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

Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency (Cal/EPA)

Health Professional Summary

California Department of Public Health (CDPH)

Background

The Cal/OSHA lead standards are based on lead toxicity information that is now over 30 years old. Current scientific information clearly demonstrates harmful effects of chronic, low-level exposures to lead in adults, at levels well below those currently allowed by the standards. The CDPH Occupational Lead Poisoning Prevention Program (CDPH-OLPPP) is recommending that the allowable level of lead in the air workers breathe be lowered to reflect current medical/toxicological knowledge of lead. The modeling work performed by OEHHA provides essential information used by CDPH to make that recommendation.

In order to determine what air lead level will maintain workers' blood lead levels (BLLs) low enough to adequately protect their health, we need to characterize the relationship between the concentration of lead in the air over a 40-year working lifetime and BLLs in the range associated with harmful effects on health. Because there are no studies of workers on this relationship for the BLLs (5 – 30 micrograms of lead per deciliter of blood (µg/dL)) and timeframe (40 years) of interest, we have to use a model to predict this relationship.

A "physiologically-based pharmacokinetic (PBPK)" model is a mathematical model that represents the absorption, distribution, metabolism, and excretion of a substance in the human body. Models are made up of multiple compartments that correspond to the organs and tissues in the body with connections between the compartments via the blood. The connections between compartments follow the physiology of the body (e.g., blood exiting the gut compartment goes to the liver compartment). Mathematical equations represent the concentration of the substance in the compartment and movement between compartments. The equations are derived from experimental studies of humans and sometimes animals. Models are widely used in studying pharmaceuticals as well as toxic substances.

PBPK models for lead can be used to predict how much lead will be in the blood and other tissues after exposure to a specific concentration of airborne lead for a specific length of time. For example, a model can estimate workers' BLLs after 1 year of workplace exposure to 5 micrograms of lead per cubic meter of air (5 $\mu g/m^3$).

The existing Permissible Exposure Limit (PEL) for lead in air was based on results of pharmacokinetic modeling of lead. Since Federal OSHA established the PEL in 1978, however, additional models have been developed. These models take into account information on lead pharmacokinetics and exposure/absorption of particulate matter not available in 1978. Therefore, CDPH-OLPPP concluded that a new effort to model the relationship between BLLs and air lead levels was required. Because CDPH-OLPPP does not have expertise in PBPK modeling, we contracted with the Office of Environmental Health Hazard Assessment (OEHHA) to perform the modeling. The results of OEHHA's modeling work, together with new information on the BLLs at which health effects occur, are the basis of our recommendation to Cal/OSHA for a PEL that protects workers' health. A summary of the OEHHA modeling report is presented below.

OEHHA Modeling Report Summary

Introduction

The principal tasks CDPH-OLPPP requested OEHHA to perform were to:

1. Estimate the concentrations of lead in workplace air inhaled by workers without respiratory protection that would result in specified lead concentrations in workers' blood (5, 10, 15, 20, and 30 µg/dL) over a 40-year working lifetime. The goal of Task 1 is to inform CDPH's recommendation for a health-based PEL.
2. Estimate the time it would take for a worker's BLL to come down to 15 µg/dL from a much higher level once the worker is removed from workplace lead exposure. The goal of Task 2 is to provide CDPH with information that can be used to make

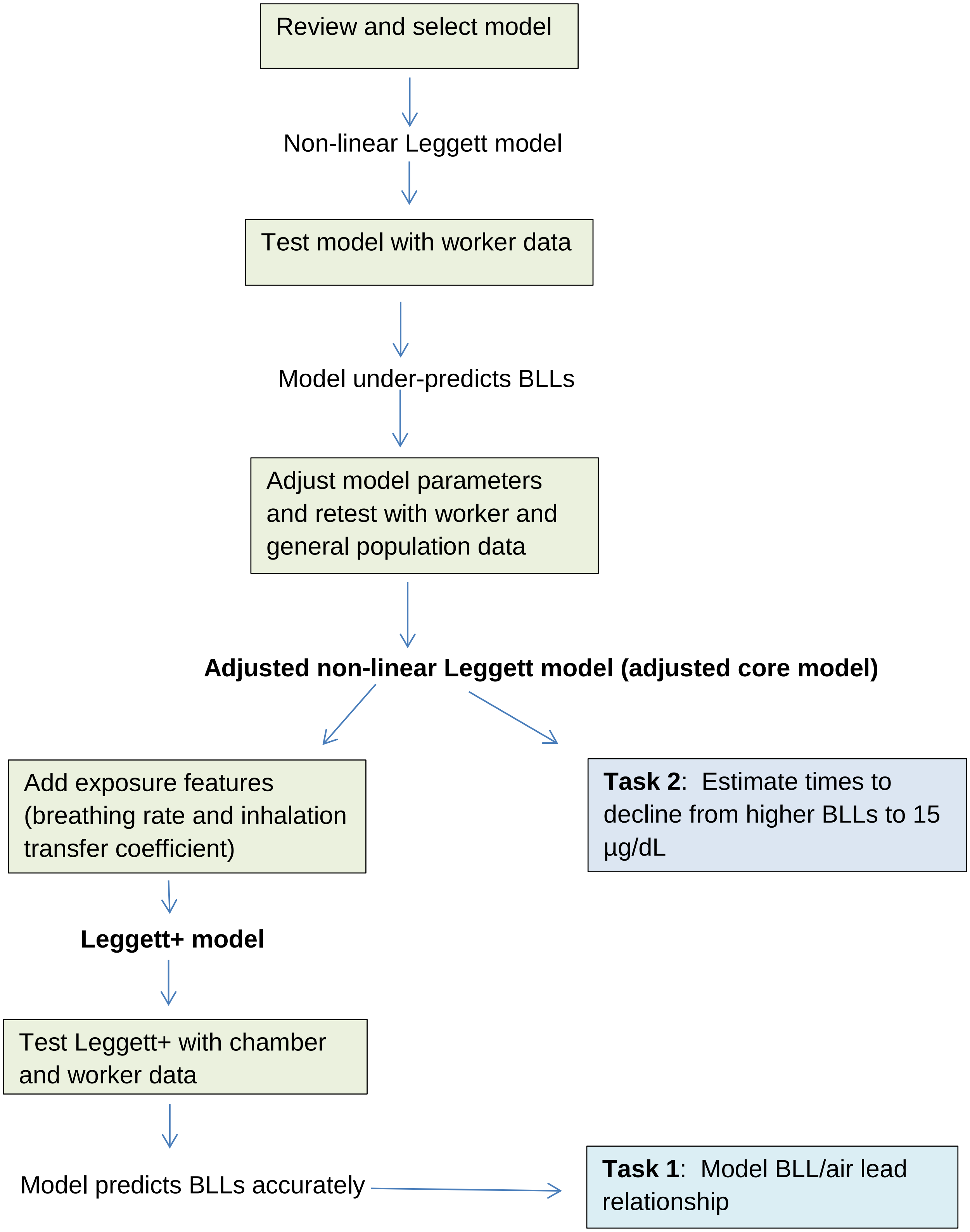
recommendations on how long workers with elevated BLLs might need to be removed from lead exposure before being returned to work.

Selecting, adjusting, and testing the model

OEHHA reviewed the advantages and limitations of several available PBPK models for lead and chose a model developed by Dr. Richard Leggett as the best for modeling worker exposure. The Leggett model is available in two versions: “linear Leggett” and “non-linear Leggett.” OEHHA chose to work with the non-linear Leggett model because it accounts for the observed non-linear relationship between BLLs and air lead levels. This non-linear relationship is not completely understood, but is likely due to saturation of red blood cells (RBCs), to which lead readily binds. A model that fails to account for this non-linear relationship can result in significant under-predictions of BLLs in workers. Leggett’s model also gave OEHHA the flexibility to adjust the model to fit occupational data as needed.

The original Leggett model was a general model not specifically designed for workplace exposure situations; therefore OEHHA needed to adjust the model and add features that simulated worker exposure. Finally, OEHHA needed to test the adjusted model to ensure that it made valid predictions before using it to complete Tasks 1 and 2. Figure 1 below lays out the steps OEHHA followed to adjust and test the model.

Figure 1: Steps to selecting, adjusting, testing, and using model



Testing model performance

OEHHA's assessment of model performance proceeded in two phases. In the first phase, OEHHA compared the BLLs measured in a large cohort of chronically-exposed smelter workers at the end of a long strike with BLLs predicted by the model. In the second phase, OEHHA made changes to the model (referred to as "calibration") to improve the fit of the model to observed worker data and tested the performance of the adjusted model.

Model calibration to observed data

OEHHA selected data from five lead worker cohorts (including smelter workers, battery workers, lead glass-based paint factory workers, and lead workers from undisclosed settings), as well as autopsy data from the general population, to check how well the non-linear Leggett model predicted blood and other tissue lead levels resulting from chronic exposures.

If the model is an accurate representation of lead pharmacokinetics in chronically exposed workers, it will: 1) predict BLLs very close to actual measured BLLs in chronically-exposed workers; 2) perform well regardless of length of exposure; and 3) predict lead levels in bone and other tissues in line with observations from chronically-exposed workers and the general population.

The initial test of the non-linear Leggett model indicated that it significantly under-predicted BLLs in the cohort of 59 smelter workers. On average the model predicted post-strike BLLs 4.1 µg/dL lower than measured BLLs. OEHHA then adjusted blood, bone, and urine clearance parameters to improve the fit of the model to the observed smelter worker data. Finally, they performed multiple tests to ensure that predictions from the adjusted model compared well to observed data from additional worker cohorts.

OEHHA's adjustments to the non-linear Leggett model significantly improved its predictive ability. The final adjusted model predicted BLLs on average 0.9 µg/dL lower than observed BLLs in the smelter cohort. OEHHA verified that the model performed well regardless of job tenure, indicating that uptake and elimination of lead in bone and other long-lived tissue compartments were preforming well. The predicted levels of lead in bone and other tissues were also reasonable when compared to observed levels in other worker cohorts and the general population. The adjusted non-linear Leggett model was now ready for completing Task 2, estimating the length of time it takes for a worker's elevated BLL to drop to a safer level.

Exposure features added to the model

As stated previously, the Leggett model was not designed to address workplace exposure situations, so OEHHA needed to add a workplace exposure component to the adjusted non-linear Leggett model. The added exposure component includes a default breathing rate and a coefficient for the fraction of inhaled lead transferred to the blood (inhalation transfer coefficient). This new model is called Leggett+.

Breathing rate

OEHHA assumed that a worker breathes in 26 cubic meters of air a day based on 10 hours of moderate activity, 6 hours of light activity, and 8 hours of resting activity daily.

Inhalation transfer coefficient (ITC)

In order to model BLLs resulting from inhalation exposure to a constant workplace air lead level, OEHHA needed to determine how much of the lead in the air a worker breathes is transferred to his or her blood. The amount transferred to blood depends on the concentration of lead in air, the solubility of the particles, and where in the respiratory tract they are deposited, which in turn depends on both particle size and breathing rate. Transfer also depends on the conditions in the gut for particles that deposit in the upper airways and are swallowed (e.g., stomach empty or full).

Generally, smaller particles will deposit deeper in the lung (alveolar region), while coarser particles tend to be deposited in the head and ciliated regions of the respiratory tract where they are cleared by ciliary action or secretions and swallowed. Very small particles are more likely to 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 determining the fraction of inhaled lead transferred 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 with 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. OEHHA assumed an average gut absorption factor of 30% based on published studies in humans of absorption during three conditions when lead enters the gut – after hours of fasting, with liquid between meals, or during meals.

Deriving the inhalation transfer coefficient

OEHHA calculated the fraction of inhaled lead transferred to blood using: 1) published particle size distribution data from a variety of workplaces with differing operations that generate a range of particle sizes (fine to coarse); and 2) a recently developed model that predicts the fraction of lead deposited in the head and lung regions based on particle size distribution, breathing rate, and other parameters.

OEHHA extracted particle size distribution data from a study of four different industries (secondary smelting, radiator manufacturing, battery manufacturing, and lead powder manufacturing). Particle size mass median aerodynamic diameters (MMADs) were 4.9, 1.3, 14.1, and 15.1 µm respectively. Next, using the Multi-path Particle Dosimetry v. 2 model (MPPD2) and the MMADs from the study, OEHHA predicted the fraction of lead that deposited in the head, upper airways (ciliated), and lower airways (alveoli) for all four occupational settings and five different activity levels (resting, sitting, light, moderate, and heavy). Finally, OEHHA calculated the percentage of inhaled lead transferred to the blood of an exposed worker according to the following equation:

Fraction of lead transferred to the blood (ITC) = (fraction deposited in the alveoli x 100% lung absorption) + (fraction deposited in the ciliated and head regions x 30% gut absorption)

Table 1 presents the ITCs for all four occupational settings and all five activity levels (range 28% – 32%, midpoint 30). Two additional analyses of the data were conducted: assuming an average breathing rate of 25 liters/minute during the exposure period; and weighting activity levels in the same way that weighting factors were used to derive a 24-hour breathing rate. These also yielded ITCs in the range of 29 – 31%. OEHHA selected 30% as the default ITC.

OEHHA data indicate that, while particle size distribution has a significant impact on the total fraction of inhaled lead deposited in the head and upper airways and on the fraction deposited in the alveoli, the fraction ultimately transferred to the blood does not vary greatly by particle size distribution. Battery and lead powder manufacturing, which have much larger particle sizes (MMAD 14.1µm; 15.1µm) had similar ITCs to smelting and radiator manufacturing, which have much smaller particle sizes (MMAD 4.9 µm; 1.3µm). The smaller fraction deposited in the alveoli when particle sizes are large, is offset by a larger fraction deposited in the head and upper airways, which is subsequently swallowed and absorbed through the gut.

Table 1*: Inhalation transfer coefficient by worker group and activity level

Activity Level	**Inhalation transfer coefficient**			
	Secondary smelting	Radiator manufacturing	Battery manufacturing	Lead powder manufacturing
Resting	29%	31%	30%	31%
Sitting	31%	32%	30%	30%
Light work	30%	31%	30%	30%
Moderate work	28%	32%	31%	30%
Heavy work	28%	30%	30%	30%

*Table B-6a in full OEHHA report

Testing performance of Leggett+ model

OEHHA tested the Leggett+ model with data from a chamber study and an occupational study that included individual level BLL and air lead exposure data. The chamber study included 24 subjects who were exposed to lead 23 hours/day (air lead concentrations for two different experiments: 3.2 µg/m^3; 10.9 µg/m^3) for about 16 weeks in a controlled exposure chamber; the occupational study included 16 chronically exposed battery plant workers (air lead concentration: 8 – 166 µg/m^3). OEHHA extracted data for each study subject on beginning BLL, ending BLL, total daily lead intake, and duration of exposure. Because not all the desired information was available in both studies, some assumptions were made. Using Leggett+, OEHHA modeled each subject’s BLL at the end of the exposure period and compared it to their measured BLL.

The average difference between subjects' measured and predicted BLLs was very small (0.83 µg/dL chamber study; -0.15 µg/dL occupational study). Further tests of model performance also indicated that there was no systematic bias in the predictions and that the model performed well regardless of exposure duration. These analyses indicated that OEHHA's default breathing rate and coefficient for the transfer of inhaled lead to blood were reasonable. Once confident that Leggett+ was performing well, OEHHA proceeded to Task 1.

Task 1 results: Air lead/BLL relationship

Using the Leggett+ model, OEHHA estimated the 8-hour time-weighted-average (TWA) air concentrations that yield BLLs in the range of 2 – 30 µg/dL for the 50th percentile worker after 40 years of workplace exposure. The 95th percentile BLLs were calculated from the 50th percentile BLLs using the standard statistical formulas for determining percentiles of a lognormal distribution (see Table 2). CDPH-OLPPP asked that OEHHA model the 95 percentile worker because the goal of CDPH-OLPPP's recommended PEL is to protect 95% of the working population.

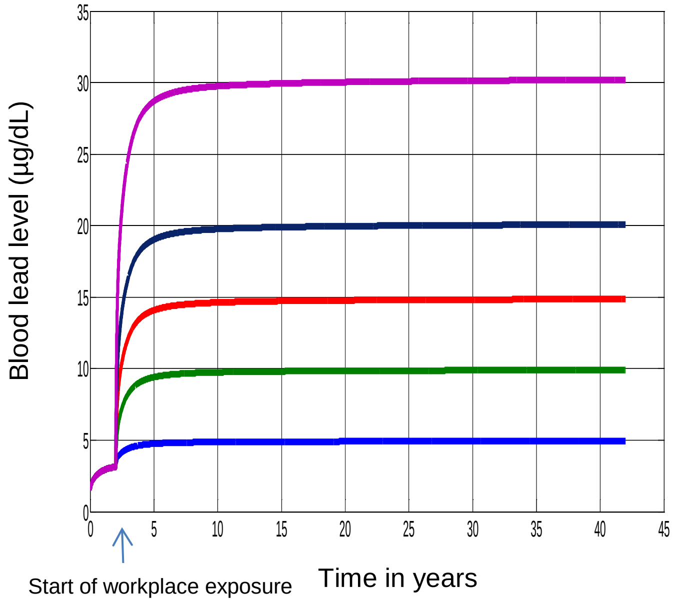
Table 2*: PbA concentrations and corresponding BLL in 95th percentile worker

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

*Excerpted from Table 2 in the full OEHHA report

Figure 2 shows that BLLs climb rapidly during the first year of ongoing workplace exposure and continue to climb at a much slower rate for the remaining 39 years of exposure. While the BLL may not be increasing substantially during these 39 years, there is a significant increase in bone lead levels; this lead in the bone is slowly released into the blood throughout a worker's lifetime.

Figure 2*: Rise in BLL in the 95th percentile worker who reaches the limit BLL over 40 years of workplace exposure to a constant 8-hr TWA air concentration[1]



*From Figure 1 in the full OEHHA report

[1] 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.

Task 2 results: BLL decline

Under the current Cal/OSHA-required medical removal protection program (MRP), whenever employees' BLLs exceed specified limits, they must be removed from high lead exposure work areas until their BLL returns to a lower level. Using the adjusted non-linear Leggett model, OEHHA simulated the time it may take to decline to a BLL of 15 µg/dL after removal from workplace exposure for a range of elevated BLLs and exposure histories. See Table 3. OEHHA used 15 µg/dL because CDPH-OLPPP recommends that a worker with an elevated BLL not return to a job with lead exposure until his or her BLL is below 15 µg/dL. For comparison, the current level at which a worker may return to lead work is 40 µg/dL.

Table 3*: Days for BLL to decline to 15 µg/dL for 95 percentile worker after removal from workplace exposure

Exposure duration	BLL at beginning of MRP (µg/dL)				
	20	30	40	50	60
	Days to decline to 15 µg/dL				
1 year	45	277	605	940	1329
10 years	67	432	865	1362	1989
25 years	69	447	899	1448	2172
40 years	69	454	919	1481	2259

*Excerpted from Table 3b of the full OEHHA report

Note the substantial increase in the time it takes to decline to 15 µg/dL from higher initial BLLs. This difference is due to a greater proportion of lead accumulating in the skeleton as BLLs rise.

Conclusion

OEHHA reviewed the available pharmacokinetic lead models and selected the non-linear Leggett model as the best for modeling worker exposure. OEHHA then adjusted the model to better fit observed data in workers and the general population, and tested the resulting adjusted model to ensure that it accurately predicted BLLs. OEHHA also added a new exposure component to the model (breathing rate and inhalation transfer coefficient) to address workplace exposure situations; they named this new model Leggett+. OEHHA compared BLLs predicted by Leggett+ to BLLs measured in a controlled chamber study and a worker field study to confirm that the added exposure component was reasonable. Finally, OEHHA proceeded to Tasks 1 (modeling the air lead/BLL relationship) and 2 (estimating BLL time to decline). The data generated by OEHHA's modeling efforts meets the goals outlined for these tasks and will be used by CDPH-OLPPP for making recommendations to Cal/OSHA for revising the lead standards in light of new information on the health effects of lead at low levels.

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The full OEHHA modeling report is available online (www.cdph.ca.gov/Programs/CCDPHP/DEODC/OHB/OLPPP/CDPH%20Document%20Library/OEHHALeadRept-Full.pdf).
A general public summary is available online (www.cdph.ca.gov/Programs/CCDPHP/DEODC/OHB/OLPPP/CDPH%20Document%20Library/OEHHALeadRept-GenPublicSummary.pdf).