isrp iowa superfund research program
semi-volatile PCBs: sources, exposures, toxicities

EPA IRIS Bimonthly Public Science Meeting
PCBs: Effects Other Than Cancer

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Science Topic 3

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

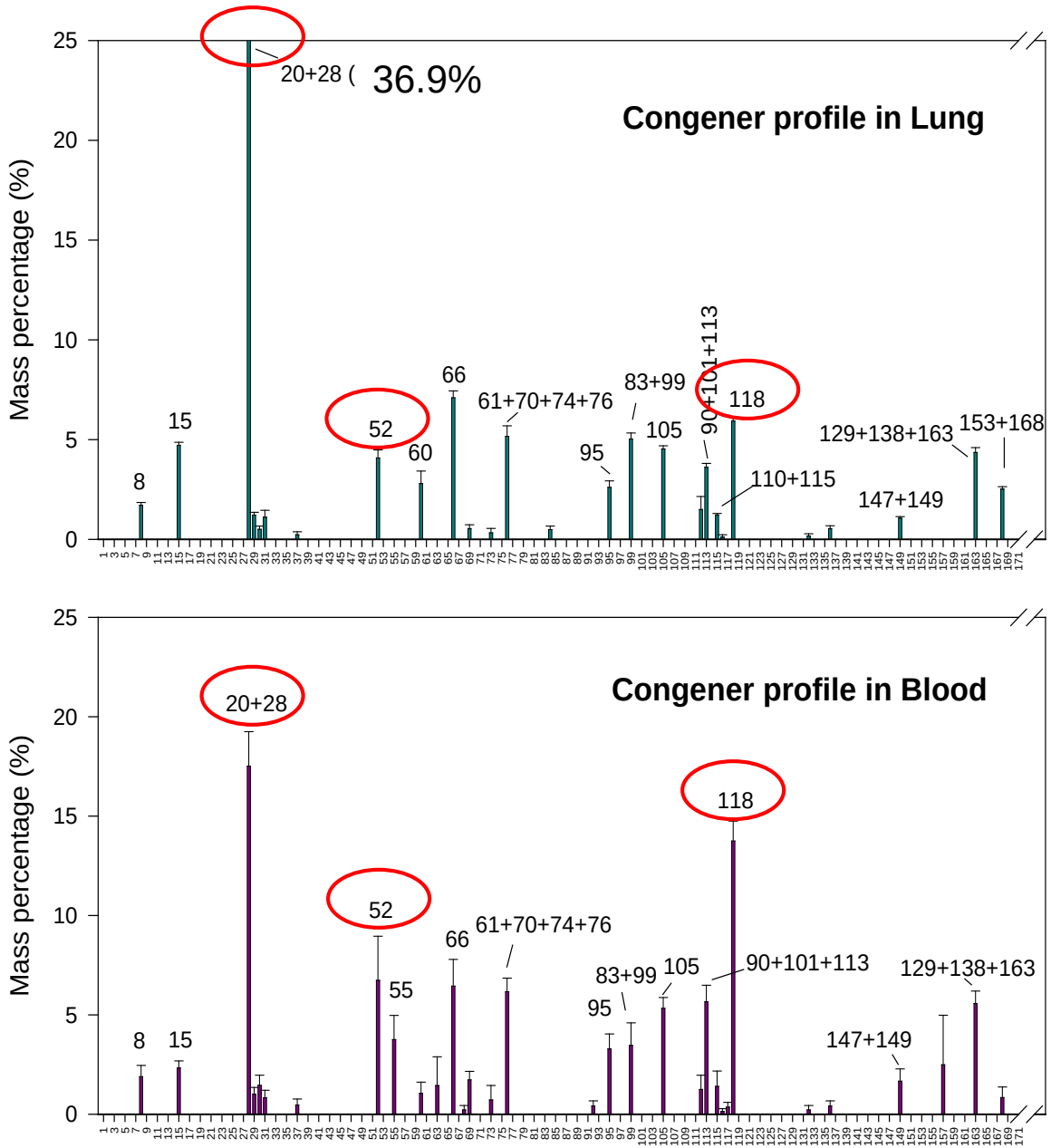
Hu et al. ES&T, 2010; Hu et al. ES&T, 2012

Rat inhalation studies show rapid distribution and metabolism and toxicity of inhaled PCB mixtures

- **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
- **CAM+ Subchronic Inhalation Study**
- Toxicity at 340 ug/rat (1.4 mg/kg)

CAM Subchronic Inhalation Study

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



Inhalation studies of mixtures

	Animals	Vapor source	Conc. (µg/m^3)	Dose (µg)	Observed effects
1956 Treon et al.	Rats	Aroclor 1254	1500†	13280†	Histopathologic lesions in liver
1999 Casey et al.	Adolescent male rats	Aroclor 1242	0.9	2.3*	Histopathological changes in the thyroid and thymus, **increases** in serum T3 and T4, decrease in exploratory behavior, diminished weight gain (?)
2010 Hu et al.	Male rats	Aroclor 1242 Subacute	8200	981	Diminished weight gain
2012 Hu et al.	Female rats	CAM Subchronic	520	100	Minimal effects, only minor change in blood GSH/GSSG (no change in T4)
2015 Hu et al.	Female rats Whole-body & Nose-only	CAM+ Subchronic	533	339 WB	Diminished weight gain, mild change in hepatocytes, **decrease** in T4
				457 NO	Diminished weight gain, mild change in hepatocytes, **decrease** in T4, increase in lipid peroxidation.

† Estimated by measuring HCl formation after thermal decomposition of Aroclor vapor.
*Estimated using questionable respiratory parameters.

Science Topic 4

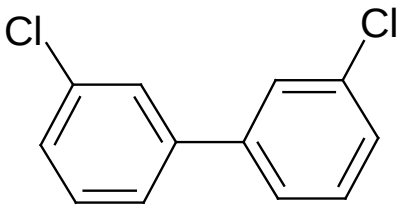
Suitability of Available Toxicokinetic Models for Reliable Route-to-Route, Interspecies, and/or Intraspecies Extrapolation

Hu X. et al. Env Int, 2014 doi:10.1016/j.envint.2013.10.017

Science Topic 4:

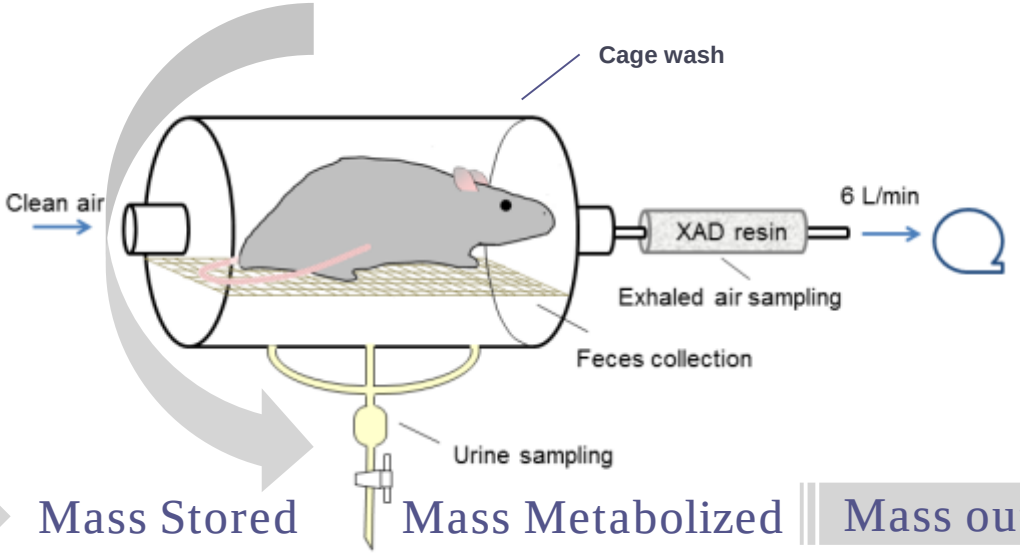
[^{14}C]-PCB11 Study

3,3'-Dichlorobiphenyl



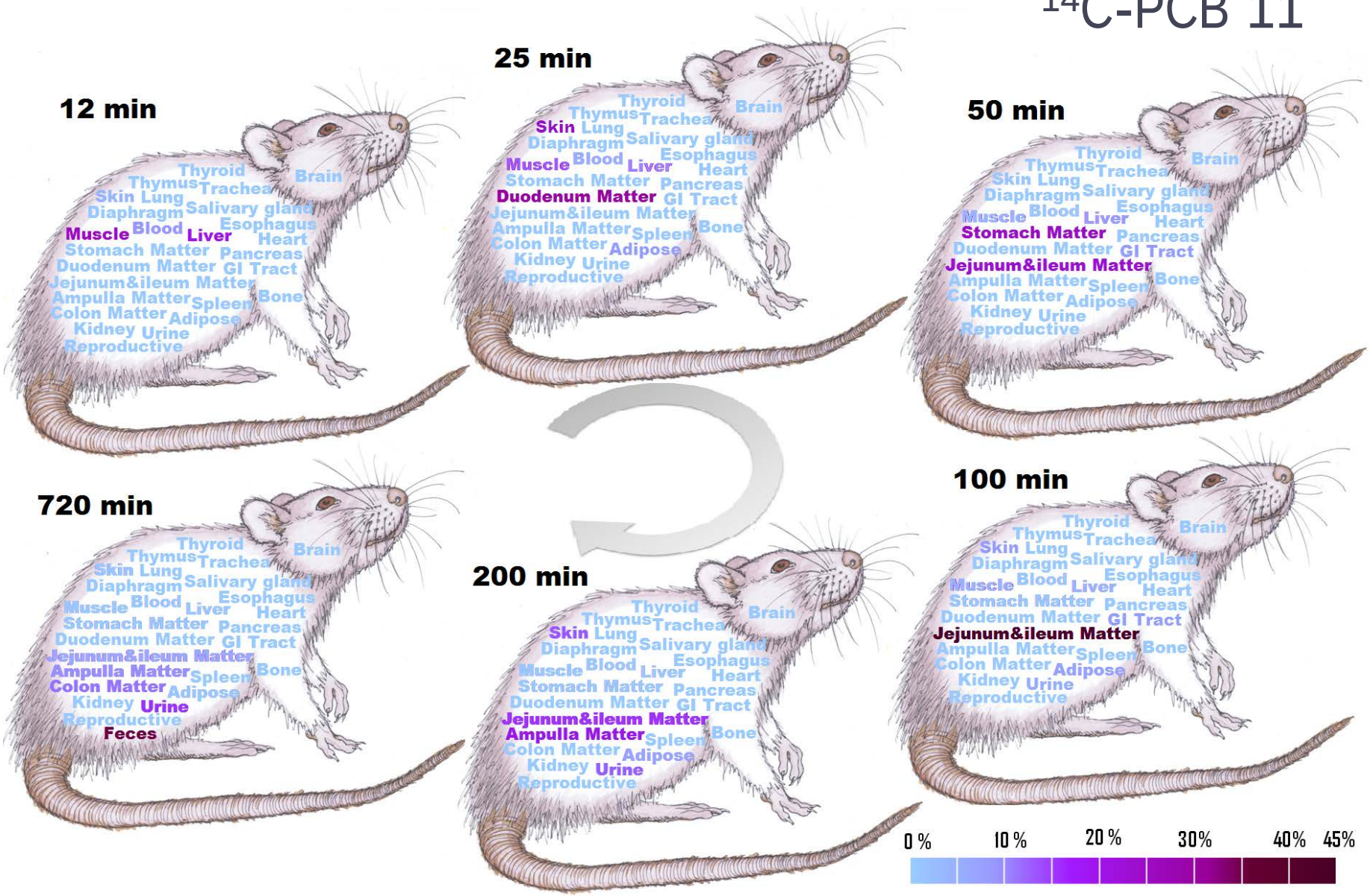
- Even though we find PCB 11 in the indoor air of every home and school, virtually nothing is known about its fate and toxicity
- Objective: To determine the fate of PCB 11 in rats

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



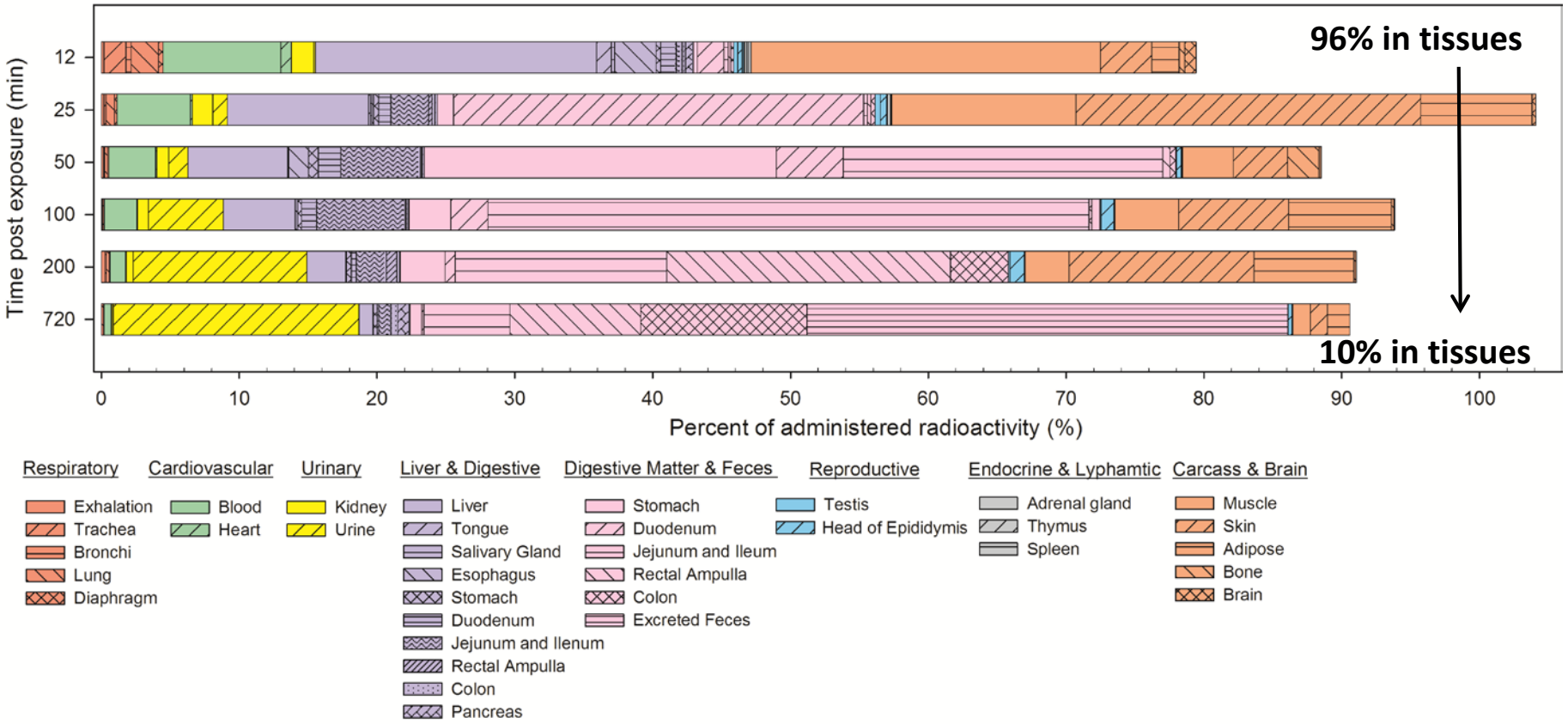
Hu X. et al. Env Int, 2014 doi:10.1016/j.envint.2013.10.017

^{14}C-PCB 11



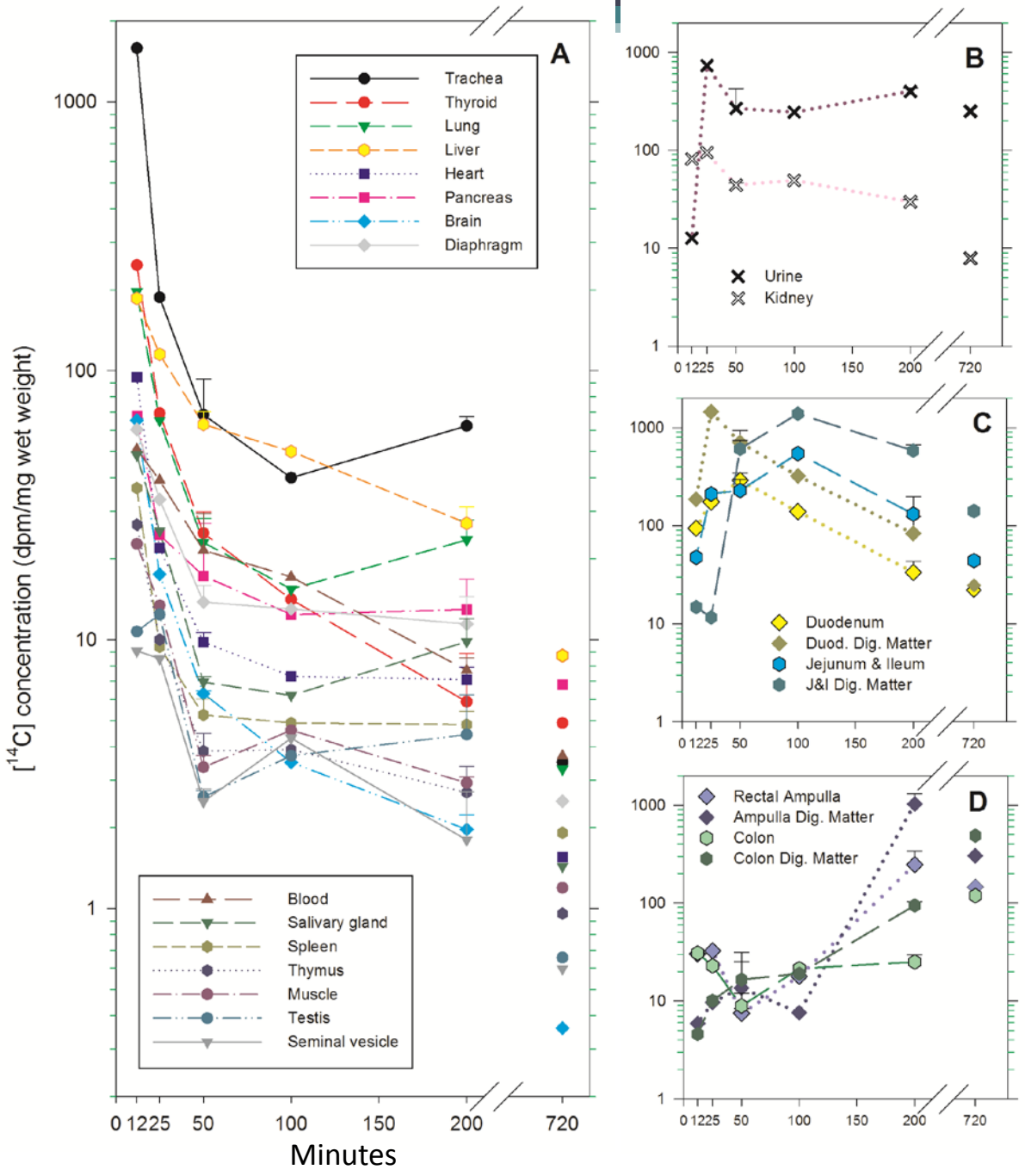
Hu X. et al. Env Int, 2014 doi:10.1016/j.envint.2013.10.017

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.

Hu X. et al doi:10.1016/j.envint.2013.10.017



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

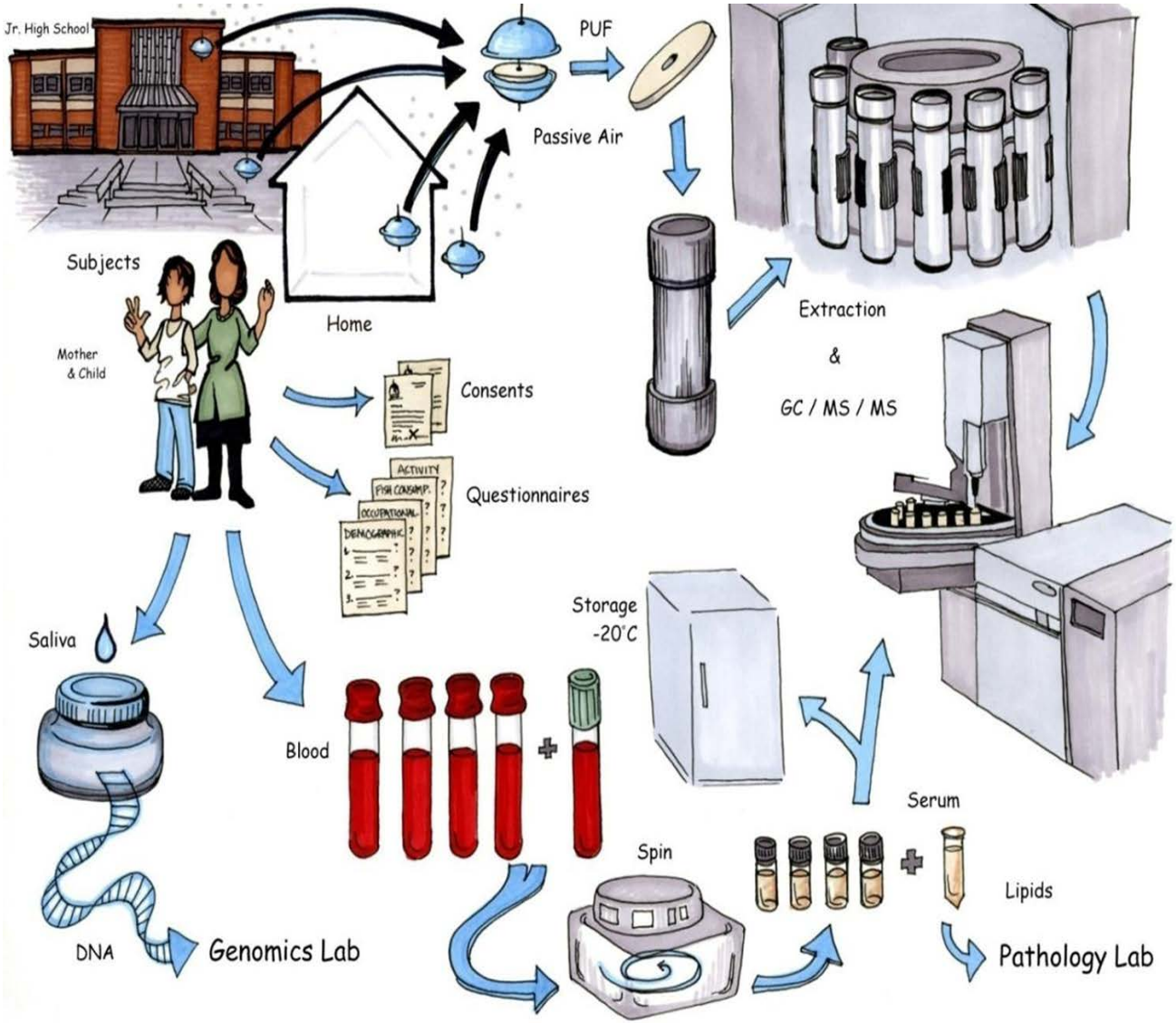
PCB11 and ^{14}C-PCB11 animal studies

- 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 ($t_{½}$ = 10-30 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**

The END

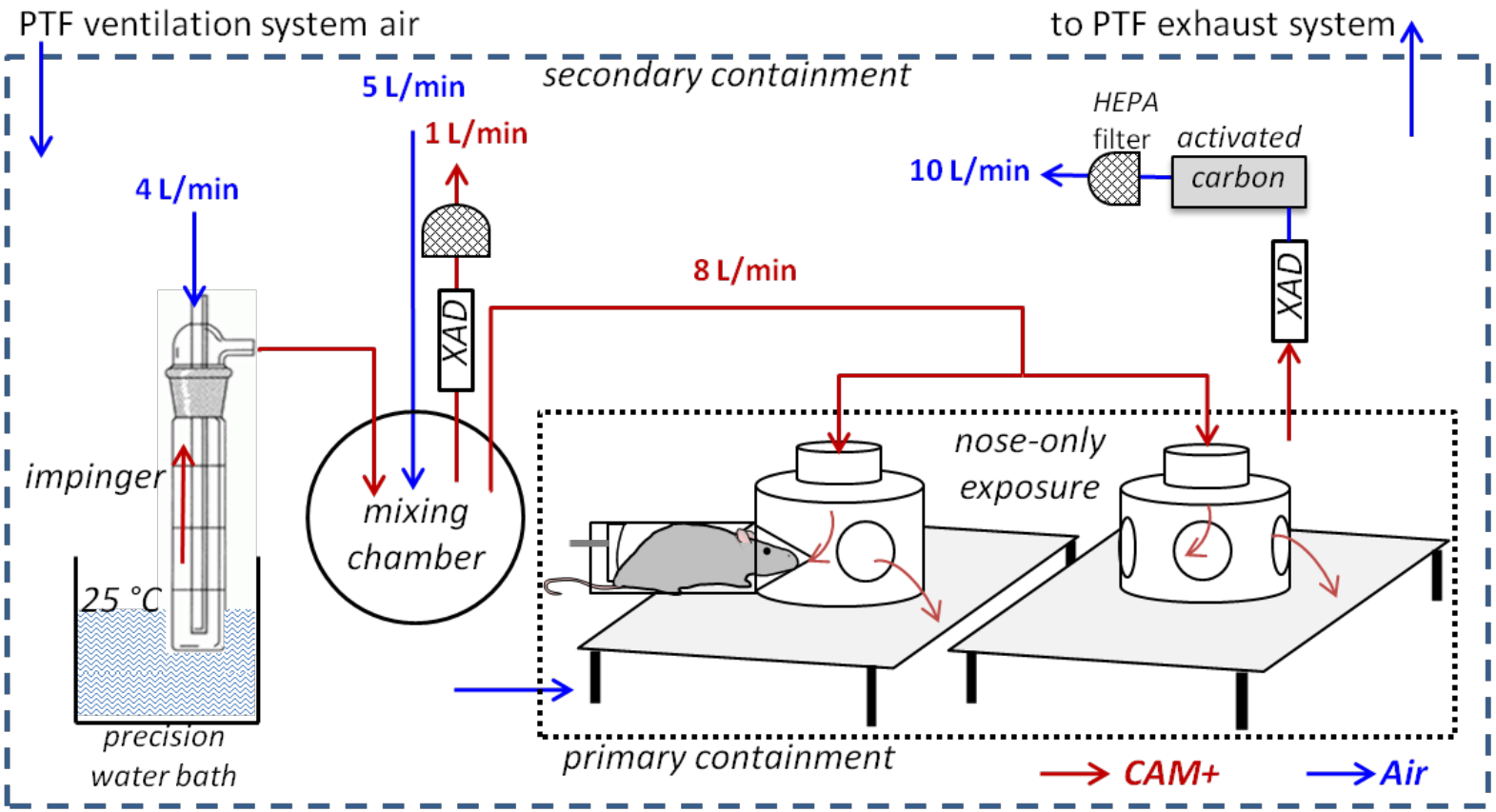
Ampleman et al. ES&T, 2015, doi:10.1021/es5048039

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



AESOP Study Design

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

Histopathology – altered tissue

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

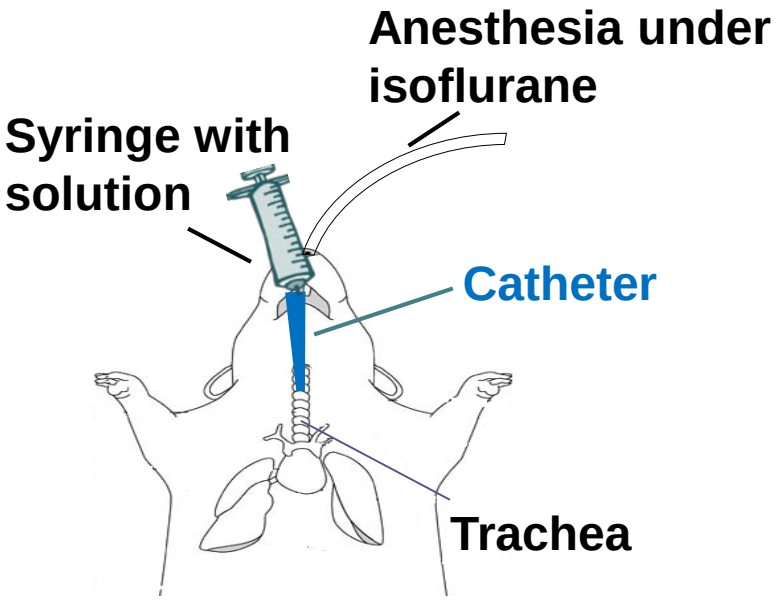
PCB 52 and PCB 95 were selected as representative congeners for their predominance in air and their toxicological importance.

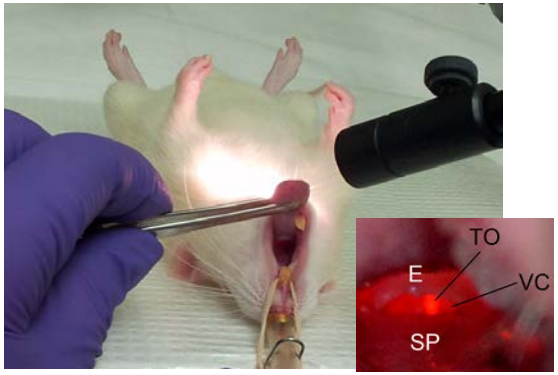
Vapor pressures of congeners representing major atmospheric PCB homologues.

PCB homologue	Di	Tri	Tetra	Penta
mass percent of ∑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**

[a]Values from sampled Chicago air (Hu et al. 2010)
[b]Values from equations by Falconer and Bidleman (1993)

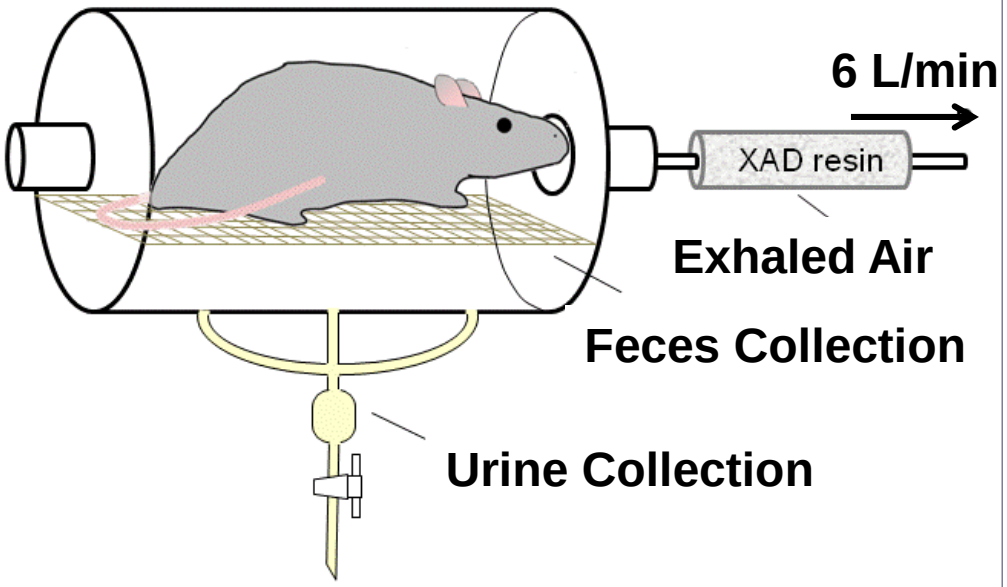
Intratracheal Exposure

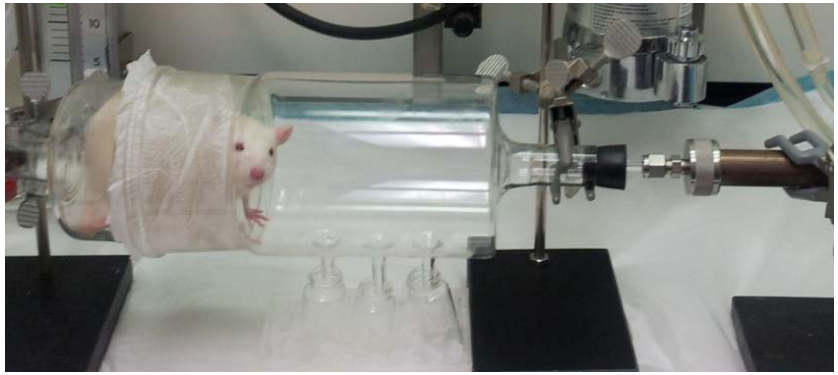




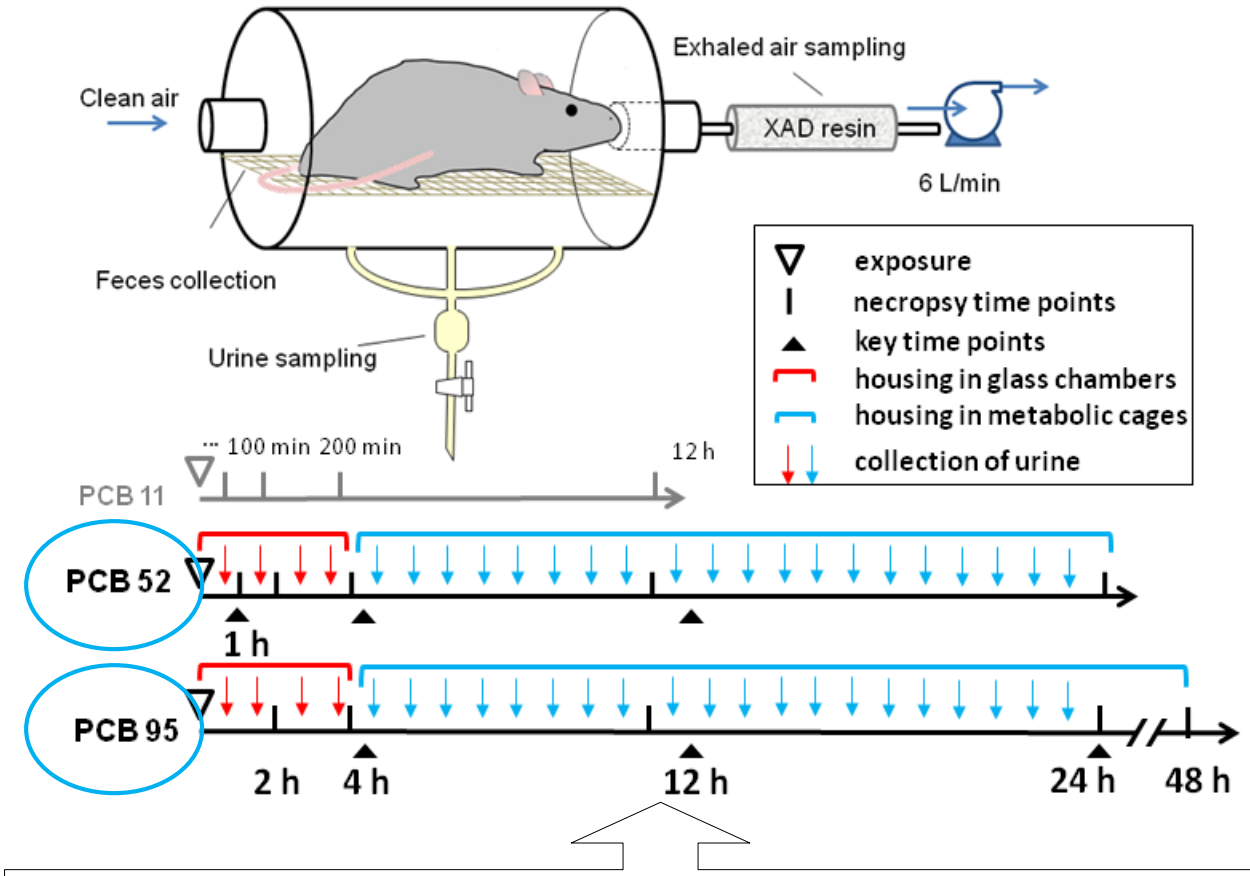
Solution: Radiolabelled [^{14}C]-PCB 52 and 95 emulsified in saline (1% Hexane and 0.1% Tween80)

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

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

Where Exp_{PCBj} is PCB exposure for the jth congener,
T_i is the time spent in location *i* in hours per year;
Q is the inhalation rate in $m^3 \; d^{-1}$; 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 µg/m³**