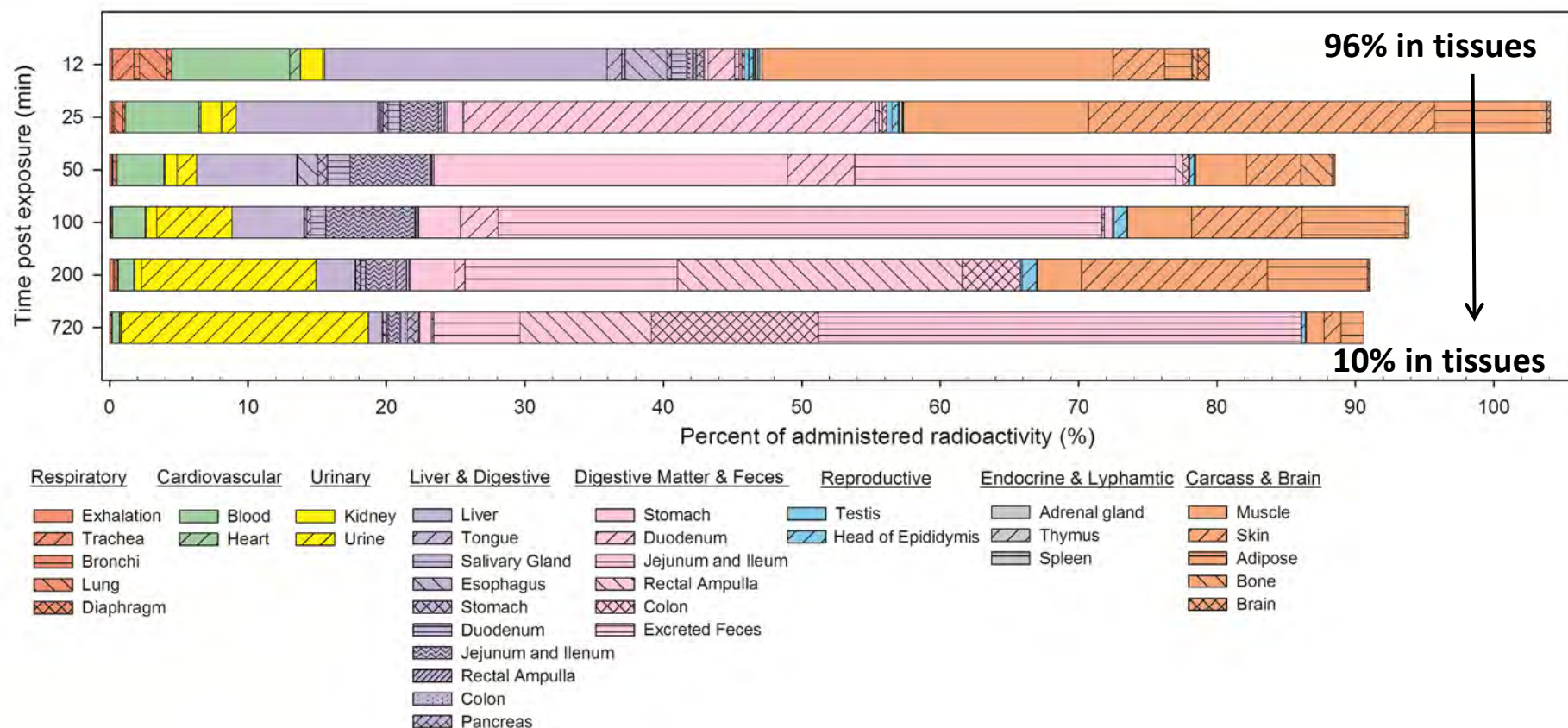


- Even though we find PCB 11 in the indoor air of every home and school, virtually nothing is known about its fate and toxicity
- Objective: To determine the fate of PCB 11 in rats

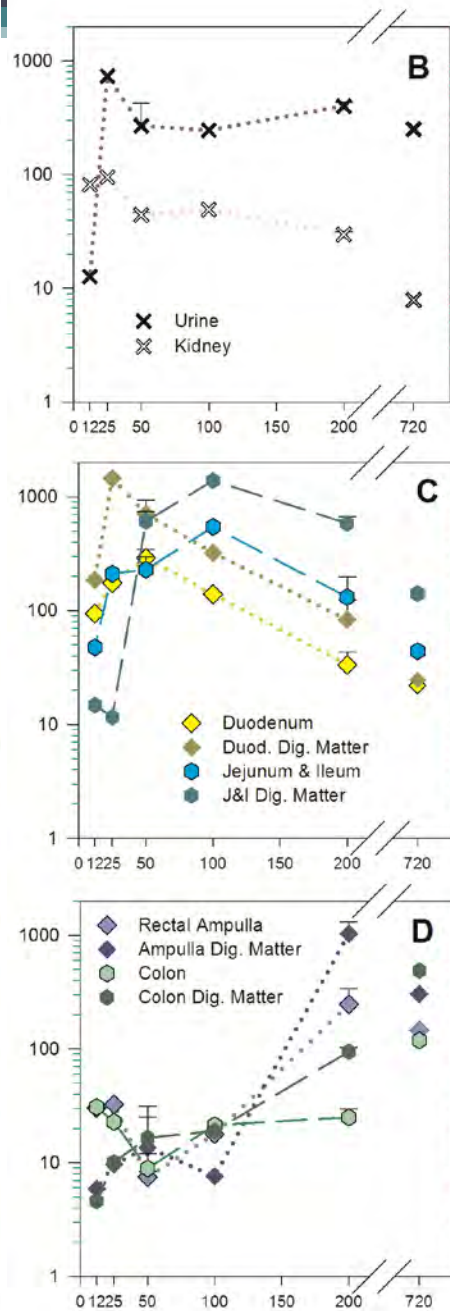
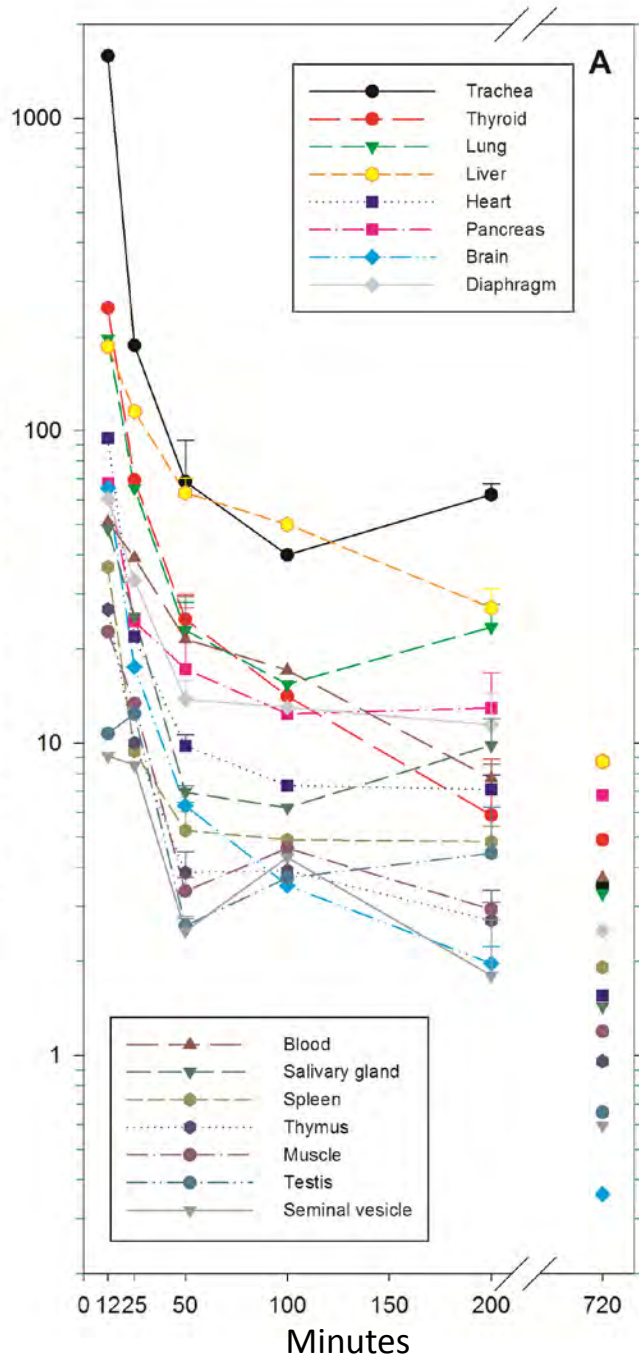
Instill [^{14}C]-PCB 11 into the lung and evaluate the ADME



The majority of dose is excreted in hours



- Fecal elimination is the major pathway of excretion.
- Exhaled PCB 11 accounts for <0.2% of administered dose.
- Absorption of PCB in lung is complete.

[¹⁴C] concentration (dpm/mg wet weight)

Rapid elimination from most tissues

Phase	$t_{1/2-1}$	$t_{1/2-2}$
Trachea	9 min	2.6 hr
Thyroid	14 min	5.3 hr
Lung	13 min	3.7 hr
Liver	24 min	3.7 hr
Heart	12 min	3.9 hr
Pancreas	21 min	7.7 hr
Brain	12 min	2.7 hr
Diaphragm	18 min	3.9 hr
Blood	33 min	4.1 hr
Salivary gland	14min	4.3 hr
Spleen	15 min	6.3 hr
Thymus	14 min	4.7 hr
Muscle	14 min	6.4 hr
Testis	17 min	3.9 hr
Seminal vesicles	19 min	4.1 hr

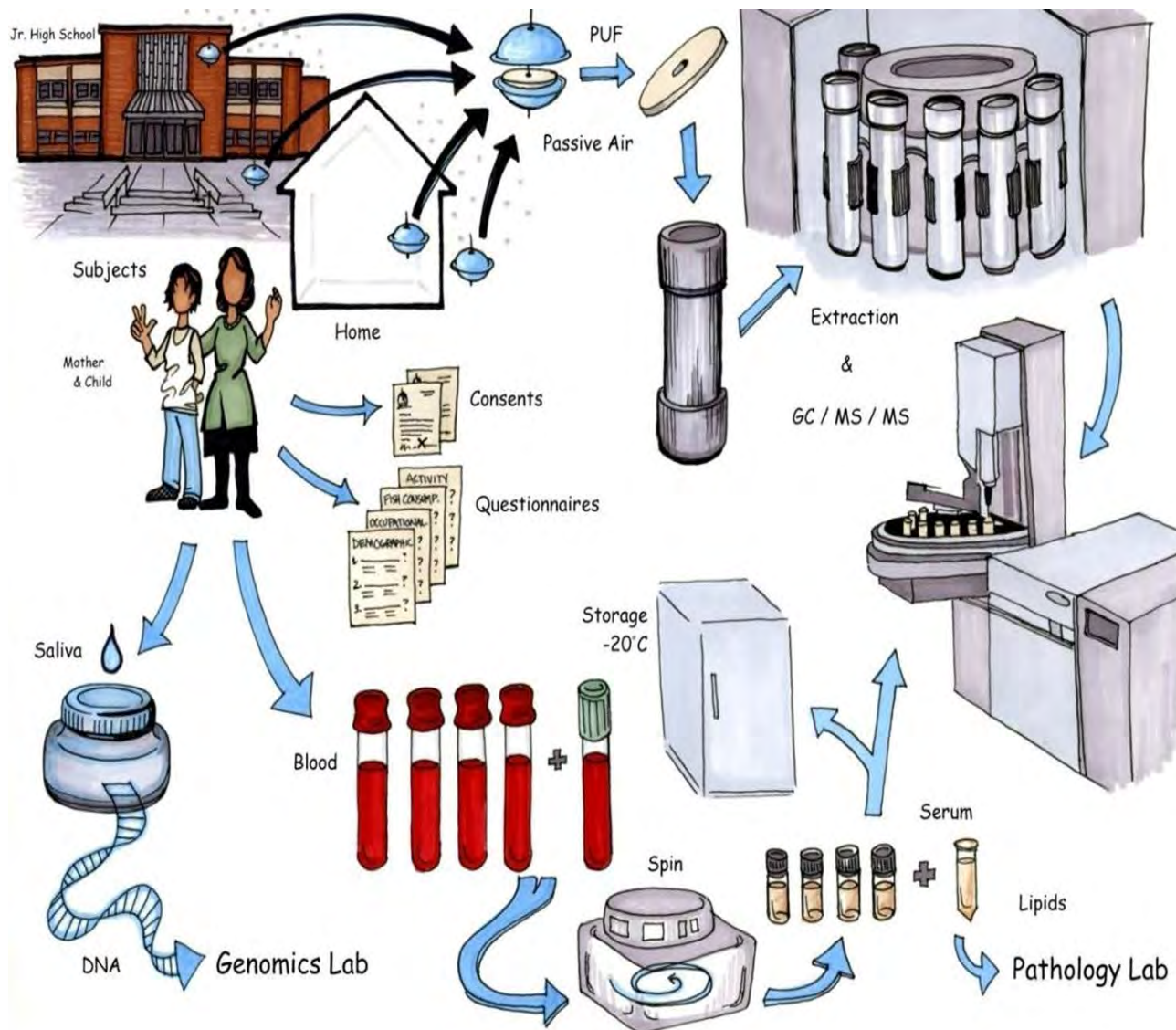
PCB11 and ^{14}C -PCB11 animal studies

- Complete and fast uptake of inhaled PCB
 - PCB11 is 99.8% absorbed after lung exposure.
- Rapid distribution of PCB11
 - High tissue concentration of PCB11 at 12 min after exposure
 - Delayed uptake in adipose tissue and other fatty tissues (skin, epididymis)
- Extremely fast elimination of PCB11 and metabolites
 - 50% of dose excreted by 12 h
 - 37% of dose in intestinal digestive matter that was about to be excreted
 - The initial elimination phase is very short ($t_{1/2} = 10\text{-}30$ min)
 - **Biomarkers may demonstrate same-day exposures**
- Phase II metabolites dominate in systemic circulation
 - PCB11 and OH-PCB11s decay most rapidly to minimal levels within 25 min
 - **Phase II metabolites serve as better biomarkers of PCB11 exposure**



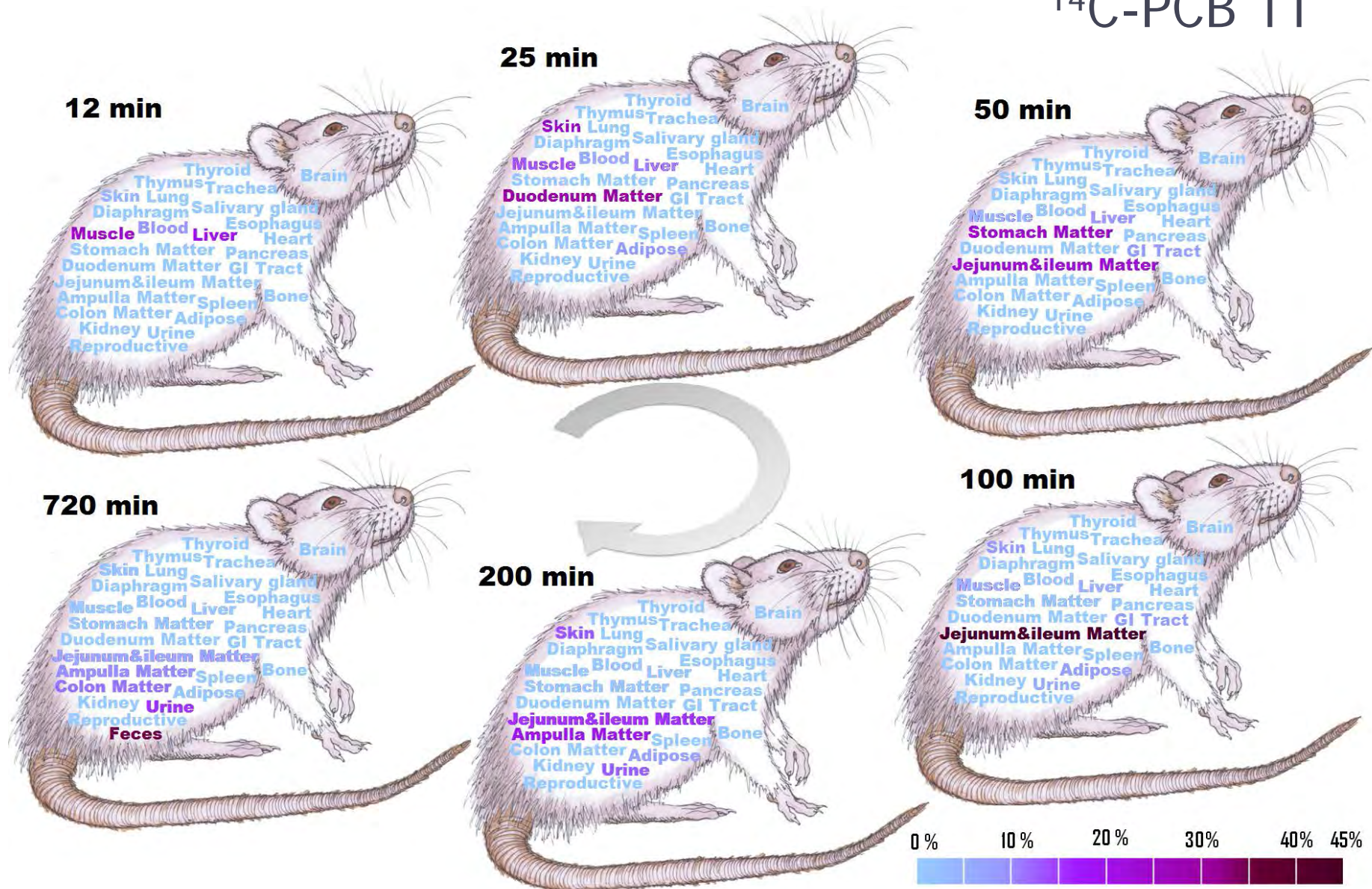
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Science Topic 2: Evaluation of Epidemiological Studies for PCB Dose-Response Assessment

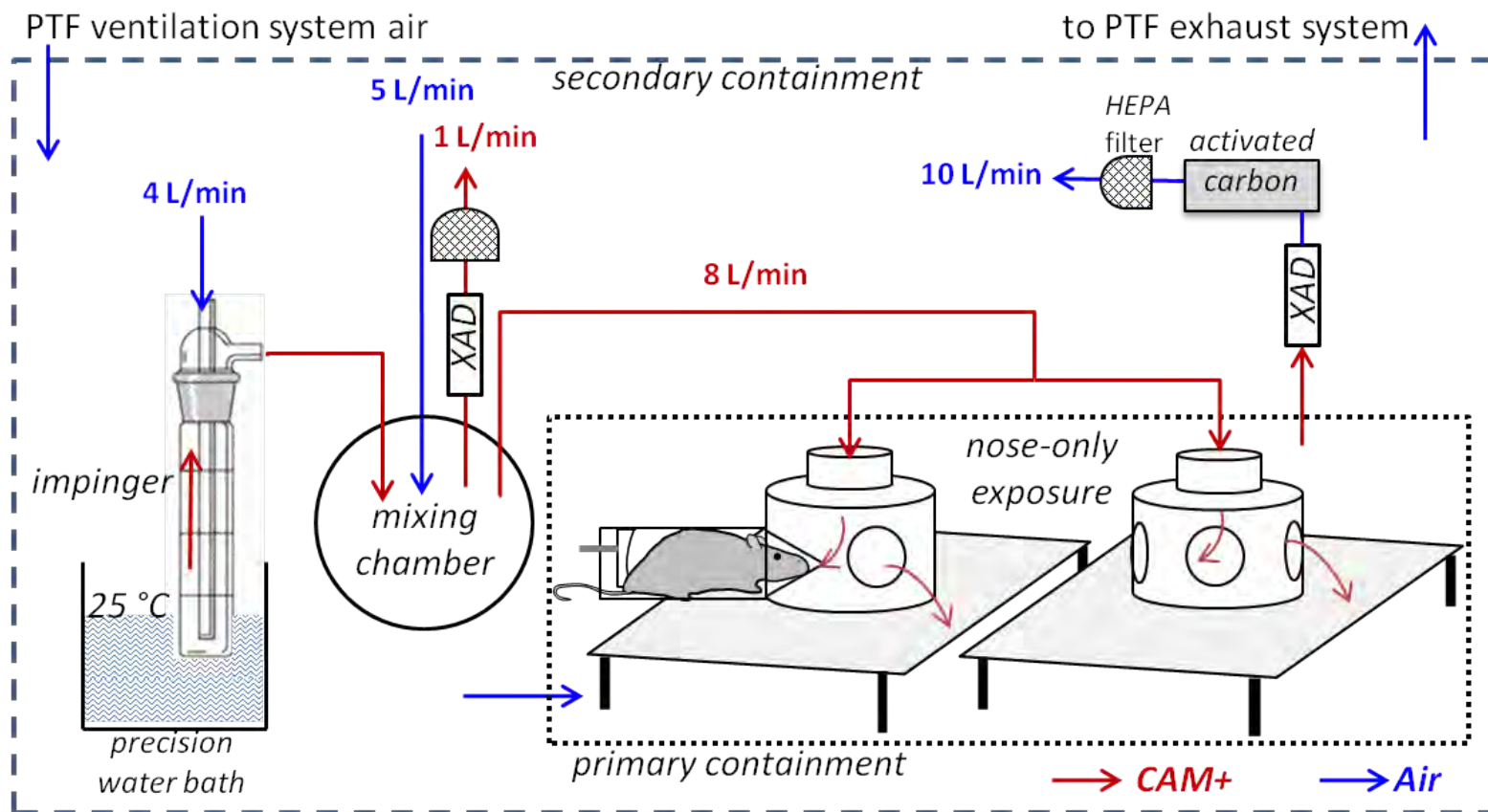


AESOP
Study
Design

^{14}C -PCB 11



Generation and Exposure System for CAM+ mixture



Toxicity Assessment – AOP Biomarkers

Disrupted Enzymes

CYP1A1, 1A2, 1B1, 2A1, 2B1, 3A1
UGT1A1, GST1A1, SULT1A1, SULT2A1, SULT1E1 (liver and lungs)

Oxidative Stress & Inflammation

Lipid peroxidation and Glutathione (liver, lung, blood)
Oxidative stress responsive genes (liver)
Inflammatory cytokines/chemokines (serum)
Hematology parameters

Neurotoxicity

Thyroid hormones: T3, T4, TSH (serum)
Gross neurotoxicity (prenatal study)

Immunotoxicity

Cytokines/chemokines (serum), B cell function,
CD4+/CD8+ T-cell population (thymus, spleen)

Developmental Toxicity

Implantation rate, litter size, body size, Postnatal survival
Thyroid hormones: T3, T4, TSH (serum)

Genotoxicity

DNA strand breaks
Chromosome breaks and loss

lung, liver, kidney,
spleen, thymus, lymph nodes,
adrenal glands, and ovaries/testis

Histopathology – altered tissue

PCB 52 and PCB 95 were selected as representative congeners for their predominance in air and their toxicological importance.

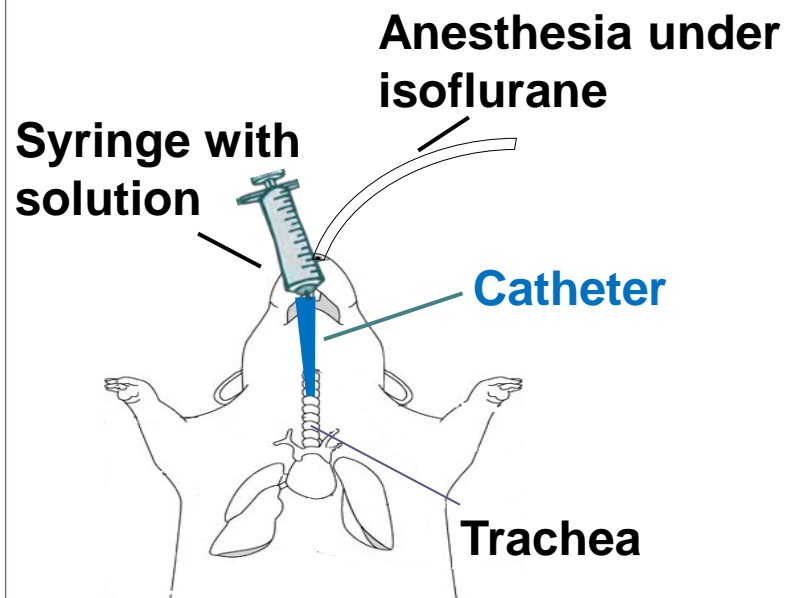
Vapor pressures of congeners representing major atmospheric PCB homologues.

PCB homologue	Di	Tri	Tetra	Penta
mass percent of Σ PCBs in Chicago air ^a	21%	29%	15%	20%
median vapor pressure ^b (Pa)	0.1527	0.0392	0.0112	0.0028
representative congener	PCB 11		PCB 52	PCB 95
vapor pressure of RC ^b (Pa)	0.0868		0.0161	0.0053

^aValues from sampled Chicago air (Hu et al. 2010)

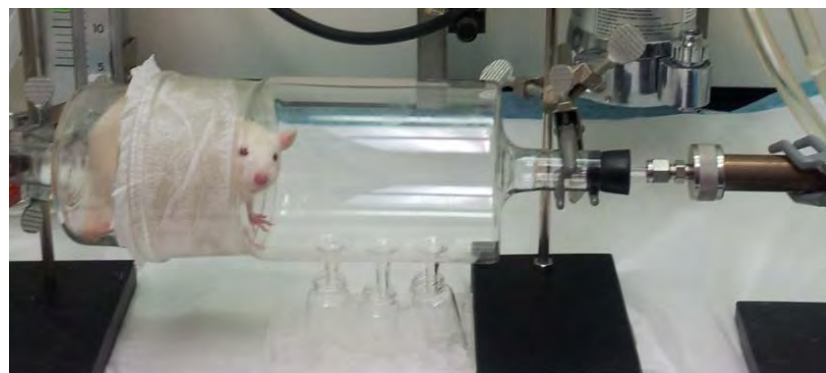
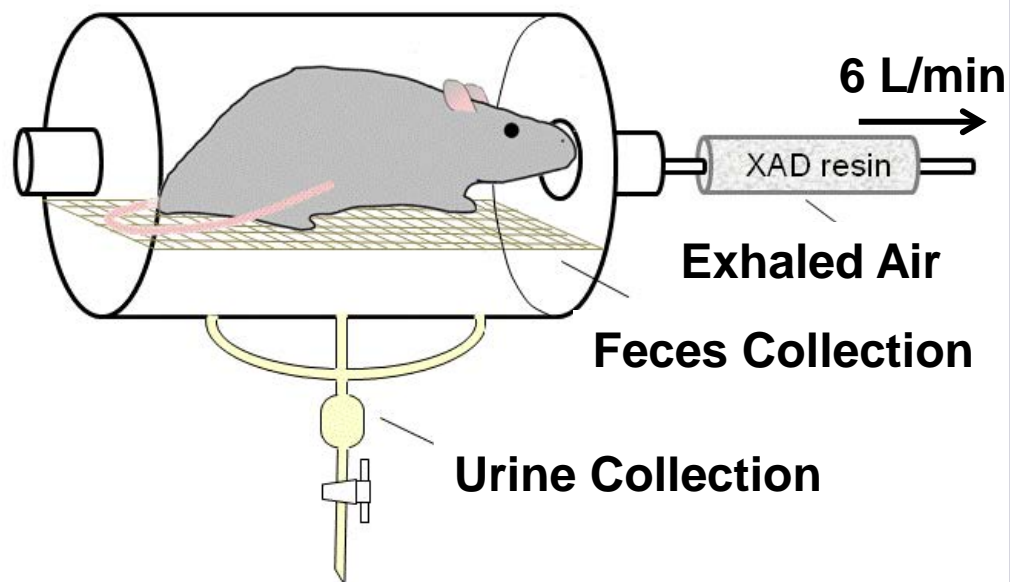
^bValues from equations by Falconer and Bidleman (1993)

Intratracheal Exposure

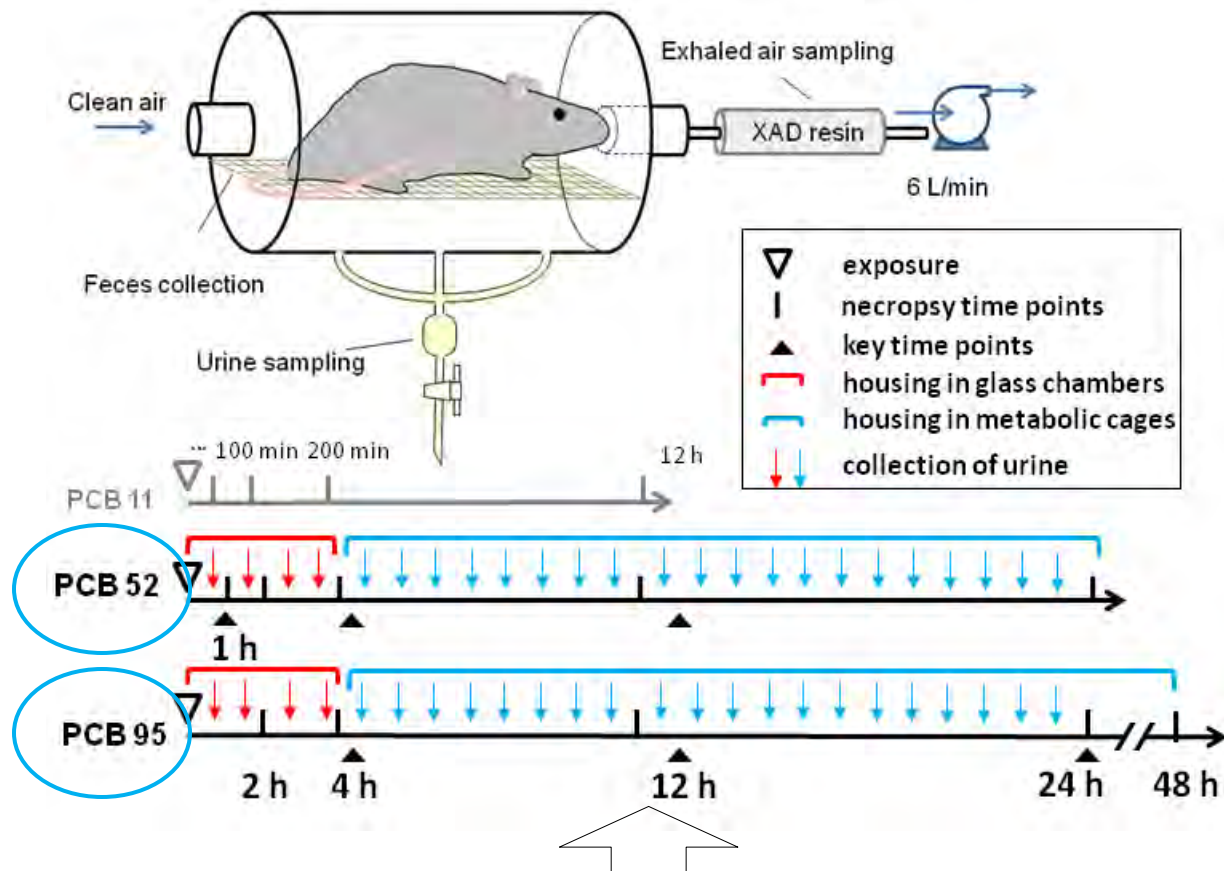


Solution: Radiolabelled [^{14}C]-PCB 52 and 95 emulsified in saline (1% Hexane and 0.1% Tween80)

Postexposure Sampling



Schematic of postexposure sampling and design of serial necropsy.



Necropsy:

-34 organ and tissues

- 5 digestive matter in GI tract (stomach, duodenum, jejunum & ileum, rectal ampulla, and colon)

Cumulative Urine excretion

- collected urine
- chamber water rinse
- rat fur wiping

Cumulative Exhalation of PCB11

- collected XAD
- chamber hexane/acetone rinse
- chamber wall wiping

Modeling Approach

$$Exp_{PCBj} = \sum_{i=1}^3 T_i * Q * [PCBj] [=] (\mu g \text{ yr}^{-1})$$

Where Exp_{PCBj} is PCB exposure for the j th congener,
 T_i is the time spent in location i in hours per year;
 Q is the inhalation rate in $\text{m}^3 \text{ d}^{-1}$; and
 $[PCB]_j$ (ng m^{-3}) is the measured airborne concentration of PCB_j .

T_i values have been obtained for three locations (home, schools, and outside) using time-activity questionnaires completed each year.

- Generation: 520 $\mu\text{g}/\text{m}^3$

