A modeling approach for estimating Benzo(a)pyrene and Lead in human milk

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Addresses evaluation of health risks from stationary source emissions

- OEHHA is responsible for providing health risk assessment guidance so that risk assessors can estimate exposure and health risks posed by stationary emission sources including stack emissions from industrial sources.

- OEHHA's guidance includes both air dispersion and multiple exposure pathway models to estimate health risk.

The Problem to be solved

For some chemicals that deposit and transfer in the environment:

There is no chemical specific model for estimating exposure from multiple (inhalation and non-inhalation) pathways (routes).

Example, milk is an ingestion exposure pathway that transfers some chemicals from a mother to her infant or from local cows to milk drinkers.

Two new models for estimating mother's milk concentrations of polycyclic aromatic hydrocarbons (PAHs) and lead from the chronic dose to the mother are presented next

Why is the Mother's Milk Pathway Important?

- OEHHA is mandated to ensure that infant and children's health is protected by our risk assessment procedures (SB-25).

- The mother's milk pathway can be a significant source of exposure particularly for lipophillic, poorly metabolized chemicals such as dioxins, furans and PCBs.

- Recent research suggests that infants may be 10 times more sensitive than adults to carcinogens and noncancer health impacts, in particular neurotoxicity.

Xenobiotic Chemicals Detected in Cow Milk and Human Milk

- A wide variety of xenobiotic chemicals have been detected in mother's and cow's milk.
- Chemicals detected in milk include pharmaceuticals, heavy metals, dioxins and furans, PCBs, perchlorate, PAHs, and poly brominated biphenyls.
- The Hot Spots program is particularly concerned with PCB's, dioxins, furans, PAHs and toxic metals because they are emitted into the air by stationary sources in relatively large quantities.

Deliberate experiments to measure the transfer of toxicants from Cow's feed to Cow's Milk

- A measured toxicant daily dose is fed to the cow until steady state is reached and then the concentration of the chemical is measured in the cow's milk.

- The milk-to-feed ratio is established as a transfer coefficient (**Tco**). This model in units of (mg/liter)/(mg/day) appears in the animal product chapter of the guidance document in units of day/liter.

Limitations to this approach:

- The cow transfer coefficient may not directly represent a human transfer coefficient because:

  -absorption, distribution, metabolism and/or excretion may not be identical in both species.

- Deliberate toxicant dosing experiments are prohibited in humans.

A “Natural” Experiment to Estimate PAH transfer from Mother to Mother’s Milk

- Women who smoke while nursing are inhaling a fairly constant daily dose of PAHs.
- Zanieri et al. (2007) measured individual PAHs in 11 smoking and 21 nonsmoking women’s milk and determined the number of cigarettes smoked.
- Used published summary statistics but OEHHA has requested raw data from the authors.
- The approximate dose of individual PAHs from smoking a cigarette has been estimated by Ding et al (2005).

An estimate of BaP transfer from smoking mothers to Mother's Milk

- Average dose of benzo(a)pyrene (BaP) per cigarette is 0.01 µg/day.
- Average number of cigarettes smoked = 5/day
- Average concentration of BaP in mother's milk from smoking mothers is 0.52 µg/L
- Average concentration of PAHs in mother's milk of nonsmoking mothers is 0.02 µg/L (LOD)
- Assuming background exposure is equivalent in the two groups the net contribution from cigarettes is 0.5 µg/L.
- This gives a Tco of 0.5/0.05 =10 day/L. (may be high due to under reporting of smoking frequency)

Human milk transfer estimate using a Steady state pbpk dioxin model (Smith 1987)

- Cm = (Emi)(t1/2)(f1)(f3) / (f2)(0.693)
- Cm = chemical concentration in milk (mg/kg milk)
- Emi = average daily maternal intake of contaminant (mg/kg-BW/day)
- BW = body weight (kg)
- t½ = terminal half life in the body tissue (days)
- f1 = proportion of chemical in mother that partitions into fat (e.g. 0.8)
- f2 = proportion of mother's body weight that is fat (e.g. 0.33 = kg-fat/kg-BW)
- f3 = proportion of breast milk that is fat (e.g. 0.04 = kg-fat/kg-milk).

Smith and Tco model relationship

- Emi = Conc. In food * Intake rate / body weight

- s_x is the tissue fraction
-
- Tco = (Emi)(t1/2)(f1)(f3) / (Emi)(BW)(f2)(0.693)

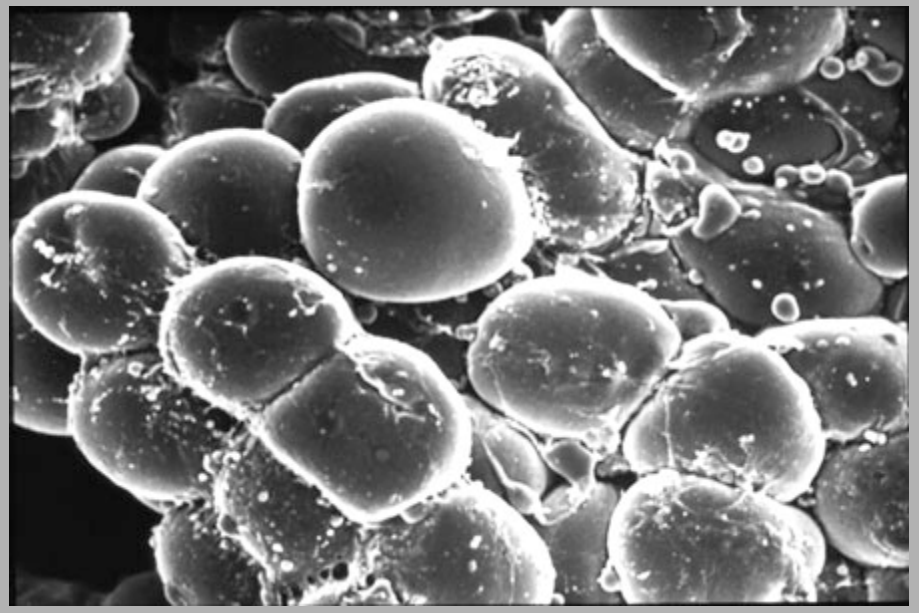
which can be simplified to:

- Tco = (t1/2)(f1)(f3) / (BW)(f2)(0.693) [fat]

- Tco = (t1/2)(sf1)(sf3)/(BW)(sf2)(0.693) [soft tissue]

BaP kinetics in the mother

- by age 25



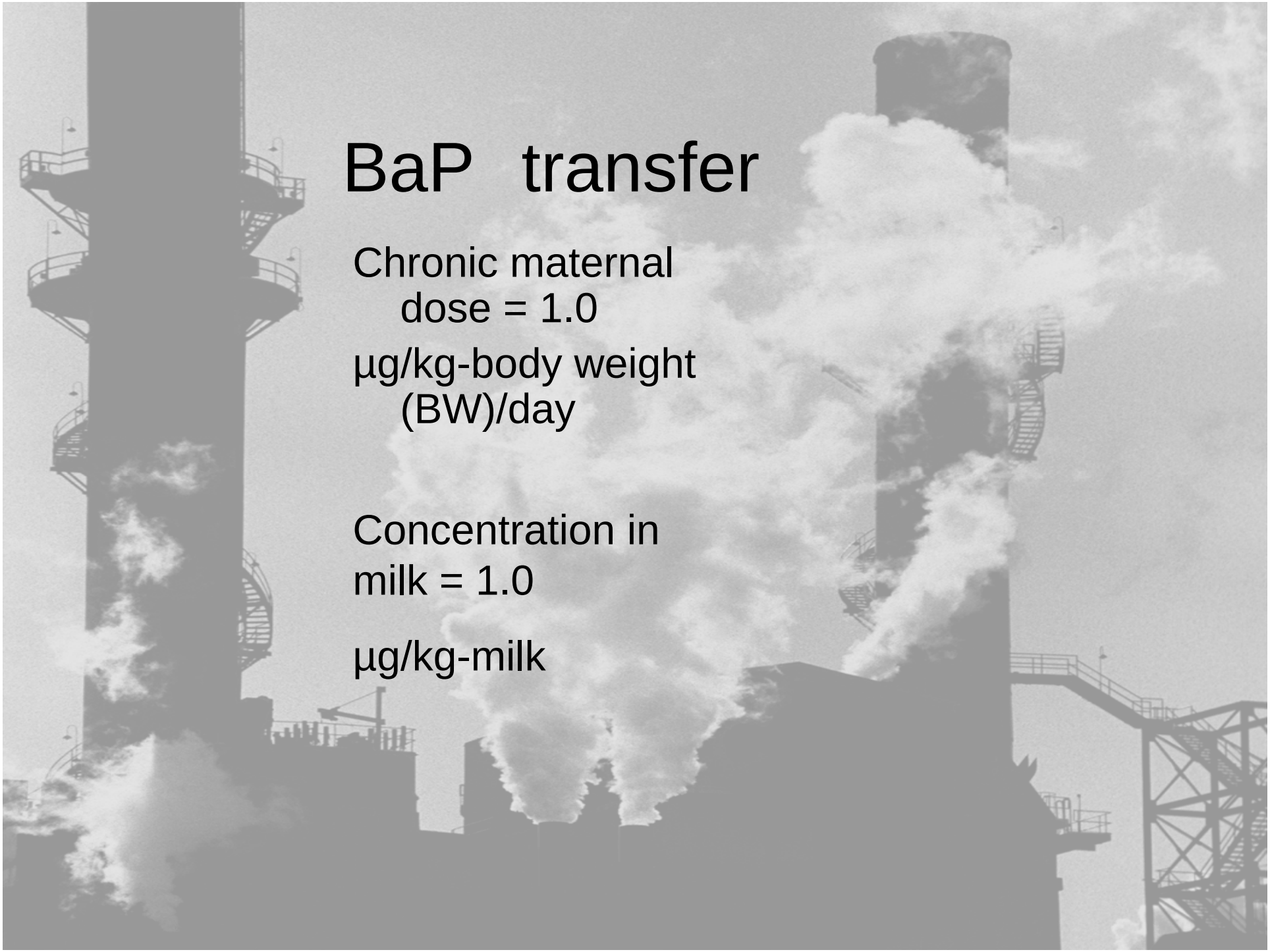
~80% of BaP body burden accumulates in fat tissue

- during pregnancy and lactation

Equilibrates with fat in milk (small impact on mother's fat burden assumed)

Other information about how the body treats BaP (building blocks for a pbpk model)

- absorption
  - 50% (inhale),8%(ingest) (Poulin 2002, Grova, 2002)
- metabolism
  - 60% (Grova 2002, Wiersma 1983)
- elimination
  - T1/2 = 152 days



BaP transfer

Chronic maternal dose = 1.0

µg/kg-body weight (BW)/day

Concentration in milk = 1.0

µg/kg-milk

BaP Model Comparisons and adjustments

- human versus cow milk bio-transfer factor comparison (adjusted for body weight).

Despite potential differences in excretion, metabolism and absorption, remarkable close

- Other adjustments and simplifications

Human

- 3.5 $x10^{-2}$

Cow

- 1.6 $x10^{-2}$

- smoking may influence milk volume
- fat content varies over lactation period
- metabolism may be dose dependent (e.g. Enzyme induction, saturation of pathways)
- Oral and inhaled absorption differences are likely to be substantial

Lead behavior in the mother

- With a constant daily dose of lead a steady state is reached.

95% of lead body burden accumulates in the skeleton

- during pregnancy and lactation—new steady state.

Bone releases lead

Transfer of Lead during lactation

- Gulson et al (1999) measured blood lead changes during lactation in 15 women
- observed a 40% increase in blood lead during lactation

Lead Lactational Transfer

Li et al (2000) measured lead in blood and milk of 132 women

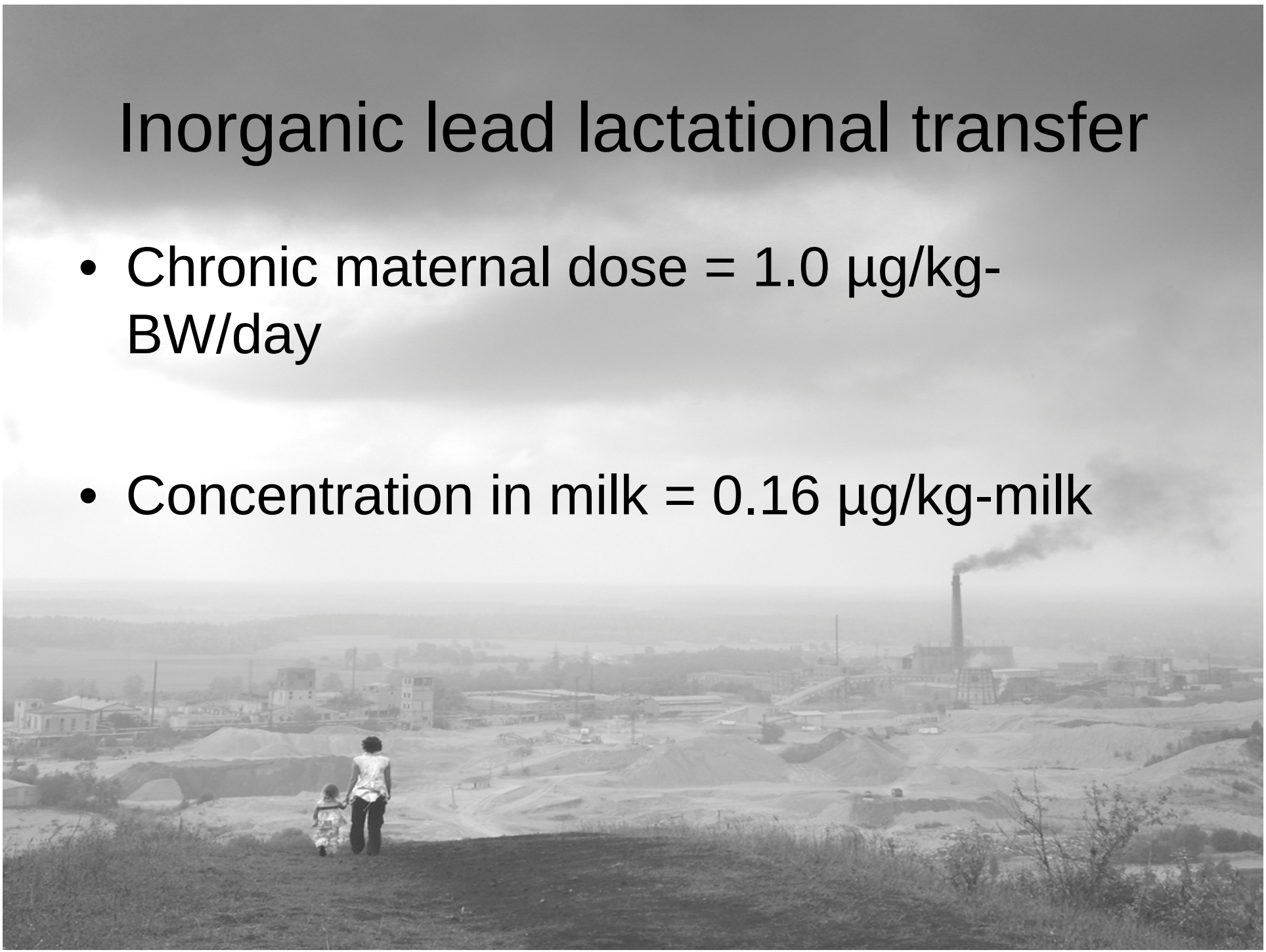
- 12 women had high exposures
- 119 women had background exposures
- Blood to milk transfer ratios were highest for low blood levels ~ 5%

Other information about how the body treats Inorganic lead (building blocks for a pbpk model)

- absorption
  - 35% (inhale), 10% (oral) (Hursh 1969, Barry 1975, Castellino, 1995)
- soft tissue volume
  - 88% of body weight 5% mammary tissue (ICRP, 2003)
- bound fraction in blood
  - 50% red cells (Castellino 1995, O'Flaherty 1998)
- elimination
  - t1/2 = 33 days (Rabinowitz, 1976)

Inorganic lead lactational transfer

- Chronic maternal dose = 1.0 µg/kg-BW/day
- Concentration in milk = 0.16 µg/kg-milk



Infant daily dose of lead

Default values used in calculating dose

- infant body weight = 6.5 kg
- human milk ingestion rate = 0.9 kg/d
- average infant dose = 0.02 µg/ kg/ BW/ d

Human intake at the receptor by pathway (µg Pb /kg body wt. - day):

30-Year Exposure Scenarios

- Inhalation 0.39
- Dermal absorption from soil 0.095
- Incidental soil ingestion 0.19
- Human milk ingestion (2y/30) 0.001

9-Year Exposure Scenario

- Inhalation 0.58
- Dermal absorption from soil 0.18
- Incidental soil ingestion 0.95
- Human milk ingestion (2y/9) 0.005

Lead Model comparisons & adjustments

- human versus cow milk bio-transfer factor comparisons (body weight adjusted).

Human
- 2.5 x10-4

Cow
- 2.6 x10-4

Despite potential differences in excretion, metabolism and absorption, remarkable close

Other simplifications and adjustments

- lung absorption is nonlinear – higher absorption at lower doses and is influenced by particle size
- lung versus oral absorption
- gut absorption is very low when food is present

Summary

- Determined a method for estimating lead and PAH concentrations in mothers milk from maternal dose for use in the Hot Spots risk assessment model.
- Demonstrated how an infant's dose of lead from mother's milk compares to the dose from other pathways of chronic exposure.

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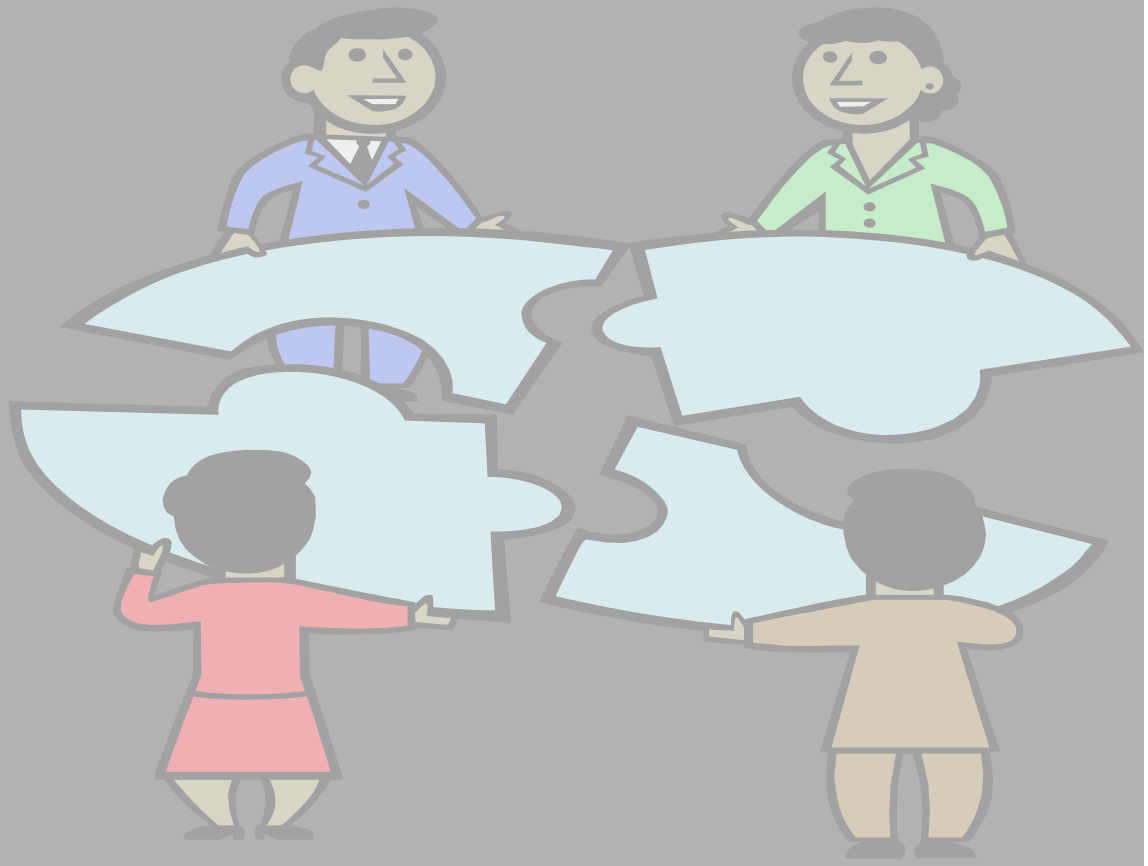

Transfer coefficients in animal products used by OEHHA

Cow Transfer chemical	Milk/feed (day/liter)
Sodium arsenate	6.2×10^{-5}
Beryllium chloride	9.1×10^{-7}
Cadmium	1.0×10^{-3}
Sodium chromate	1.0×10^{-5}
Lead	**2.6×10^{-4}**
Mercuric nitrate	9.7×10^{-6}
Nickel	1.0×10^{-3}
Aroclor 1254	**1.0×10^{-2}**
2,3,7,8-TCDD	**4.0×10^{-2}**
Benzo-a-pyrene	**1.6×10^{-2}**