Estimating Workplace Air and Worker Blood Lead Concentrations using an Updated Physiologically-Based Pharmacokinetic (PBPK) Model

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Outline of Presentation

- Background and purpose of project
- OEHHA's tasks
- Overview of process
- Results of modeling work

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Background

- California Department of Public Health (CDPH) is making recommendations to Cal/OSHA to change the current workplace standard for lead (Pb)
- Estimates of workplace air concentrations (PbA) of Pb that result in blood lead levels (BLLs) are needed
- These estimates were originally established with the help of a predictive model

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OEHHA's Tasks

Chronic workplace exposure scenarios:

- **Task 1**: Calculate 8-hr TWA air concentrations of Pb for a range of BLLs for CDPH
- **Task 2**: Estimate the length of time it takes for BLLs to decline from a much higher level to a target BLL of 15 µg/dL

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Why a Model is Needed

- Need to characterize PbA/BLL relationship over 40-year working lifetime
- No studies of PbA/BLL at low BLLs and 40 years

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Q: Why a PBPK Model?
A: Nature of how the human body handles Pb

- **Absorption**
  - Lungs – more efficient
  - Gut – less efficient
- **Distribution** (uptake, storage and release)
  - Blood– days - weeks
  - Soft tissue –months to years
  - Bone –decades
- **Elimination**
  - Feces
  - Urine

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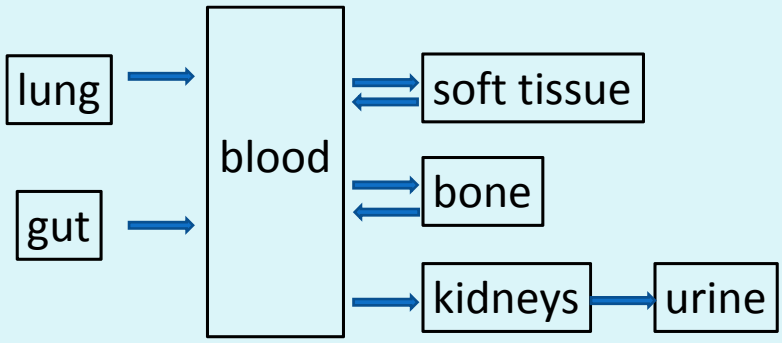
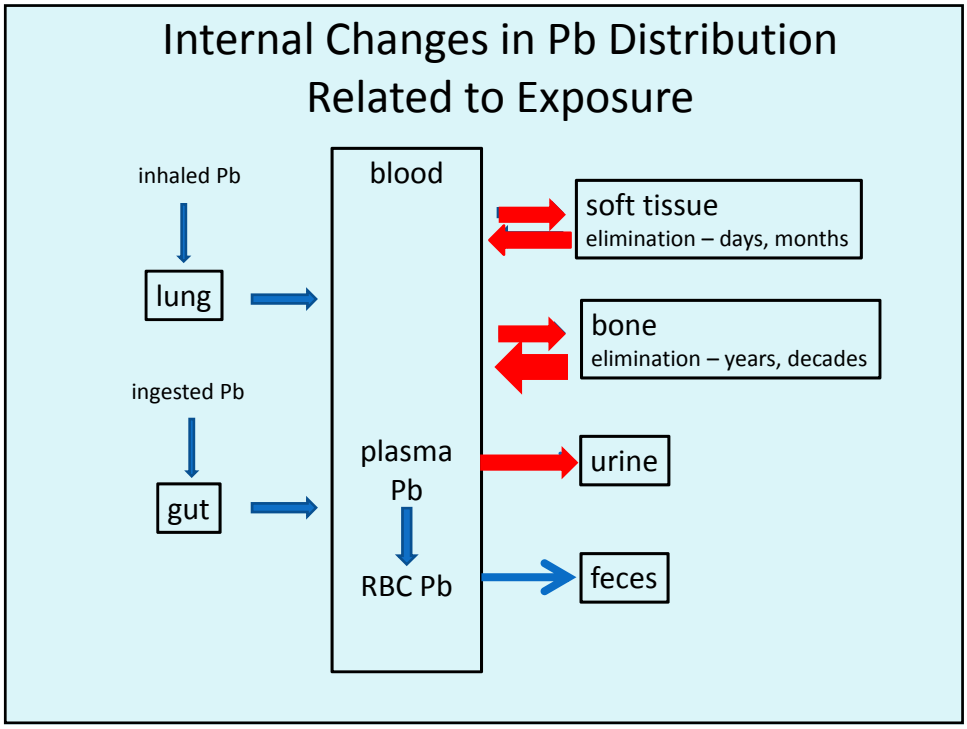
What is PBPK Modeling?

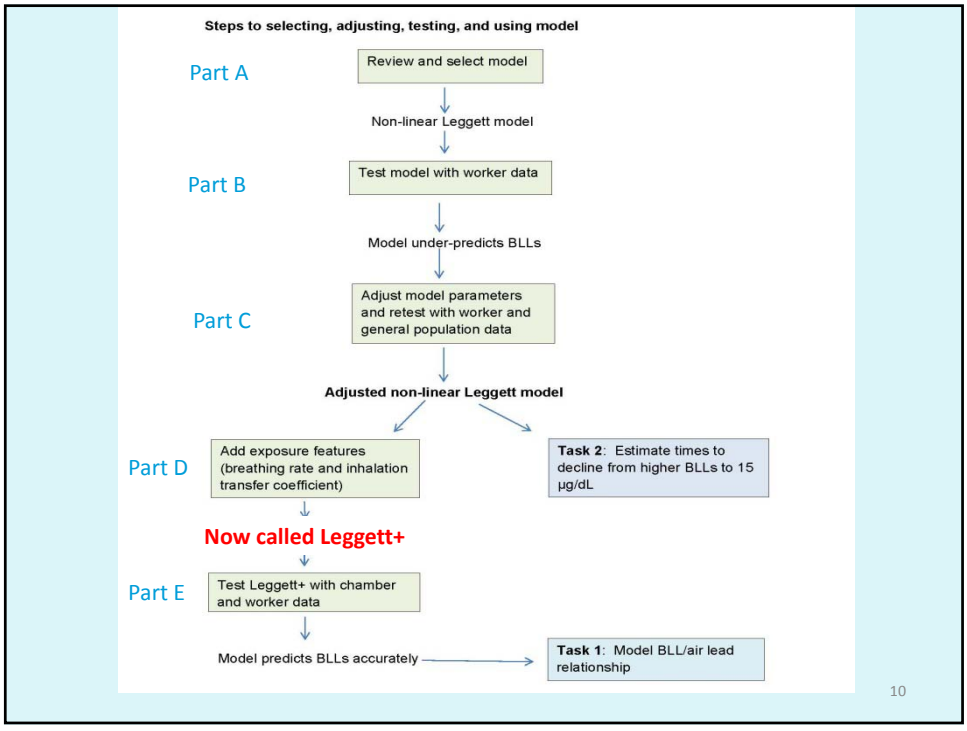
mathematical model representing:

- Absorption
- Distribution
- Metabolism
- Elimination

What is PBPK Modeling?




Internal Changes in Pb Distribution Related to Exposure
inhaled Pb
lung
ingested Pb
gut
blood
plasma Pb
RBC Pb
soft tissue
elimination – days, months
bone
elimination – years, decades
urine
feces


Steps to selecting, adjusting, testing, and using model
Part A
Review and select model
Non-linear Leggett model
Part B
Test model with worker data
Model under-predicts BLLs
Part C
Adjust model parameters and retest with worker and general population data
Adjusted non-linear Leggett model
Part D
Add exposure features (breathing rate and inhalation transfer coefficient)
Task 2: Estimate times to decline from higher BLLs to 15 µg/dL
Now called Leggett+
Part E
Test Leggett+ with chamber and worker data
Model predicts BLLs accurately
Task 1: Model BLL/air lead relationship
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Part A

Review and select model

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Reasons for Choosing Leggett Model

Time dependent

Adequate structure

- copes with saturation in RBC
- accounts for differential bone Pb accumulation

Sufficiently accessible and flexible

- Modular design

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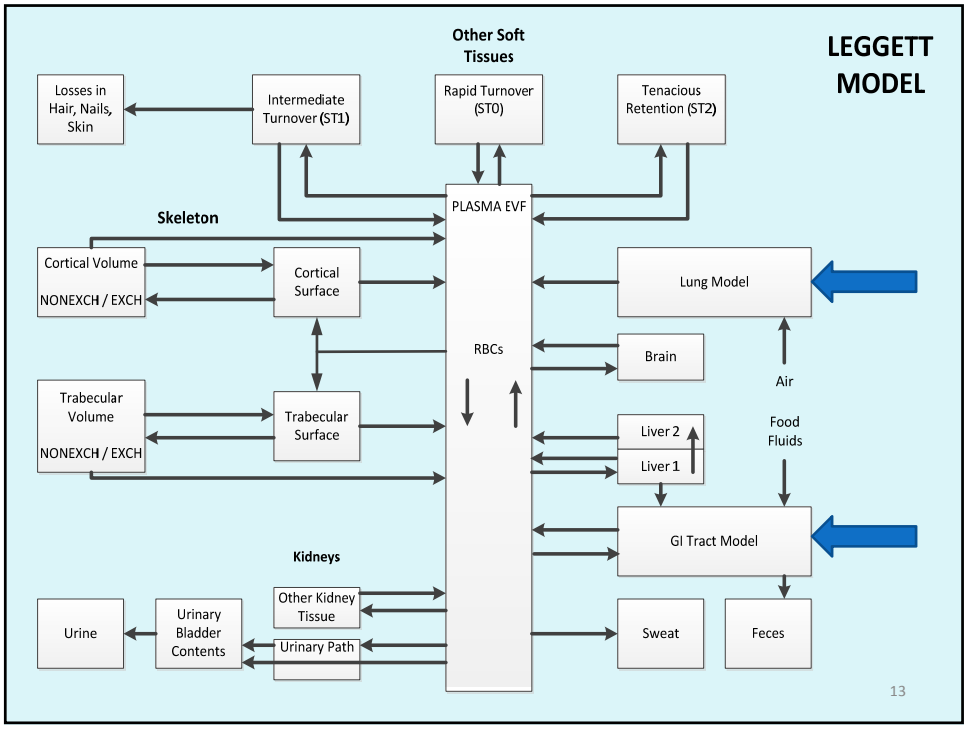

Part B

Test core model with worker data

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ASARCO Data (Hattis 1981)

59 smelter workers

- BLL history (1970s)
  - Pre employment
  - Before 9-month strike
  - Upon return from strike
- Length of employment

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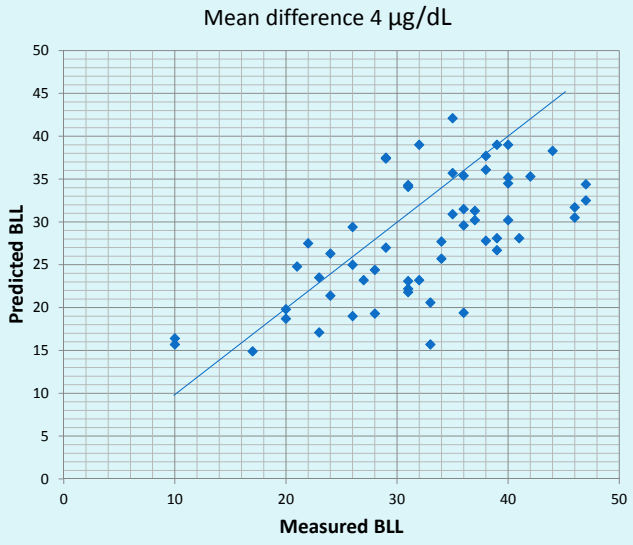
Initial Test of Model



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Part C

Adjust core model and retest with worker data

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Influential Parameters in Model*

- Cortical bone – uptake and elimination
- Trabecular bone – uptake and elimination
- Urine – clearance
- RBC - binding limits

*Fleming et al. 1999; Nie et al. 2005 ; O'Flaherty 2000

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Data used to Check and Adjust Bone Parameters

- ✓ ASARCO smelter workers (Hattis 1981)
- ✓ Canadian smelter workers (Nie et al. 2005)
- ✓ Autopsy studies with uncertainty bounds - adults in the U.S. general population (Leggett 1993)

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Data used to Check and Adjust RBC and Urine Parameters

- ✓ Pb glass-based paint factory workers (Hirata et al. 1995)
- ✓ Storage battery factory workers (Lee 1982)
- ✓ Pb workers from medical practice (Manton and Cook 1984)
- ✓ Autopsy studies - adults in the U.S. general population with uncertainty bounds (Leggett 1993)

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Five Tests

Main check for accuracy and reliability (smelter data)

1. Accuracy - model predicted versus measured blood Pb
2. Reliability - model performance (measured – predicted blood Pb) consistent regardless of length of exposure (job tenure)

Other checks for accuracy

3. Ratios of predicted versus measured bone Pb
4. Slope of predicted versus measured urine and plasma Pb
5. Ratios of Pb in major body tissues/body compartments in the model

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Final Adjustments (µg/day or µg/dL RBC)

Parameter	Original Leggett	Adjusted Leggett	Nie et al. (2005)
C-bone to blood	8.22×10^{-5}	**1.60×10^{-5}**	1 to 27 $\times 10^{-5}$
T-bone to blood	49.3×10^{-5}	**1.97×10^{-5}**	0.4 to 22 $\times 10^{-5}$
Blood to C-bone	46.2×10^{-4}	**3.81×10^{-4}**	1.5 to 7.2 $\times 10^{-4}$
Blood to T-bone	46.2×10^{-4}	**2.82×10^{-4}**	2.8 to 6.3 $\times 10^{-4}$
RBC Saturation	350	**270***	NA
RBC Threshold	60	**0**	NA

*Derived by O'Flaherty from experiments on nonhuman primates (1996)

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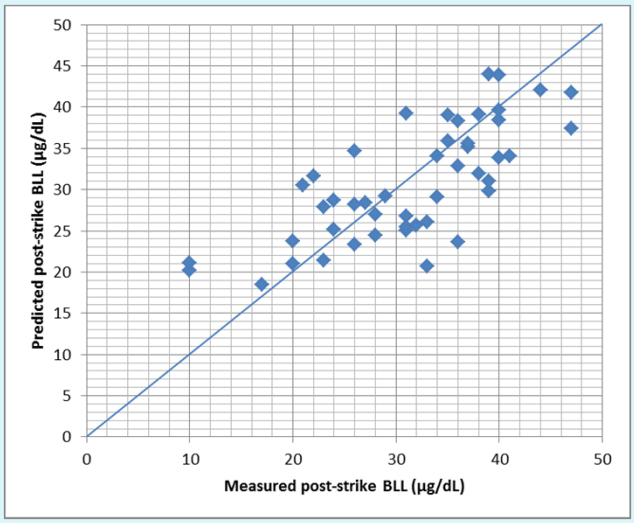
Test 1: Accuracy

Mean difference 0.88 µg/dL



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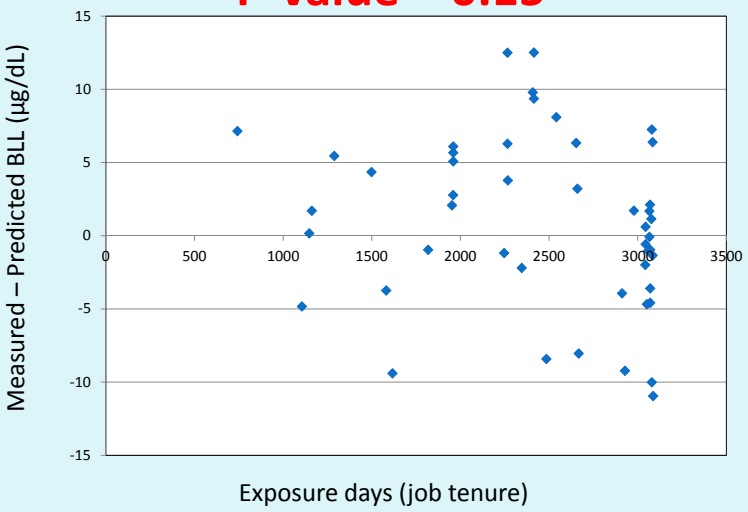
Test 2: Consistency/Reliability

P-value = 0.15



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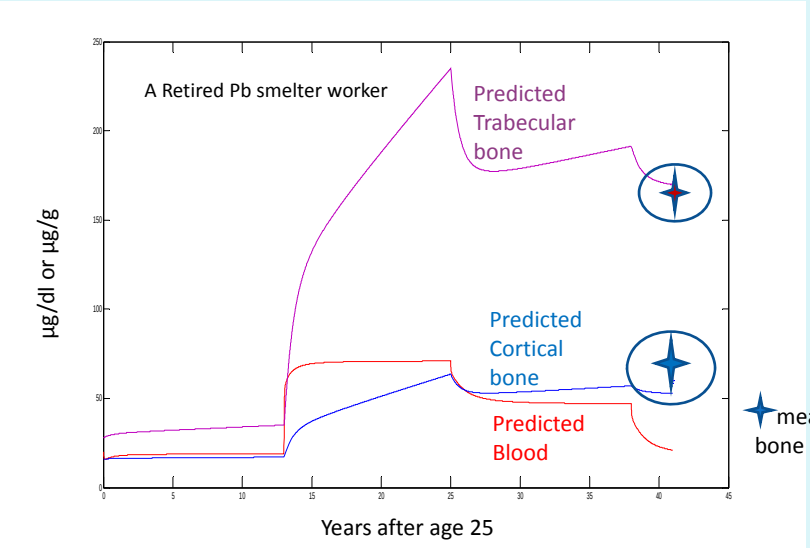
Test 3: Ratio of Predicted and Measured Bone Pb

Measured Ratios between 2 - 3



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Summary of Worker Data

Manton and Cook (1984)

- 36 patients from a medical practice
- Serum and whole blood

Lee (1982)

- 234 male battery factory workers
- Work duration 4.4 years
- Area air concentrations 70 – 380 µg/m^3
- Urine sample means ± 1 SD (µg/L); BLL (µg/dL)

Hirata et al. (1995)

- Four workers in leaded glass-based paint factory
- Two years of exposure history
- Area air Pb conc. 22 – 1331 µg/m^3
- 60 sets of blood and urine; 15 months of follow up

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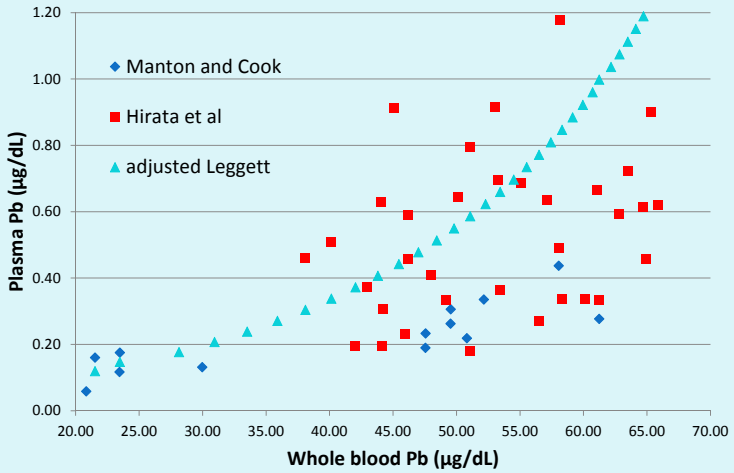
Test 4a: Slope of Predicted and Measured Pb in Plasma Relative to Whole Blood



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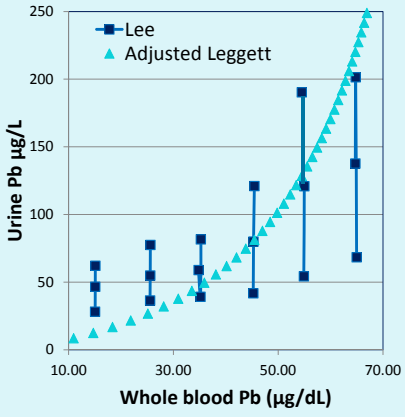
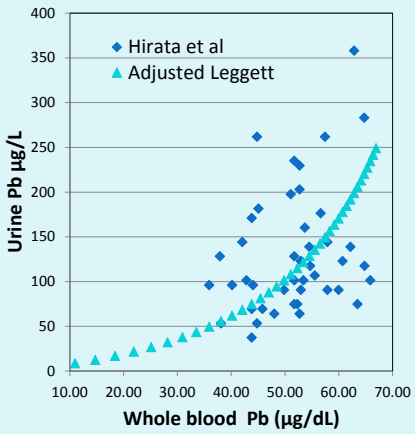
Test 4b: Slope of Predicted and Measured Pb in Urine Relative to Whole Blood

Lee 1982



Hirata et al. 1995



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Autopsy data and Leggett Summary

- Leggett derived reference organ distributions from postmortem data collected in the 1960s and 1970s
- Multiple data sets were combined and uncertainty bounds derived by Leggett

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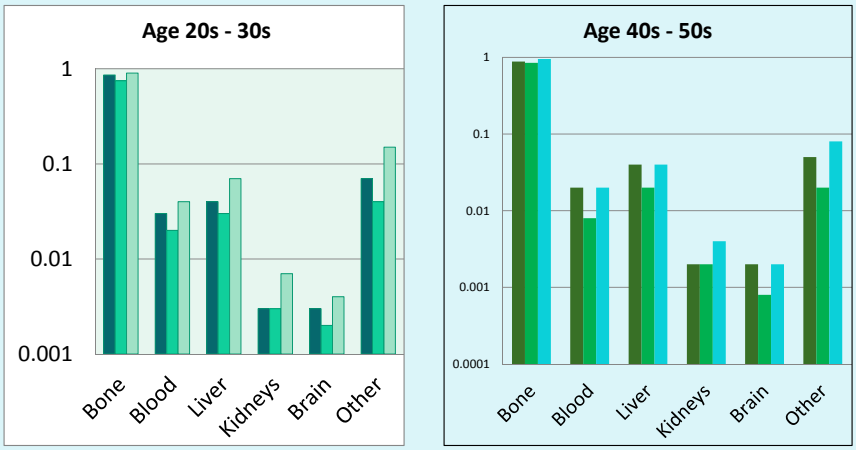
Test 5: Distributions
Autopsy Data and Model Predictions



Left – Model Prediction
Middle – Post Mortem lower bound
Right – Post Mortem upper bound

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Summary of Findings ASARCO smelter cohort

- Slope of predicted/measured BLL is near one (test for accuracy)
- Slope of model performance/length of exposure is not significantly different from zero (test for reliability/consistency)

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Summary of Findings - factory workers, smelters, patients, post mortem adults

- Slope of plasma/whole blood consistent with data from worker cohorts
- Ratios of trabecular/cortical bone are reasonable when compared to worker data
- Ratios of tissue/body burden are reasonable when compared to autopsy data

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Part D

Add exposure features

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Major Factors in Workplace Exposure

- Breathing rate
- Inhalation transfer coefficient
- Fraction of day exposed
- Air concentration

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Default Weighted Breathing Rate (BR)

BR*	m^3/hr	hours	m^3
Moderate	1.80	10	18
Light	0.84	6	5
Resting	0.35	8	3
Weighted Breathing Rate (m^3/day)			**26**

*Source – USEPA EFH 2009 also cited in OEHHA 2012

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Inhalation Transfer Coefficient (ITC)

(Pb inhaled that is transferred to blood)

Amount transferred depends on:

- Particle size distribution
- Breathing cycle and volume
- Deposition and mode of clearance
- Absorption rates

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Workplace Particle Size Studies

Park and Paik (2002) –

- 117 workers in smelting, radiator, battery, and lead-powder industries
- Average PbA 26 – 1084 µg/m^3

- Liu et al. (1996) –
  - 50 breathing zone samples in a brass foundry
  - Mean PbA 32 – 621 µg/m^3
- Spear et al. (1998) – 4 lead compounds

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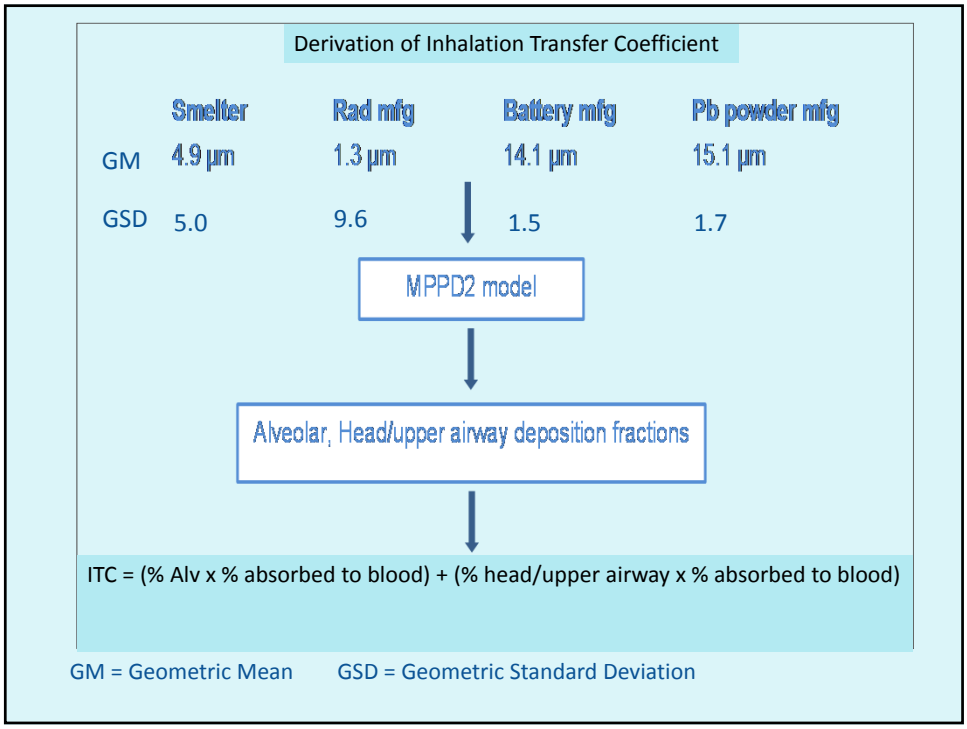

GM = Geometric Mean GSD = Geometric Standard Deviation

Deposition Analysis (Park and Paik 2002)

Region of respiratory tract	Radiator workers	Battery workers
GM (µm), GSD	1.3, 9.6	14.1, 1.5
	Percent deposited	
	Resting	
Total	74.3%	99.7%
Ciliated and head	62.6%	99.1%
Alveolar	11.7%	0.6%
	Heavy work	
Total	71.1%	99.4%
Ciliated and head	58.6%	98.8
Alveolar	12.5%	0.6%

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Transfer and Absorption of Deposited Particles

- Absorbed to blood from deep lungs –100% over 24 hours (assuming particles highly soluble)
- Moved to throat, swallowed and absorbed to blood from gut

Castellino et al. (1995), Leggett (1993)

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Inhaled Particles Absorbed to Blood from Gut in Three Environments:

AF_F = 12% ➢ 2/24 hrs x 0.12 +

AF_{FL} = 19% ➢ 10/24 hrs x 0.19 +

AF_E = 50% ➢ 10/24 hrs x 0.50 +

2/24 hrs x 0 (no Pb)

Food (3% – 20%)

Fluid alone (8% – 30%)

Empty (30% – 70%)

Gut Absorption = 30%

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ITC

Example from Battery Manufacturing, Heavy Activity:
(Alveolar x Lung Absorption) + (Ciliated & Head x Gut Absorption)
(0.6% x 100%) + (98.8% x 30%) =
30.2%

Occupational setting	TWA ITC
Secondary smelting	29%
Radiator manufacturing	31%
Battery manufacturing	29%
Lead powder manufacturing	31%

So we went with an ITC = 30% (same % as gut absorption)

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Workplace Exposure Model

- BR
  - ➢ 26 m^3/day
- ITC
  - ➢ 30%
- fraction of each day
  - ➢ 0.228

8 / 24 hours per day x

250 / 365 workdays days per year

- PbA
  - ➢ Measured 8-hour TWA (µg/m^3)

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Part E

Test Leggett+ (Core + exposure) with chamber and workplace data

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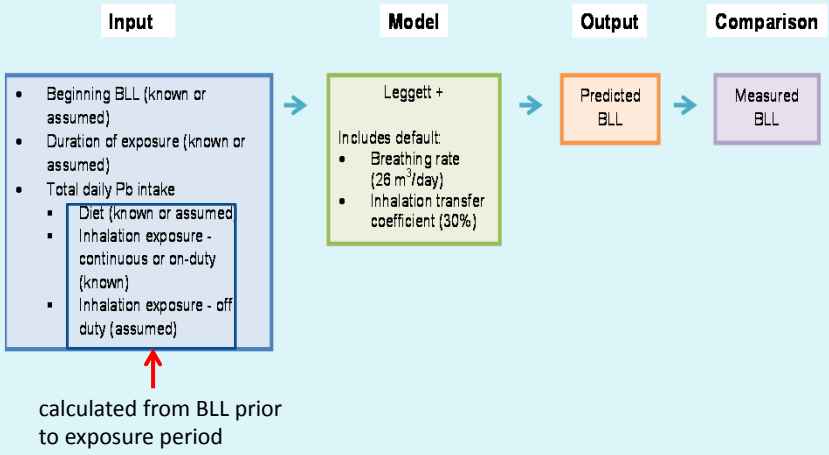
Model Testing Process



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Williams et al. (1969) Data

- 29 battery factory workers
- PbA and BLL reported for each study subject
- PbA ranged from 8 µg/m^3 (office workers)
  - 166 µg/m^3 (factory workers)
- 20-years of exposure assumed (Hodgkins et al 1992)
- Pre employment BLL of 20 µg/dL assumed (Gross 1979)

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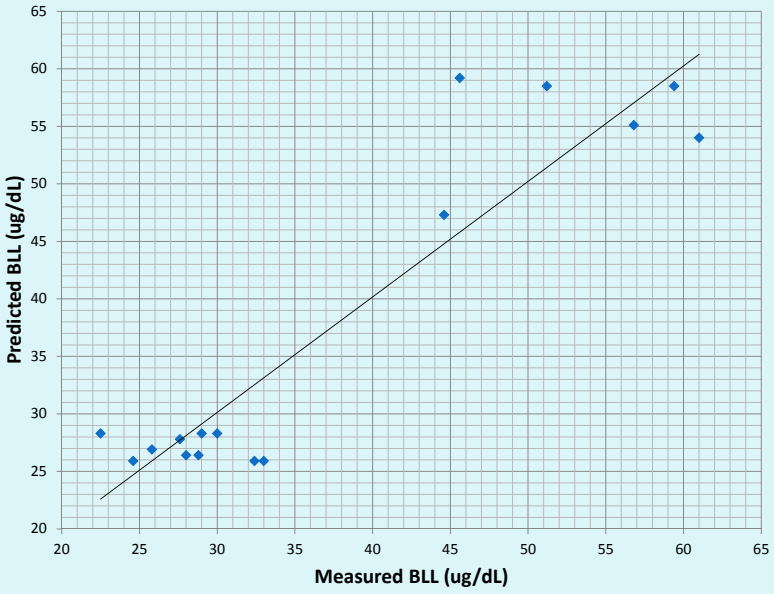
Check for Systematic Bias – Williams et al. 1969



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Griffin et al (1975) Data

- 31 healthy adult male volunteers
- Two chamber studies
  - 23-hr exposure periods over ~ 16 wks
  - Monitored oral intake of Pb
  - Maintained continuous air concentration (23-hr)
    - 10.9 µg/m^3
    - 3.2 µg/m^3
  - Measured pre experiment and periodic BLLs during exposure

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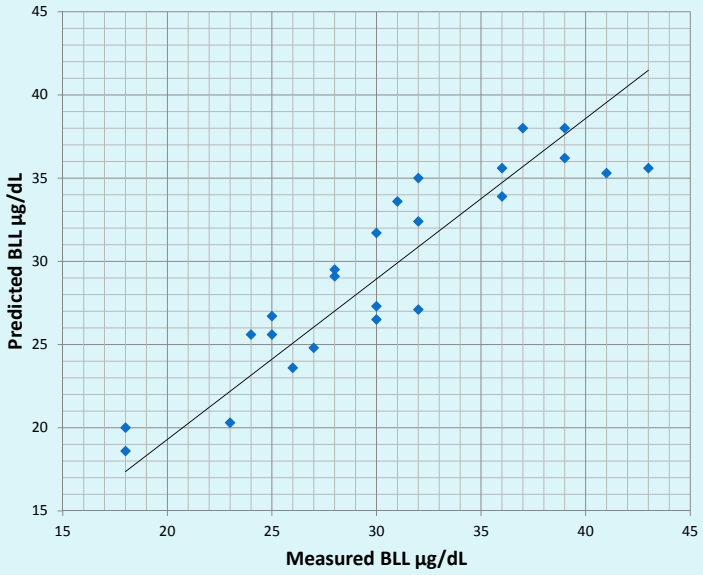
Check for Systematic Bias – Griffin et al. 1975



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Conclusions

- Evidence that Leggett+ predicts BLLs consistently and without significant bias
- Established air:blood lead relationship
- Established exposure:elimination rate relationship

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OEHHA's Tasks

- Chronic workplace exposure scenarios:
  - Task 1a: Calculate 8-hr TWA air concentrations for a range of BLLs – median worker
  - Task 2a: Estimate the length of time it takes for BLLs to decline – median worker

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Accounting for Inter-individual Variability: Geometric Standard Deviation (GSD)

- Task1b: Needed to represent the spread of a log normal distribution of BLL in a population
- Task2b: Used to represent the inter-individual variation of BLL once lead enters the body

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Accounting for Inter-individual Variability

- USEPA (Griffin 1999 analysis of two large cohorts)
  - ➢ Median GSD 1.4 – 1.7
- OEHHA analysis of experimental and worker cohorts
  - ➢ Median GSD 1.4 – 1.97

GSD, 1.6

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Task 1b: Air Blood Relationship

PbA and corresponding BLL in 95th percentile worker*

8-hr TWA PbA (µg/m3)	BLL µg/dL
0.5	5
2.1	10
3.9	15
6.0	20
10.4	30

* Assuming inter-individual variability is log-normally distributed

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Task 2b: Blood Pb Elimination Times

95th percentile worker after removal from workplace exposure*

Exposure duration	BLL at beginning of MRP (µg/dL)		
	20	**30**	40
	Months to decline to 15 µg/dL		
1 year	1.5	9.1	19.8
10 years	2.2	14.2	28.4
25 years	2.3	14.6	29.5
40 years	2.3	**15**	30.1

* Assuming inter-individual variability is log-normally distributed

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Major Limitations of Leggett+

Not examined for:

< 30 days of exposure

BLLs > 60 µg/dL

Childhood exposures

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Experts

Earlier versions of this document were reviewed by five independent peer reviewers selected for their expertise in the fields of :

- Toxicology and pharmacokinetics,
- occupational medicine,
- industrial hygiene,
- mathematics,
- physiologically-based pharmacokinetic (PBPK) modeling

Their invaluable expertise contributed to the development of the final document.

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http://oehha.ca.gov/air/exposure_assess/pbpkwrkshop2013.html

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