1 Introduction

The California Department of Public Health's Occupational Lead Poisoning Prevention Program (CDPH-OLPPP) is in the process of recommending changes to the Cal/OSHA standards relating to workplace exposures to lead. CDPH-OLPPP contracted with the California Environmental Protection Agency's (Cal/EPA) Office of Environmental Health Hazard Assessment (OEHHA) to provide physiologically-based pharmacokinetic (PBPK) modeling to support that effort. The support consists primarily of two tasks using PBPK modeling to predict:

1. the ranges of concentrations of inorganic lead in workplace air in micrograms per cubic meter ($\mu g/m^3$) that would result in blood lead levels (BLLs) of interest (5, 10, 15, 20, and 30 micrograms per deciliter [µg/dL]) for the 50^{th}, 90^{th}, and 95^{th} percentile of workers exposed to lead by inhalation.
2. the rate of BLL decline to 15 µg/dL - the level proposed by CDPH-OLPPP - following cessation of occupational lead exposure that resulted in BLLs in a range from 20 to 60 µg/dL with exposure histories from 1 to 40 years.

Completion of these tasks will supply important information supporting the consideration of a revised lead standard: Task 1 model predictions of the air concentrations resulting in certain BLLs will inform the choice of a health-based permissible exposure limit (PEL) intended to ensure that BLLs in workers would stay below a level proposed by CDPH-OLPPP. Task 2 supports the prediction of the length of time overexposed workers will have to be kept away from workplace exposure in order for their BLL to return to 15 µg/dL.

This document begins with a description of OEHHA's methods for selecting and modifying the lead model, predicting blood lead, analyzing the time for BLLs to return to 15 µg/dL from a range of higher BLLs. It is followed by a discussion of the ways OEHHA has updated the model and the limitations and uncertainties that remain. The final Section summarizes OEHHA's work and its concluding statements. Appendix A covers the review, selection, modification, and testing of the candidate model for predicting blood levels from workplace exposure to lead. Appendix B reports the procedures for

deriving an exposure module and adding it to the adjusted core model to accommodate workplace exposure conditions. This appendix then (Leggett+) reports the procedures for checking accuracy of the combined model, Leggett+. Finally, Appendix C defines acronyms that appear throughout this report.

2 Methods and Results

2.1 Selection and modification of lead model

In order to complete the two above-mentioned tasks, OEHHA evaluated the available models to determine which model best describes what is known about the complex pharmacokinetics of lead and could be most easily modified to estimate worker exposure. The results of this review are summarized below. A detailed comparison and evaluation of these multi-compartmental biokinetic models, including a summary of each model's conceptual structure, advantages, and limitations, is in Appendix A. OEHHA reviewed the following models:

- Leggett (1993) model
- O'Flaherty (1993), (1995); O'Flaherty et al. (1998); O'Flaherty (2000) model
- Bert et al. (1989) model

The U.S. Environmental Protection Agency's Adult Lead Model (U.S. EPA 2003) is a steady-state model that is unable to accommodate the time-dependent requirements of the above tasks, and was eliminated from further consideration. The All-Ages Lead Model (U.S. EPA 2005), based on the Leggett model, was also considered for this project. However, it had not been released in final form at the time of this report and was therefore not considered further.

As discussed in Appendix A, OEHHA found the Leggett model to be the best suited for use in an occupational lead exposure scenario because it:

- is sufficiently flexible to allow modeling of the required scenarios.
- has an optional algorithm allowing for nonlinear kinetics to account for red blood cell saturation at higher BLLs.

- provides a good fit to data from humans exposed to environmental lead and limited data from lead workers.

Dr. Leggett coded his published model in FORTRAN (**For**mula **Tran**slating System*)*, which is an old computer language. Our preferred platform for PBPK modeling is Matrix Laboratory™ (MATLAB) (MATLAB 2012). Therefore, OEHHA coded the Leggett model into script language used by MATLAB. We then compared the output from the original and nonlinear models recoded in MATLAB with the output generated by the author (personal communication with Dr. Leggett, 2011) to ensure that the coding was accurate.

2.2 Predicting blood lead from workplace air and vice versa (Task 1)

To support the development of a new PEL, OEHHA used the Leggett model (nonlinear version) with added exposure features to predict workplace airborne lead concentrations that would lead to BLLs of interest to CDPH-OLPPP following various simulated 40-year workplace exposures.

2.2.1 Model adjustments and assumptions

In preparation for these tasks, OEHHA modified the Leggett model by: 1) adjusting bone, urine clearance, and blood parameters to improve the fit of the model to observed data; 2) assuming a time-weighted average breathing rate of 26 m^3/day, which reflects time-weighted breathing rates based on assumed activity levels for workplace and non-workplace exposure to airborne lead; and 3) setting a default value of 30% for transfer of inhaled lead to blood ("inhalation transfer coefficient") for particles in the size range found in industrial settings. We named the modified version of the Leggett model "Leggett+", to distinguish between the original model and the version OEHHA modified. These new features are described in detail and tested in Appendices A and B. We describe the derivation of the ITC briefly here because it introduces a new approach to estimating the transfer of inhaled lead to blood from exposures in the workplace.

2.2.2 Inhalation transfer coefficient

For any given air lead concentration, the proportion of inhaled particles that deposits in the head, ciliated regions of the lung, and alveoli is determined by the size of the particles and the individual's breathing rate. Generally, smaller particles will deposit deeper in the lung while coarser particles tend to be deposited in the head and ciliated regions where they are cleared by ciliary action or secretions and swallowed. Very small particles will to a large extent be exhaled.

The chemical form of the inhaled lead affects its solubility and therefore influences absorption from the respiratory tract and gut. For purposes of developing a coefficient for the transfer of inhaled lead to blood, OEHHA chose to make the cautious assumption that lead is inhaled in a highly soluble form and that inhaled lead particles deposited in the alveolar region of the lung are absorbed to the blood within a day with essentially 100% efficiency. Particles deposited in the head and ciliated regions of the lung are cleared to the gut where they are absorbed with less efficiency.

Particle size distribution has been considered a significant influence on the percentage of inhaled lead transferred to the blood although, as will be shown later, the fraction ultimately transferred to the blood does not vary greatly by particle size distribution in the range 1 – 15 µm mass median aerodynamic diameter (MMAD). This is because the decrease in the fraction deposited deep in the lung when particle sizes are large is offset by an increase in the total head deposition fraction (larger particles are not exhaled but deposit in the head region) and subsequent swallowing and gut absorption.

In order to determine what default value to use for the percentage of inhaled lead transferred to the blood we: 1) reviewed published literature on particle size distribution in a variety of industrial workplaces with differing lead operations that generate a range of particle sizes (fine to coarse) and extracted particle MMADs; 2) estimated the proportion of inhaled lead particles that deposits in the head, ciliated regions of the lung, and the alveoli, using the reported MMADs and the Multi-path Particle Dosimetry version 2 model (MPPD2) (ARA 2012); and 3) derived a transfer factor according to Equation 1:

Eq. (1): Inhalation transfer = (alveolar deposition x lung absorption) + (ciliated and head region deposition x average gut absorption).

We calculated inhalation transfer coefficients for four different industrial settings (two that generate finer particles and two that generate coarser particles) and five activity levels (resting, sitting, light work, moderate work, heavy work). We selected 30% as our default inhalation transfer coefficient (ITC) after analyzing the data in three different ways. We calculated:

1) an ITC for each occupational setting assuming an average BR of 25 L/min during the exposure period (range 30.1% - 30.5%).
2) ITCs for all four occupational settings and all five activity levels (range 28% - 32%, midpoint 30%).
3) a time-weighted average (TWA) transfer coefficient for each occupational setting using the same activity weighting factors we used to derive a 24-hr average breathing rate (range 29% - 31%; midpoint 30%).

The reader is referred to Appendix B for a full discussion of the rationale and assumptions used for deriving the default value.

Validation of the Leggett+ Model

As mentioned previously, OEHHA adjusted the bone, urine clearance, and blood parameters in the Leggett model to improve the model fit to observed worker data. We performed multiple tests of the model to ensure that predictions in the range of BLLs of interest to CDPH-OLPPP from the adjusted model compared well to tissue lead levels measured in workers and the general population. We were able to verify that the adjusted Leggett model predicted BLLs after chronic exposures very close to measured BLLs; the model performed well regardless of job tenure; predicted levels of lead in blood, urine, and bone compared well to measured levels in chronically-exposed workers; and predicted levels of lead in all tissues compared well to measured levels in the general population.

Once OEHHA was comfortable that the core model described above was performing well, we added an exposure component (BR and ITC) to the core model so that we

could model workplace exposures based on personal breathing zone lead concentration. To test its performance, we used Leggett+ to reproduce (to the extent possible) exposure scenarios in a published field study and a chamber study, and compared model predictions to measured BLLs from each study. These comparisons show that, in the range of BLLs of interest to CDPH-OLPPP, the Leggett+ model predicts BLLs similar to observed BLLs in these studies (see Appendix B).

2.2.3 Simulating Workers' Blood Lead using Leggett+

The simulations in this report assumed a standard background BLL of 1.5 µg/dL based on the background levels observed in the U.S. general population (Schober et al. 2006). This BLL represents constant exposure to an ambient air level of 0.006 µg/m^3 (the 2004 annual average level in California [SCAQMD 2008]), along with 14.6 µg/day of background oral intake from all non-work sourcesor a combined uptake of 1.8 µg/day (see Table 1). There is uncertainty in estimating individual background intake, but the background constitutes a small fraction of total exposure for most lead workers. Inputs and assumptions used in simulating the specific exposure scenarios requested by CDPH-OLPPP are shown in Table 1.

Table 1: Parameters employed in OEHHA's application of the Leggett+ model[1]

Parameter definition	Units	Value	Reference
Age at start of exposure	years	25	Based on retirement at age 65
Exposure duration	years	40	high-end assumption
Initial blood lead concentration	µg/dL	1.5	(CDC 2009; Schober 2006)
Workplace airborne lead concentration (PbA)	µg/m^3	0.5 - 210	back calculated (Tables 2 & 3a)
Transfer fraction of inhaled lead to blood	unitless	0.30	(see Appendix B)
Breathing rate[2]	m^3/day	26	(see Appendix B)
Background lead intake after absorption	µg/day	1.8	Back-calculated to maintain BLL at 1.5 µg/dL
Yearly exposure fraction	days/year	250/365	(U.S. EPA 1991)
Body weight	kg	73	(ICRP 2002)
BLL geometric standard deviation (GSD) in U.S. population.	unitless	1.6	(U.S. EPA 2011: Griffin et al. 1999)

[1] dL, deciliter; m^3, cubic meter; µg, microgram, kg, kilogram;[2] Breathing rates for sedentary, light, and moderate activity are weighted by work and non-work time in a day and by the yearly exposure fraction. A more detailed description of our assumptions appears in the Appendices and below under the section entitled: Limitations and Uncertainty (see text).

We used the Leggett+ model and the parameters listed in Table 1 to estimate the constant air concentrations that yield BLLs in the range of 2 – 30 µg/dL for the 50th percentile worker after 40 years of workplace exposure. We calculated the 90th and 95th percentile BLLs from the 50th percentile BLLs using Equations 2 and 3 - the standard statistical formulas for determining percentiles of a lognormal distribution.

Eq. (2): BLL (50th percentile) = BLL (95th percentile) / GSD $^{1.64}$

Eq. (3): BLL (90th percentile) = BLL (50th percentile) x GSD $^{1.282}$

The results are presented in Table 2.

Table 2: Workplace air lead concentrations (PbA) and corresponding BLL[1]

8-hr TWA PbA (µg/m^3)	Predicted BLL (µg/dL)		
	50th percentile	90th percentile	95th percentile
0.5	2.3	4	**5**
0.8	2.7	**5**	6
2.1	4.6	8	**10**
2.4	**5**	9	11
2.8	5.5	**10**	12
3.9	6.9	13	**15**
5.0	8.2	**15**	18
6.0	9.3	17	**20**
6.5	**10**	18	22
7.5	11	**20**	24
10.4	14	25	**30**
11.5	**15**	27	32
12.6	16	**30**	35
17.6	**20**	37	43
25.0	25	46	54
34.0	**30**	55	65

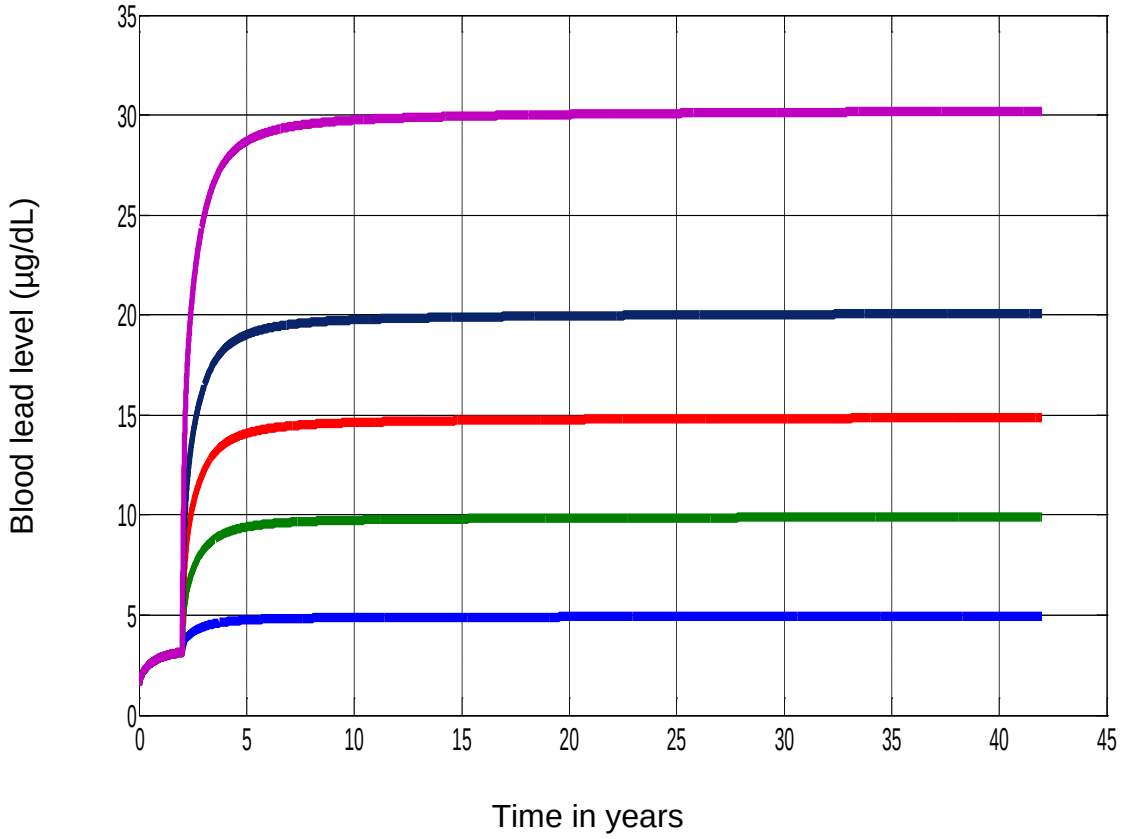
[1] BLL, blood lead level; µg/dL, microgram per cubic deciliter; assumptions as in Table 1; 8-hr TWA, eight hour time-weighted average workplace air concentration given ambient and oral background intake leading to a BLL of 1.5 µg/dL; workplace air lead concentrations (PbA) (in micrograms of lead per cubic meter of air [µg/m^3]); BLL, blood lead level; BLL values that CDPH-OLPPP asked OEHHA to model are in **bold.**

To obtain the 90th and 95th percentile BLLs, we assumed that individual variability in BLL in the U.S. general population is lognormally distributed with a GSD of 1.6. A GSD of 1.6 in the U.S. general population is suggested by Griffin et al. (1999) and has been adopted by the U.S. EPA (2011). However, before selecting a GSD of 1.6, OEHHA verified that it reasonably represents the variability in BLLs in studies of children, adult volunteers, and workers (for a description of our analysis, see section 3.2.1 Population BLL variability). As described previously, we applied the GSD to the 50th percentile BLL to derive the 90th and 95th percentile BLLs.

Figure 1 depicts the rise in BLL in the 95th percentile worker who reaches the limit BLL gradually over 40 years of workplace exposure. After achieving a stable background BLL with two years of exposure to background (non-workplace) sources of lead alone,

workplace PbA is added to background lead for 40 years. Note that BLLs climb rapidly during the first year of workplace exposure and continue to climb at a slower rate over the next two years and a very slow rate for the remaining years of exposure.

Figure 1: Rise in BLL over 40 years in the 95th percentile worker [1]



[1] BLL, blood lead level; corresponding 8-hr TWA air lead concentrations for BLLs of 5, 10, 15, 20, and 30 µg/dL are 0.5, 2.1, 3.9, 6.0, and 10.4 µg/m^3 respectively.

2.3 Time to decline to target BLL following removal from workplace exposure (Task 2)

Under the current Cal/OSHA-required medical removal protection program (MRP), whenever an employee's BLL exceeds specified limits he or she must be removed from high lead exposure work areas until his or her BLL returns to an acceptable level. Using the adjusted core model (Leggett+ without the exposure module), OEHHA simulated the time it may take to decline to a lower BLL for a range of elevated BLLs and exposure histories of interest to CDPH-OLPPP. OEHHA considered two different scenarios for

modeling time to decline. In the first scenario, workers reach the BLL limit at the end of the exposure period. In the second scenario, workers reach the BLL limit within the first year of exposure and the BLL limit is maintained for the remainder of the exposure period.

2.3.1 Scenario one: Constant PbA resulting in identified BLLs

OEHHA used Leggett+ to estimate the constant 8-hr TWA air concentration that would result in BLLs of 20, 30, 40, 50, and 60 µg/dL (referred to as "limit BLLs") at the end of the exposure period (Table 3a). Daily exposure was then reduced to background level at the end of the exposure period, and the time needed for each BLL to decline to 15 µg/dL was predicted (Table 3b).

Table 3a: Workplace air lead concentration (PbA) (µg/m^3) for different durations of exposure corresponding to the BLL reached[1]

BLL (µg/dL) reached	Exposure Period			
	1 year	10 years	25 years	40 years
20	23	18	18	18
30	44	35	34	34
40	75	60	60	59
50	125	101	100	100
60	210	169	166	166

[1]PbA, workplace air lead concentrations; BLL, blood lead level predicted by the model for the 50th percentile worker; µg/dL, microgram per deciliter

The workplace air concentrations found in Table 3a are within the range of air concentrations measured in lead-related industrial and construction workplaces (Hodgkins et al. 1992; Liu et al. 1996; Virji et al. 2009; Vork 2003).

At the end of each exposure period, the absorbed daily dose was reduced to the background level that sustained a BLL of 1.5 µg/dL, and the time needed for each BLL to decline to 15 µg/dL was predicted. The days needed to decline to 15 µg/dL for the 50th, 90th, and 95th percentile worker for each of five exposure periods appear in Table 3b. For example, 166 µg/m^3 of workplace air concentration together with background

levels of ambient air and oral sources of lead over 40 years produced a BLL of 60 µg/dL (Table 3a column 5). It took an average of 1045 days for the BLL to return to 15 µg/dL for the median worker (Table 3b column 7). We estimated the 90th and 95th percentiles from 50th percentile BLLs using Equations 2 and 3 - the standard statistical formulas for determining percentiles of a lognormal distribution.

Table 3b: Days for BLL to decline to 15 µg/dL after removal from workplace exposure (limit BLL reached at the end of exposure period)[1]

Exposure duration	Percentile	BLL at beginning of Medical Removal Protection (µg/dL)				
		20	**30**	**40**	**50**	**60**
		Days to decline to 15 µg/dL				
1 year	50th	21	128	280	435	615
	90th	38	234	511	795	1123
	95th	45	277	605	940	1329
10 years	50th	31	200	400	630	920
	90th	57	365	731	1151	1681
	95th	67	432	865	1362	1989
25 years	50th	32	207	416	670	1005
	90th	58	378	760	1224	1836
	95th	69	447	899	1448	2172
40 years	50th	32	210	425	685	1045
	90th	58	384	776	1251	1909
	95th	69	454	919	1481	2259

[1] Medical Removal Protection – Under Cal/OSHA regulations whenever an employee's BLL exceeds specified limits he or she must be removed from high lead exposure until his or her BLL returns to an acceptable level.; µg/dL, micrograms per deciliter; GSD, geometric standard deviation used to derived 90th and 95th percentile estimates = 1.6. See Table 1. OEHHA applied a standard statistical equation for a lognormal distribution of BLLs in the worker population because no measure of variability was given by (Leggett 1993) or (O'Flaherty 1993), (O'Flaherty et al. 1998), (O'Flaherty et al. 2000).

Note the substantial increase in the time it takes to decline to 15 µg/dL for higher limit BLLs. The time needed to decline to 15 µg/dL after 40 years of exposure reaching a BLL of 60 µg/dL (two half-lives) is about five times longer than the time needed to decline to 15 µg/dL after 40 years of exposure reaching a BLL of 30 µg/dL (one half-life). This striking difference is due to a greater proportion of lead accumulating in the