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Physiologically Based Pharmacokinetic Modeling of Airborne Lead in Support of Development of an Occupational Exposure Limit for Department of Defense Workers

Lisa M. Sweeney, PhD, DABT, CHMM

UES, Inc.

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1.0 SUMMARY

The Department of Defense (DOD) commissioned the National Research Council (NRC) to assess the potential health effects associated with exposure of DOD personnel to lead (Pb) at firing ranges. In that report, NRC concluded that the current Occupational Safety and Health Administration permissible exposure limit and the blood lead levels (BLLs) on which it was based were not sufficiently protective of worker populations covered under the general industry standard. In support of future selection of an occupational exposure limit, the relationship of airborne Pb levels to BLLs is of interest to the DOD. A subset of the BLLs identified as relevant to the management of health risks of exposed workers was selected as targets for extrapolation to equivalent airborne Pb values. The existing O'Flaherty physiologically based pharmacokinetic model for Pb in humans was modified to facilitate probabilistic simulations of DOD worker population BLLs, after determining parameter distributions of model inputs that were sensitive determinants of final predicted BLLs. Under working lifetime exposure, workplace airborne Pb time-weighted average concentrations of 0.80, 3.6, 6.5, or 9.7 $\mu\text{g}/\text{m}^3$ were predicted by the model to maintain BLLs below 5, 10, 15, or 20 $\mu\text{g}/\text{dl}$, respectively, in the 95th percentile full-time Pb-exposed DOD employee.

2.0 INTRODUCTION

2.1 Background

The Department of Defense (DOD) commissioned the National Research Council (NRC) to assess the potential health effects associated with exposure of DOD personnel to lead (Pb) at firing ranges (NRC, 2013). In that report, NRC concluded that the current Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) and the blood lead levels (BLLs) on which it was based were not sufficiently protective of worker populations covered under the general industry standard DOD, which includes firing range personnel. Based on the NRC recommendations, subject matter experts across the DOD have worked and are working toward the goal of developing a new exposure limit for DOD workers exposed to airborne Pb in any workplace setting. This current stage of the work documents the prediction of airborne concentrations Pb anticipated to maintain BLLs below 5, 10, 15, or 20 $\mu\text{g}/\text{dl}$ for the vast majority of DOD workers exposed to Pb under full-time, working-lifetime occupational exposure, in the absence of significant occupational exposure by other routes.

2.2 DOD Risk Management of Pb

Having concluded that the current OSHA Pb standard was insufficient to protect workers, the NRC (2013) provided risk management options based on various expert groups' recommendations, but they did not endorse any particular strategy or definition of "elevated" BLL for workers. In response to the NRC (2013) report, the Office of the Deputy Under Secretary of Defense (Installations and Environment), now the Office of the Assistant Secretary of Defense for Energy, Installations, and the Environment (OASD-EIE), decided on a phased approach. Firstly, to revise the risk management options for measured BLLs in the DOD, followed by development of airborne exposure levels that would be predictive of BLLs of

concern (the current phase), and subsequent development of impact analyses, the selection of an occupational exposure limit (OEL), and the implementation of the OEL (Figure 1).

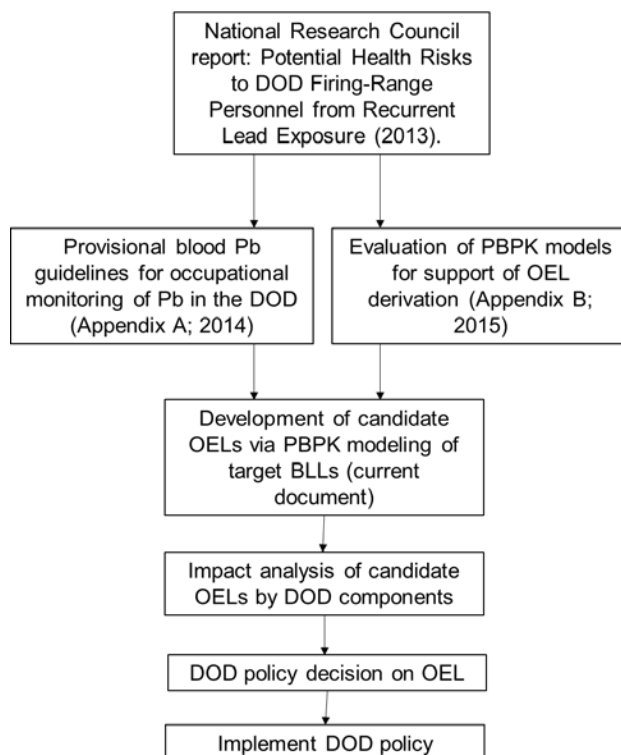


Figure 1. Outline of steps in the assessment and management of risks of airborne Pb to the health of DOD workers.

The U.S. Army Public Health Command (USAPHC) was assigned the initial task, and the multidisciplinary team of Dr. Desmond Bannon, Carol Tobias, and Alice Weber prepared a report entitled Provisional Blood Lead Guidelines for Occupational Monitoring of Lead Exposure in the DOD (USAPHC, 2014). The report was reviewed and, after revision, endorsed by relevant DOD subject matter expertise communities: the Tri Service Toxicology Consortium (TSTC), Tri Service Occupational Medicine Working Group (TSOMWG), and Tri Service Industrial Hygiene Working Group (TSIHWG). As the title indicates, the recommendations of the USAPHC report were framed as target blood levels (rather than an external concentration), consistent with approaches of other organizations (American Conference of Governmental Industrial Hygienists [ACGIH], 2006; and Centers for Disease Control and Prevention [CDC], 2012a). Based on their review of the literature on health effects of Pb at levels below 40 µg/dl, the authors urged the adoption of health based management guidelines for Pb modeled after those endorsed by the American College of Obstetrics and Gynecology (Kosnett et al., 2007). The authors recommended replacing OSHA (1978) guidelines for removal at 60 µg/dl, and return to work at BLL <40 µg/dl with more stringent guidelines, with multiple management recommendations (at BLLs above 5, 10, 20, 30, 40, and 80 µg/dl). The USAPHC document was further reviewed by OSHA and the National Institute of Occupational Safety and Health (NIOSH) prior to being finalized (predecisional) in 2016. These revisions have been

incorporated into the revised guidance for DOD occupational medical surveillance and examination (DOD, 2017), and are provided as Appendix A.

During the review of the USAPHC (2014) report, the Office of the Deputy Under Secretary of Defense initiated a concurrent effort to address aspects of monitoring and medical health surveillance programs needed to implement the USAPHC recommendations. Specifically, members of the TSOMWG and TSIHWG indicated a preference for the derivation of airborne Pb levels corresponding to the BLLs associated with the lower levels of concern identified by USAPHC. Mechanistic models for prediction of blood Pb, such as biokinetic or physiologically based pharmacokinetic (PBPK) models, can readily incorporate multiple routes of exposure (e.g., baseline dietary exposure, plus occupational inhalation exposure). Mechanistic models, in contrast to empirical or regression models, are generally more amenable to extrapolation to exposure conditions that differ from those under which the model was parameterized (U.S. Environmental Protection Agency [EPA], 2006). The Office of the Under Secretary of Defense (Installations and Environment), in consultation with representatives of the implementing Working Groups (TSOMWG and TSIHWG) and the TSTC, requested that the Naval Medical Research Unit Dayton (NAMRU Dayton) evaluate the available pharmacokinetic models which could be used to derive airborne Action Levels (AL) or OELs for Pb. Models were evaluated with respect to their ability to simulate the outcome of various human studies involving Pb exposure and also with respect to their suitability for extension to untested scenarios (e.g., present day populations with lower background levels of Pb). The two models under consideration, the O’Flaherty model and Leggett+ model, were similar in their ability to simulate the selected studies. The O’Flaherty model, however, was recommended for future application to OEL development due to being more physiologically-based and more accurately describing urinary vs. biliary clearance of Pb. That work underwent administrative review and was approved by the TSTC, TSOMWG, and TSIHWG (Sweeney, 2015). Appendix B is based on the Sweeney (2015) report.

2.3 Key Limitations of this Work

This work does not propose OELs, but because the reported extrapolations are intended to support the selection of OELs, it is appropriate to consider that OELs are intended to protect “nearly all workers” (Threshold Limit Value definition, ACGIH, 2006), but are not absolute guarantees of worker safety. The choice of benchmark, the 95th percentile predicted BLL in healthy men and women with full-time, long term exposure, is thus consistent with established occupational health practices.

This report does not specifically address criteria for enrollment in medical surveillance in which airborne Pb levels and other considerations will play a role. The information derived in this report will inform decisions for medical surveillance policy development. It is anticipated that occupational medicine physicians will consider individual-specific factors, such as known renal impairment and actual exposure frequency and intensity (both past and present), when counseling employees.

The PBPK model used does not explicitly consider national origins outside of the U.S., overseas residence, and certain hobbies (e.g., pottery, recreational shooting) that may contribute to an individual’s Pb body burden or other atypical exposures outside of employment.

The model assumes that the only quantitatively important route of occupational exposure is inhalation. This assumption excludes reliance on the candidate OEL (cOEL) for situations

where significant dermal occupational exposure may result in direct dermal uptake or indirect, oral uptake (e.g., through hand-to-mouth transfer).

Default estimates of the transfer (net absorption) fraction of inhaled Pb to blood were used to develop the DOD-wide guidance. The guidance could be modified for specific settings (e.g., shoot houses) if future investigations indicate substantial differences in fractional uptake of different forms of Pb. As noted by Vork et al. (2013), characteristics such as particle size may influence lung deposition and uptake.

3.0 METHODS

3.1 Approach

3.1.1 Overview. The process toward identifying and establishing an updated OEL for Pb has involved several steps so far, and is ongoing and potentially still evolving (Figure 1). The process of developing cOELs via PBPK modeling of BLLs designated as risk management benchmarks, shown as a single block in Figure 1, was also comprised of several steps and is delineated in Figure 2. These steps are described in the rest of this section; for some steps, greater detail is provided in Appendices. The current effort built off of the earlier DOD BLL guideline development (USAPHC, 2014) and PBPK model evaluation (Sweeney, 2015). The DOD-endorsed BLL guidelines largely echo previously published recommendations (Kosnett et al., 2007); a summary table of the health-based management guidelines as adapted for inclusion in a recent revision of the DOD Occupational Medical Examinations and Surveillance Manual (DOD, 2017) is provided as Appendix A. An abbreviated version of the model evaluation report and additional information on model parameter values are provided as Appendix B.

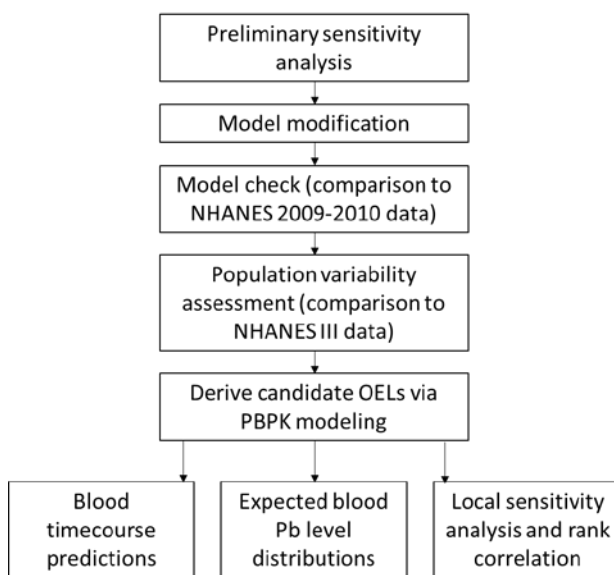


Figure 2. Steps in the process of developing candidate OELs (cOELs) for airborne Pb exposure in the DOD.

3.1.2 Transitional Activity. After conclusion of the model comparison activity, DOD subject matter experts engaged in a transitional activity intended to set the stage for the guideline derivation activities. In order to move from acceptable blood Pb levels to acceptable airborne levels, it was recognized that choices would need to be made regarding the level of protection, assumptions made regarding the exposed population, and distinctions made as to which BLLs are permissible vs. those for which management is recommended but not mandatory. Deliberations around these decisions were deemed necessary to develop consensus and buy-in from the toxicology, occupational medicine, and industrial hygiene communities prior to conducting the pharmacokinetic modeling, as well as to identify DOD-specific data that could contribute to the modeling effort. As a result of this process, the 2016 participants (1) agreed that the focus was long-term exposure to airborne Pb by inhalation; (2) recommended that airborne equivalents should be developed for two of the six BLL targets with risk management guidelines (USAPHC, 2014) and (3) endorsed the use of probabilistic modeling to determine airborne concentrations at which 95% of healthy workers with full-time occupational lead exposure starting at age 18 years will maintain BLL below the target.

The 2016 group also recommended the use of sensitivity analysis for identification of at-risk populations and to identify key parameters for probabilistic modeling (Appendix C). Participants identified the opportunity to use information from the industrial hygiene (IH) module of the Defense Occupational and Environmental and Health Readiness System (DOEHRS) to characterize the age and gender distributions of DOD workers potentially exposed to Pb. These data and their interpretation and use in population simulations are described in Appendix D.

An interim BLL-to airborne Pb extrapolation document (not provided) was prepared by NAMRU-Dayton in 2017. That 2017 draft document was distributed via the subject matter expert groups (TSTC, TSIHWG, and TSOMWG) to a wider DOD audience than the group that participated in the 2016 transitional activities. On the whole, the approach endorsed by the 2016 group was affirmed by the 2017-2018 reviewers. In adjudicating the comments, OASD-EIE agreed with recommendations for extrapolation of additional BLLs to airborne equivalents, minor changes in assumptions regarding the working lifetime, hours worked per year, and an update of the assumptions regarding background ambient air concentrations of Pb in the U.S. (described in Appendix D). The content of this report reflects implementation of OASD-EIE's specifications of June 2018.

3.1.3 Preliminary Sensitivity Analysis. A sensitivity analysis of the original O'Flaherty (1993) PBPK model was conducted to identify parameters that have a significant influence on the model predictions of interest. To the extent that model parameters are measurable in individuals, sensitivity analyses may aid in the identification of at-risk individuals. Blood Pb concentrations in men and women with background and occupational exposure were considered to be of interest. In particular, the analysis considered sensitivity of predicted blood concentrations for men and women born in 1952, 1966 (men), 1968 (women), and 1999 with only background exposures to Pb or with additional occupational exposures starting at age 18 years old and generally continuing for 45 years. Additional detail may be found in Appendix C, in the section "Sensitivity Analysis." Parameters pertaining to historical exposure levels of Pb via food and air were found to influence predicted values of current or future BLL. Similarly, BLL was found to be sensitive to inhalation rate and fractional uptake from the lungs. BLL was found to be sensitive to parameters contributing to the computation of glomerular filtration rate (GFR), a key

parameter in calculating the excretion of Pb. BLL was sensitive to parameters that determine the amount of Pb bound to red blood cells (RBC), specifically the hematocrit, binding affinity, and binding capacity. Due to their interrelated nature, the red blood cell parameters were carried forward for further scrutiny and consideration for potential inclusion in the Monte Carlo analysis and the variability of these parameters were considered as a group. Sensitivity of BLL to body weight (adult and child values, and curve-fitting parameters for age-dependence of body weight) was generally modest (absolute value of the normalized sensitivity coefficient $|NSC| < 0.3$), with greater influence for later birth years, and thus unlikely to be a key determinant of BLLs in 95th percentile individuals and was not carried forward for parameter refinement.

3.1.4 Model Modification and Parameter Value Refinement. Model modifications encompassed those structural changes necessary to conduct Monte Carlo simulations for the populations of interest (e.g., a mixed gender population), scenarios of interest (e.g., blood concentrations in a mixed age population on a single, specific date, vs. blood concentrations at the ends of all the individuals' working lifetimes) and to accommodate changes in how certain parameters (e.g., age-dependent inhalation rate) were calculated within the model. In addition, the variability of key model parameters needed to be considered in order to parameterize the Monte Carlo analysis inputs.

Age- and gender-specific data for the inhalation rate (U.S. EPA, 2011) were used to parameterize 6th order, age dependent polynomial equations for the central tendency rate. Interindividual variability in the inhalation rate (also based on U.S. EPA, 2011) was found to be similar across ages and for both genders. RBC binding (affinity and capacity) for Pb and hematocrit were considered together, and the DeSilva (1981) data on plasma/red blood cell concentration ratios of Pb in 103 human subjects were selected as appropriate surrogates for the combined variability of these parameters. DOEHRS data were used to determine the gender and age distributions of the assumed worker population. Estimates of background air levels of Pb were updated to incorporate changes since the publication of the O'Flaherty model. Updates to the description of background air concentrations of Pb were made based on data in U.S. EPA (2013). The development of the updated, refined parameter values was described in greater detail in Appendix C (section on "Parameter Variability") and Appendix D ("Development and refinement of parameter inputs"). The resulting version of the model is referred to as the DOD-O'Flaherty model to distinguish it from earlier versions (Beck et al., 2001; Fleming et al., 1999; Garcia et al., 2013; O'Flaherty 1993, 1995, 1998, 2000; O'Flaherty et al., 1998; Polák et al., 1996).

3.1.5 Model Check. As a check on the model predictions, the DOD-O'Flaherty model's deterministic (central tendency) gender- and age-specific BLL predictions were compared to measurements from the 2009-2010 National Health and Nutrition Examination Survey (NHANES 2009-2010; CDC, 2012b). The purpose of this comparison was to compare the model, which was developed based on studies with higher BLLs (e.g., typically 10 to 80 µg/dl), performed adequately at or below the lower end of the range of the DOD BLL management guidelines (~5 µg/dl). With the exception of the updated inhalation rates (see Appendix D), all physiological, biochemical, and anatomical parameters and exposure assumptions (e.g., media concentrations and Pb ingestion via food) were the same as in O'Flaherty (1993). Sample weights were used to derive a population-weighted median BLL for each one-year age bin per gender. The use of sample weights is necessary to derive a representative national estimate of

central tendency, due to oversampling of Hispanic persons (any race), non-Hispanic black persons, those over 80 years old, and people below 130% of the federal poverty level (Mirel et al., 2013). The quality of model predictions was evaluated based on the direction and magnitude (fold-difference) of error. For the current purpose, a model that errs on the side of overpredicting blood Pb would be preferred to one that underpredicts blood Pb levels, in order to be health protective. The International Programme on Chemical Safety (IPCS, 2010), has recommended that, for a model to be used in risk assessment, the model predictions should be, on average, within a factor of two of the experimental data.

3.1.6 Population Variability Assessment. Derivation of estimates of variability for key physiological and biochemical parameters from data in the literature was discussed in Appendix C. National population variability in exposure was derived based on comparisons of model simulations to population geometric standard deviation (GSD) of BLL determined by Maddaloni et al. (2005). For the Pb model simulations in this report, NHANES III BLLs were assumed to be measured in 1990. National census information on numbers of adults of different ages in 1990 were available in 5-year age bins (Byerly and Deardorff, 1995), so the population age distribution simulation was based on 20- to 49-year old women. Considering that age frequency was similar within this range, the slight discrepancy in matching ages was unlikely to have affected the GSD predictions. Parameterization of this age distribution is discussed in Appendix D. Age, physiological and biochemical variability among individuals incorporated into the model (see Appendix C) was insufficient to account for the observed variability in NHANES III BLLs, so these data were used to parameterize an estimate of the standard deviation (SD) for population exposure modifier (EXPOSMOD) variability, discussed in greater detail under Results and Discussion—Population exposure variability assessment.

3.1.7 Derivation of Workplace Airborne Pb-Working Lifetime Population BLL Relationships. Model simulations of a standard exposure scenario were coupled with descriptions of the populations in the updated PBPK model. The population description involved specifying the gender make up (fraction males vs. fraction females), age distributions, and incorporating parameter variability descriptions for key parameters (i.e., inhalation rate, glomerular filtration rate, and RBC binding) for a Monte Carlo simulation. Repeated Monte Carlo simulations were executed to determine the number simulated individuals necessary to reliably characterize the target metric (95th percentile value of the final predicted BLL) for the population, to test the sensitivity of the predictions to the starting “seed” values for random number generation, and to calibrate what airborne Pb concentration would yield 95th percentile final BLL values equal to the target value (5, 10, 15, or 20 µg/dl) for a given set of seed values. These considerations are discussed in greater detail in the following paragraphs.

3.1.7.1 Exposure Scenario. Workers were assumed to be exposed to a given workplace Pb concentration from age 18 until age 63 years or until January 1, 2018 (for workers with a year of birth prior to 1955). This exposure scenario assumes a working lifetime of at least 45 years (value recommended by OSHA, 2011), which is a conservative assumption. For workers already exceeding age 63 years (18 + 45), further increases in BLL would be expected to be minimal, based on inspection of the projected BLL time course (presented in Results—Characterization of DOD Worker Populations Exposed to Pb at the Candidate OELs). The cOELs for a targeted 95th percentile BLL were derived based on calibration of an additional ambient exposure

concentration (CAMB) that, for the sake of simplicity in simulation, workers were assumed to be exposed to by inhalation for 24 h/day, 365 days per year. To convert the continuous CAMB to the discontinuous workplace equivalent, assumptions about the number of working hours are required. OSHA (2011) specifies that 40 h per week for 48 weeks per year is their standard assumption. Adopting those assumptions for the current analysis results in an adjustment factor of $(24 \text{ h/day} \times 365 \text{ days}) / (8 \text{ hrs/day} \times 5 \text{ days/week} \times 48 \text{ weeks}) = 4.56$ to the acceptable concentration. The assumption that the workplace exposure occurs in addition to exposures in environmental air (CAIR in the model), results in workplace equivalent airborne concentration being computed as $(\text{acceptable CAMB}) \times 4.56 + \text{CAIR}$.

Pre-1975, the background air concentration (CAIR1) was assumed to be 0.002 mg/m^3 ($2 \text{ }\mu\text{g/m}^3$); after 1975, background concentrations were assumed to decline toward current levels (CAIR2) (O'Flaherty, 1993). In the O'Flaherty (1993) model, the current CAIR (CAIR2) was assumed to be 0.00015 mg/m^3 ($0.15 \text{ }\mu\text{g/m}^3$), the same as the prevailing primary National Ambient Air Quality Standard (U.S. EPA, 2016). In 50 counties across the U.S. in 2008-2010, the median monthly average air Pb concentration at source-oriented Pb monitors was $0.063 \text{ }\mu\text{g/m}^3$. In the same period, non-source oriented monitors in 47 U.S. counties had no monthly exceedances of the standard, and the median monthly average concentration was $0.010 \text{ }\mu\text{g/m}^3$ (U.S. EPA, 2013, Tables 2-5 and 2-6). For the current modeling effort, the description of background air concentrations was updated to reflect median Pb concentration data available for 1980 and 1990-2010 (U.S. EPA, 2013). On the basis of the U.S. EPA (2013) data, the value of CAIR2 was revised to 0.000045 mg/m^3 ($0.045 \text{ }\mu\text{g/m}^3$) and the shape of curve describing the transition from pre-1975 values to current levels was modified, as detailed in Appendix D.

3.1.7.2 Description of Exposed Population. The DOD working population exposed to Pb was assumed to be predominantly male (8% female vs. 92% male), based on 2016 data from DOEHRs. Birth year distributions for the population were also derived from the DOEHRs data. The DOEHRs data were considered to be a good, overall representation of the Pb-exposed population in DOD, but because the data were likely to have been incomplete, the age and sex distributions were selected using health-protective assumptions (see Appendix D for details).

3.1.7.3 Candidate OEL (cOEL) Determination via Monte Carlo Simulation. Monte Carlo simulations were conducted with four sets of random seed values for the variable parameters. The use of multiple randomly generated starting values is a precaution against the possibility of distorted results from use of an anomalously generated set of parameter value distributions. For the first set of random seed values, CAMB (determined to two significant digits) was varied until the 95th percentile value of the final blood Pb concentrations (PBBfinal) of 2000 simulated workers matched the target BLL (5, 10, 15 or 20 $\mu\text{g/dl}$), to identify a tentative airborne-equivalent value for CAMB (to be converted to a cOEL). For the remaining three sets of random seed values, the tentatively acceptable value of CAMB was used as the starting value, and the 95th percentile PBBfinal determined with the new seed values. The random seed set that produced the highest 95th percentile PBBfinal with CAMB set to the tentatively acceptable airborne-equivalent value (from seed set 1) was used in the final determination of acceptable CAMB, and from that, the airborne equivalent adjusted to workplace exposure rather than continuous exposure (1920 h/year vs. 8760 h/year).

3.1.8 Characterization of DOD Worker Populations Exposed to Pb at Specified Workplace Levels of Airborne Pb.

3.1.8.1 Working Lifetime Timecourse of Blood Lead Level. Simulations were conducted for men and women with birth years of 1955, 1967, and 2000 with background exposure only (controls), or background and workplace exposure. Simulations were run both deterministically (i.e., one central tendency value for parameters such as breathing rate) and probabilistically (Monte Carlo simulation of 2000 individuals with parameter values generated using random variables). Median values from Monte Carlo simulations were observed to be similar to deterministic simulations, so only deterministic results were reported.

3.1.8.2 Current BLL Distributions. Predictions of BLL as of January 1, 2018 were made for simulated populations of 2000 workers exposed at the cOELs throughout their adult working lifetimes or controls of the same age and gender. The interindividual variability of the inhalation rate, glomerular filtration rate, RBC binding affinity, and background exposure were incorporated as described in Appendix C. Age distributions, numbers of men vs. women, and changes in background airborne Pb were incorporated as described in Appendix D. Other parameter values were held constant and equal to the values in the original O’Flaherty models (e.g., O’Flaherty 1993). Simulations were conducted for the entire working population (men and women combined). It should be noted that these “current” simulations for the full working population differ from those used to derive the acceptable workplace equivalents, in that the simulations for the acceptable workplace equivalent project final BLLs for the conclusion of the working lifetime of those currently under age 63 years, rather than estimate current BLL.

3.1.9 Sensitivity Analysis. Sensitivity analyses of DOD-O’Flaherty PBPK model outputs were conducted using two approaches: local sensitivity analysis (deterministic model implementation) and rank correlation (Monte Carlo population simulations). Additionally, the impact of a dichotomous variable (gender) was assessed by inspection of the simulations producing the highest final blood Pb concentrations.

3.1.9.1 Local Sensitivity Analysis. Local sensitivity analyses of the final DOD-O’Flaherty model were conducted in essentially the same manner as the preliminary sensitivity analyses. Sensitivity analyses for calendar year-specific contributions to exposure (e.g., environmental air concentrations and food intake) and for coefficients in computed, age-dependent parameter values (e.g., glomerular filtration and respiration), were limited to proportionality constants introduced to describe age- or calendar year-independent variability. Changes in the final predicted value of the BLL at age 63 years for controls (background exposure) and after a working lifetime exposure to inhaled Pb that result from small changes in input parameters (~1 percent) were assessed for men and women with birth years of 1955, 1967, and 2000. Changes were normalized to the baseline response and baseline value of the input parameter being tested.

3.1.9.2 Rank Correlation. Rank correlation analysis was applied to the Monte Carlo population simulations for cOEL derivation. Compared to a local analysis, the rank correlation approach provides a broader assessment of the impact of input parameter values on output, takes into account interactions among parameters across the full range of predictions (rather than only in the region of central tendency), and the impact of parameter variability plays a role in the overall results.

The simulation inputs and model output (final value of BLL) were converted to ranks (i.e., the rank of the lowest value = 2000; rank of the highest value = 1). Rank correlation is preferable to value correlation when the variables have different distribution shapes. The contribution of a given parameter to the variance of the forecast value (output) is determined by squaring the correlation coefficients of the inputs and normalizing them to a total contribution of 100 percent (Decisioneering, 1996).

3.2 PBPK Model Simulations

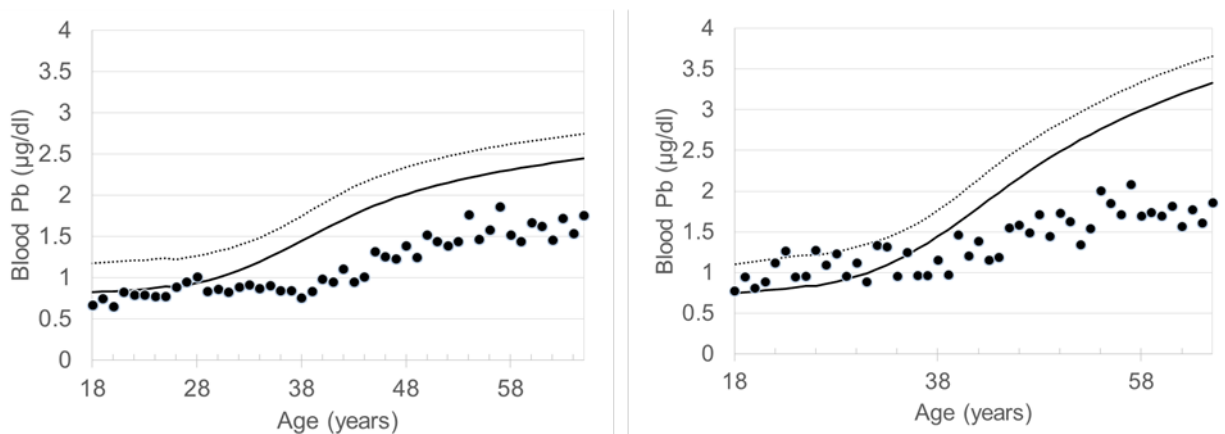
All simulations (except some discussed in Appendix B) were conducted using acslX (AEGIS Technologies). Version 3.0.2.1 of acslX was used for simulations presented in Appendix B and C). Simulations presented in the main “Results” section were conducted using Version 3.1.5.1. Final sensitivity analyses in acslX were conducted by increasing each tested parameter value by 1%. Monte Carlo simulations were conducted using the Monte Carlo Analysis File building feature in the acslX Optimization and Statistics package. Test simulations of 400-10,000 trials were conducted with the PBPK model, and it was found that the 95th percentile output predictions were stable for simulations of 1000, 2000, or 5,000 trials, so the Monte Carlo simulations presented herein were based on 2000 trials per run. For some tasks, multiple runs (referred to as Runs 1-4) of the Monte Carlo simulations were conducted with varying seed values. Run 1 would be simulated with the default random seeds (value 1 = 1234567890, value 2 = 123456789), Run 2 with value 1=1233567890 and value 2 = 123356789, Run 3 with value 1 = 1244567890 and value 2 = 124456789, and Run 4 with value 1 = 1243567890 and value 2 = 124356789. Inspection of parameter distribution ranks generated with these seed values indicated that early trials were randomly distributed (i.e., there was no need to discard early trials as a burn-in).

4.0 RESULTS AND DISCUSSION

4.1 Model Check

To test the predictive ability of the DOD-O’Flaherty model, simulations using central tendency model parameter values were compared to adult blood Pb measurements from NHANES 2009-2010 (CDC, 2012b). The model captured the observed elevation of BLL in men vs. women and older vs. younger adults. The model was found to have acceptable accuracy (acceptable accuracy being that model predictions are, on average within a factor of two of the data, per IPCS, 2010) (**Figure 3**). For all ages and both sexes combined, the model was, on average, within 40% of the central tendency values derived from the NHANES data. When considered by sex, model accuracy was similar for men and women (on average within 38% for women, within 42% for men). The experimental data for men, however, show a greater degree of scatter than the data for women, likely due to smaller group sizes for men. For both sexes, blood Pb was more accurately predicted at younger ages than older ages. For 18-33 year old adults, predictions for men and women were on average within 23 and 14% of measured values, respectively. In the 34-49 year old range, average accuracy was within 37% (men) and 60% (women). In the 50-65 year old range, average accuracy was within 70% (men) and 45% (women). Consistent underprediction of BLL by the updated model was noted for younger men in the 2009-2010 NHANES (~0.3 µg/dl for men ages 22-28 at the time, with years of birth

~1981 to 1987), a highly represented group in the DOD (median birth years for Pb-exposed DOD Pb workers were in this range in 2016; see Appendix D, Table D2). However, the degree of underprediction is low (a differential of 0.3 $\mu\text{g/dl}$), compared to a differential of ~3.9 $\mu\text{g/dl}$ between the median individual in that age group (BLL ~ 1.1 $\mu\text{g/dl}$) and the lowest BLL of potential concern (5 $\mu\text{g/dl}$) for the 95th percentile individual. Underprediction might be a greater concern if it occurred differentially in a more susceptible group, such as older men and women whose greater historical background exposure puts them at greater risk than their younger coworkers.



Lines: simulations with the DOD-O'Flaherty model; solid lines: simulations using updated background air Pb concentrations (see Appendix D), dotted line: simulations using updated physiological parameters but original O'Flaherty (1993) background air Pb concentrations. Symbols: weighted median from NHANES 2009-2010 data (CDC, 2012b); $n = 63$ to 135 (median = 94.5) female participants per one-year age bin from age 18 to 65 years; $n = 25$ to 79 (median = 44) male participants per one-year age bin from age 18 to 65 years.

Figure 3. Adult blood Pb levels in NHANES 2009-2010 for women (left) and men (right) ages 18-65 years old.

4.2 Population Exposure Variability Assessment

Using data from NHANES III (conducted in 1988-1994), Maddaloni et al. (2005) computed that the variability (GSD) of blood Pb levels for women ages 17-45 years (all ethnicities, $n = 5016$) was a factor of 2.11. Using age distributions for US women ages 20-49 years in 1990 (Byerly and Deardorff, 1995), four Monte Carlo runs with no exposure variability—only physiological and biochemical variability—were conducted simulating background exposure using the DOD-O'Flaherty model. For the four different seed values, the computed GSD ranged from 1.69 to 1.72 with a mean of 1.71, below that observed in the NHANES III data. A lognormal distribution for EXPOSMOD (a modifier on estimates of historical background exposure to Pb) was assumed (truncated at 0.01 and 1×10^{300}), and a SD for EXPOSMOD was derived through iterative Monte Carlo simulations with various estimates of the SD for EXPOSMOD. After each run, the GSD of the model output (estimated BLL in 1990 for 2000 individuals) was compared to the value computed by Maddaloni et al. (2005), and a refined estimate of the EXPOSMOD SD was entered as a model input, until acceptable agreement was achieved. In runs with the 4 different sets of seed values, the estimates of the SD for EXPOSMOD were 0.57, 0.54, 0.57, and 0.55. The average of these four values (rounded to

two significant figures) of 0.56 was used in subsequent simulations. Background variability for women with an equivalent age distribution, but for 2018 rather than 1990, was computed to assess the impact of changing background exposure and BLL level. The computed GSDs without consideration of EXPOSMOD variability were 1% lower for 2018 as compared to 1990, indicating that differences in central tendency values of background exposure had minimal interaction with variability attributable to physiological and biochemical parameters.

4.3 Candidate OEL Derivation

The cOEL is the time-weighted average (TWA) workplace air concentration that would result in an end-of-career BLL at the target value (5, 10, 15 or 20 µg/dl) for the 95th percentile Pb-exposed DOD worker with working-lifetime exposure. Working lifetime exposure is assumed to start at age 18 years old and to last for at least 45 years (longer if necessary to be consistent with the 2016 database of DOD Pb workers years of birth). Employees were assumed to work in an elevated Pb environment for 1920 h/year. For each Monte Carlo run, 2000 trials (individuals) were simulated. Using the first one of four sets of random seeds for the Monte Carlo simulations, a tentative estimate of the cOEL was derived for a 95th percentile target of 10 µg/dl. In simulations using that tentative cOEL with the second, third, and fourth sets of Monte Carlo seeds, 95th percentile estimates of PBB_{final} were 10.4, 10.6, and 10.2 µg/dl, respectively. In order to derive a health-protective cOELs, the third set of random seeds was used to calibrate values for additional continuous exposure (24 hrs/day, every day) for each of the four end-of-career BLL targets. Under working lifetime exposure, workplace TWA airborne concentrations of 0.80, 3.6, 6.5, or 9.7 µg/m³ are expected to maintain BLLs below 5, 10, 15, or 20 µg/dl, respectively, in the 95th percentile DOD Pb employee in 2018 and into the future. The candidate guidelines are reported here as two significant figures, rounded after conversion of the model input values (CAMB = 0.000165, 0.000790, 0.00142, and 0.00212 mg/m³, as TWA continuous exposure in excess of background, and CAIR2 = 0.000045 mg/m³ background exposure) to equivalent values for the occupational environment. For implementation, the recommendation would be to round to one significant digit, for a TWA OEL of 0.8, 4, 7, or 10 µg/m³. While the relationship between the cOELs and target 95th percentile BLLs is approximately linear (cOEL = $0.592 \times \text{BLL} - 2.25$, where cOEL is in units of µg/m³ and BLL is the target 95th percentile blood Pb concentration in µg/dl; $r^2 = 0.99$), use of this formula is not recommended even in the 5-20 µg/dl range as minor deviations from linearity may result in differences from the derived cOELs.

Based on the California EPA Office of Environmental Health Hazard Assessment (OEHHA's) simulations using the Leggett+ model (Vork et al., 2013), the California Department of Health (CDPH) recommended PELs for Pb to the California Department of Industrial Relations Division of Occupational Safety (Cal OSHA) (Billingsley, 2013). CDPH's recommendations were that at PELs of 0.5 and 2.1 µg/m³, BLLs would be less than 5 and 10 µg/dl, respectively, for 95% of workers exposed over a 40-year working life time. The CDPH BLL targets equate to the BLLs used to derive the lower two DOD cOELs, but with lower recommended occupational exposure levels corresponding to the targets.

4.4 Characterization of DOD Worker Populations Exposed to Pb at the cOELs

Occupational health management needs to consider both the broader work population as a whole and individual factors, such as potential past exposures. To generate sample illustrations, simulations were conducted for birth years of 1955, 1967, and 2000 with background exposure only (controls), or background and workplace exposure.

4.4.1 Working Lifetime Timecourse of Blood Lead Level. Occupational health management needs to consider both the broader work population as a whole and individual factors, such as potential past exposures. To generate sample illustrations, simulations were conducted for birth years of 1955, 1967, and 2000 with background exposure only (controls), or background and workplace exposure. The shape of the predicted timecourse for blood Pb depended on the birth year used in the simulation (Figure 4). The blood Pb levels of men born in 1955 were predicted to have risen in early adulthood of both controls and workers, due to prevailing environmental conditions (e.g., use of leaded gasoline). In contrast, median BLL of men born in 1967 was predicted to increase modestly in adulthood only for higher exposures and to decline throughout adulthood for most, with more rapid declines in controls vs. workers. Control men born in 2000 were predicted to have roughly constant BLLs throughout adulthood, while male Pb workers born in 2000 would have increasing BLLs. The central tendency BLLs of male Pb workers born in 2000 were predicted to be 0.73 µg/dl at entry into the workforce and 1.6, 4.2, 6.8 or 9.6 µg/dl at retirement at age 63 years for TWA workplace exposures of 0.8, 3.6, 6.5, or 9.7 µg/m³. For the 9.7 µg/m³ exposure, 50% of that increase was predicted to be achieved within 29 weeks and 90% of the increase achieved in 20 years (median BLL at age 40 = 3.8 µg/dl).

4.4.2 Current BLL Distributions. Cumulative frequencies of predicted January 1, 2018 BLL for the DOD working population (or same-age and same-gender controls) were generated using Monte Carlo simulations (Figure 5) assuming lifetime occupational exposures at the cOELs. Median and 95th percentile BLL predictions and predicted numbers of workers exposed at the cOEL or controls exceeding the benchmark values were summarized in Table 1.

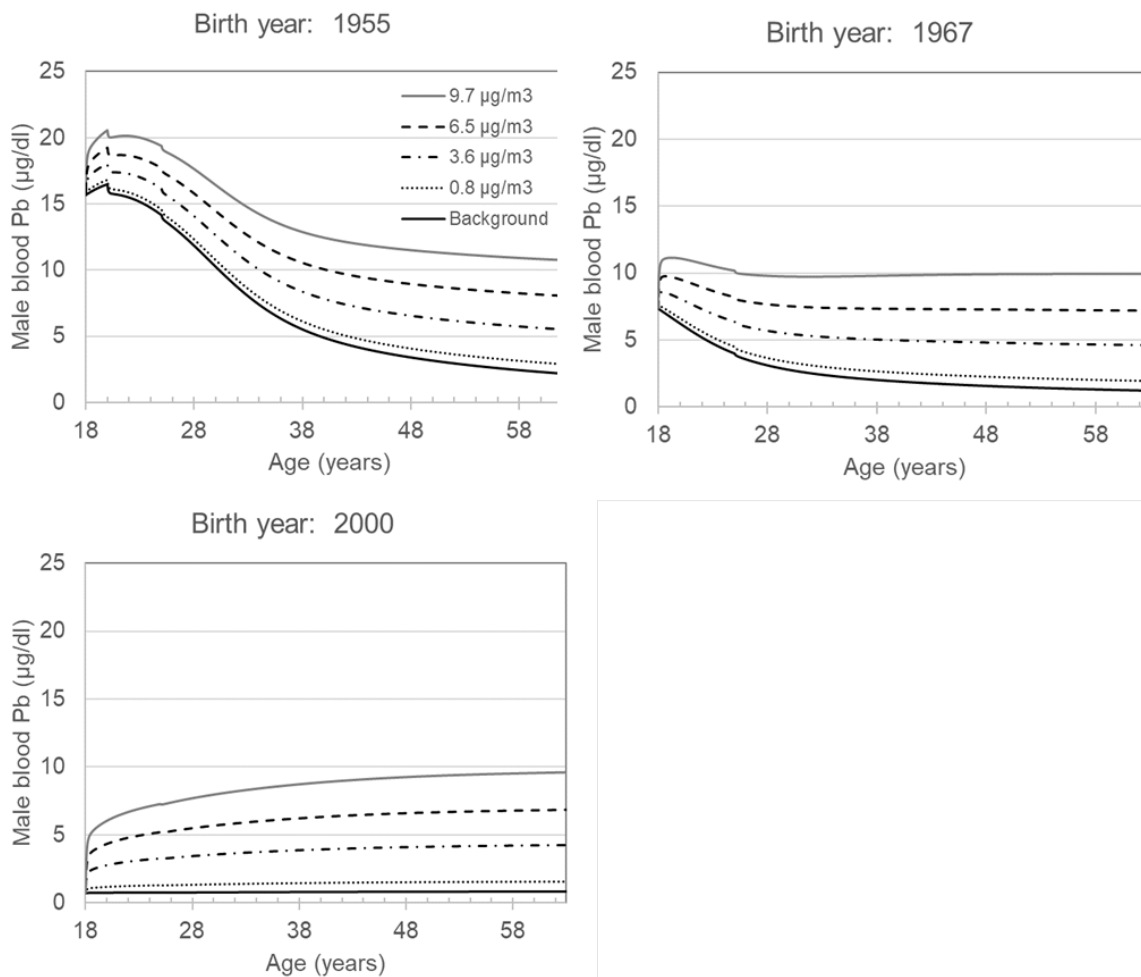
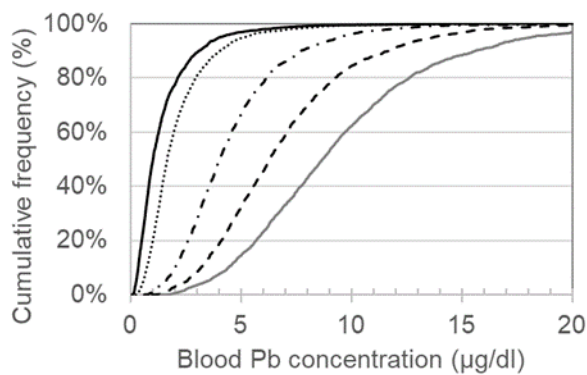


Figure 4. Predicted timecourse of blood Pb in U.S. adult men born in 1955, 1967, or 2000 using central tendency values for model parameters (exposure to background levels of airborne Pb, or Pb at the cOELs for 1920 h of occupational exposure per year for a working lifetime).



Solid black line: background; dotted line $\text{cOEL} = 0.8 \mu\text{g/m}^3$, dashed-dotted line: $\text{cOEL} = 3.6 \mu\text{g/m}^3$, dashed line: $\text{cOEL} = 6.5 \mu\text{g/m}^3$, solid gray line: $\text{cOEL} = 9.7 \mu\text{g/m}^3$.

Figure 5. Cumulative frequencies of predicted blood Pb in DOD workers or controls of the same age and gender

Table 1. Characteristics of Predicted 2018 BLL Distributions for DOD Workers or Controls

Lifetime workplace exposure	Median Blood Pb Level (µg/dl)	95 th Percentile of Blood Pb Level Distribution (µg/dl)	% Blood Pb over 5 µg/dl	% Blood Pb over 10 µg/dl	% Blood Pb over 15 µg/dl	% Blood Pb over 20 µg/dl
Background (0.045 µg/m ³)	1.0	4.0	3.2%	<1.0% ^a	<1.0% ^a	<1.0% ^a
0.8 µg/m ³	1.7	5.1	5.4%	<1.0%	<1.0%	<1.0%
3.6 µg/m ³	4.1	9.5	33.5%	3.8%	<1.0%	<1.0%
6.5 µg/m ³	6.3	13.7	68.0%	15.7%	3.4%	<1.0%
9.7 µg/m ³	8.7	18.2	85.6%	37.9%	11.7%	3.1%

^aPercentages could not be estimated with confidence due to insufficient # of Monte Carlo trials completed (2000 trials/run).

4.4.3 Local Sensitivity Analysis. The local sensitivity analyses of the final value of BLL at age 63 years as predicted by the DOD-O’Flaherty model confirmed that the population simulations of revised model incorporated key sensitive parameters for the range of cOELs developed. These parameters were the same ones identified in the preliminary sensitivity analysis (see Appendix C). Normalized sensitivity coefficients of the final value of BLL to binding affinity, binding capacity, and hematocrit ranged were did not vary from linearity (normalized sensitivity coefficient =1 or -1) by more than 10% across the scenarios tested. Sensitivity coefficients for other sensitive parameter are shown in Figure 6. Variability in background exposure naturally has less of an impact when occupational exposure predominates. Likewise, variation in inhalation rate is more important when airborne Pb is a major source, rather than ingestion. These local sensitivity findings suggest that individual characteristics that may lead to elevated blood Pb that are potentially knowable include high levels of exertion during exposure (and thus increased inhalation) and poor kidney function.

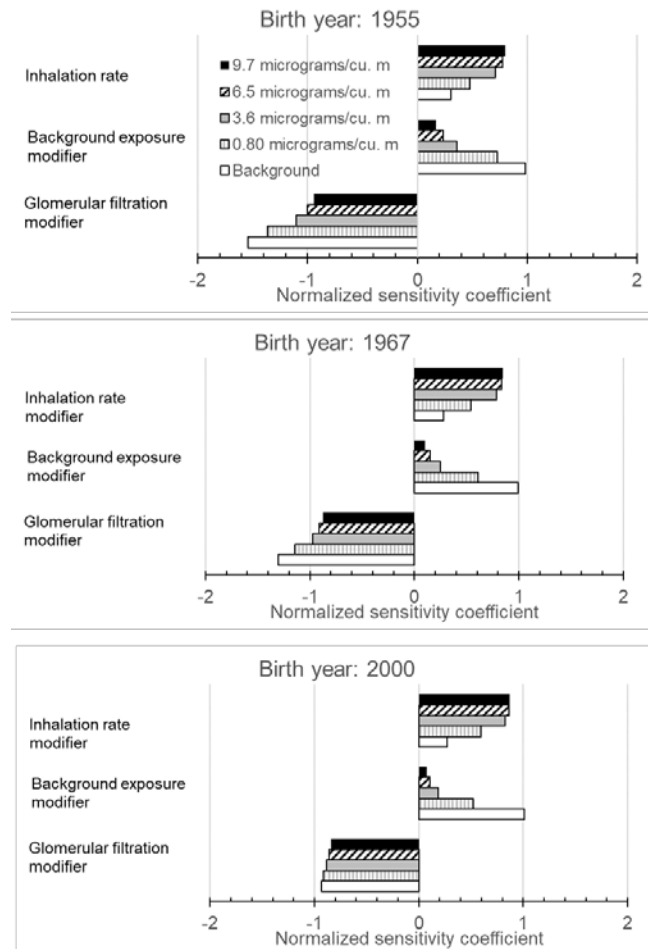


Figure 6. Local sensitivity of predicted blood Pb concentration in men at age 63 years to model parameter values.

4.4.4 Rank Correlation. The sensitivity of predicted blood Pb to the value of model parameters was determined by rank correlation of Monte Carlo simulation inputs and Pb predictions for cOEL derivation at the four target blood concentrations and for an unexposed equivalent control population (i.e., same distributions of sex and birth year). The rank correlations were converted to percent contribution to observed variability (Figure 7). For background and lower concentration occupational exposures, variability in background exposure and age were identified as potentially important contributors to overall variability, but their contribution decreases with increasing occupational exposure. Glomerular filtration provided similar contributions to population variability in BLL across the tested scenarios. The dichotomous parameter of gender was assessed for the cOELs by inspection of the 100 trials yielding the highest final BLL values. Of the top 100 trials, 8 would be expected to be women if there was no sensitivity difference. The simulations indicated that the representation of women was 3, 3, 2, 1, and 1 individual(s) in the top 100 for controls, 0.8, 4.6, 6.5, and 9.7 $\mu\text{g}/\text{m}^3$ (TWA concentration) occupational exposures. Thus there appears to be some sensitivity to gender, though DOD exposed women also tended to be slightly younger than the men (see Appendix D).

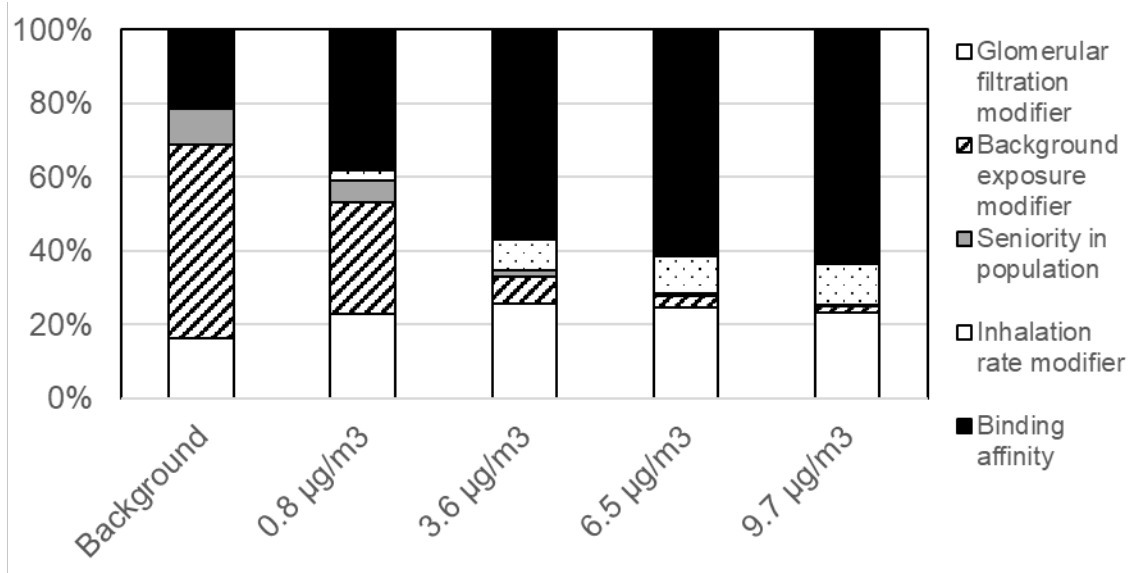


Figure 7. Contributors to variability in predicted final blood Pb concentration (working lifetime exposure) in a simulated DOD population with no additional occupational exposure (background) or four candidate OELs

5.0 CONCLUSIONS

After the DOD-sponsored NRC (2013) report on the exposure of DOD personnel to Pb at firing ranges concluded that the current OSHA PEL was not sufficiently protective of personnel, the next steps were the development of health based management guidelines for various BLLs (USAPHC, 2014; DOD 2017) and the evaluation of existing PBPK models relating airborne Pb to blood Pb (Sweeney, 2015). Probabilistic PBPK modeling to determine airborne concentrations at which 95% of healthy men and women with full-time occupational Pb exposure starting at age 18 years will maintain an acceptable BLL was chosen as the approach for guidance value derivation, rather than using a deterministic approach and assuming a level of population variability or applying a safety/uncertainty factor. The existing O’Flaherty (1993) PBPK model for Pb in humans was modified to facilitate probabilistic simulations of populations and to update/refine estimates of parameters that were sensitive determinants of final predicted blood Pb values. Demographic data for Pb-exposed DOD personnel (gender and year of birth) were used as inputs to the model. Possible TWA OELs of 0.8, 3.6, 6.5, and 9.7 µg/m³ were derived for those DOD personnel working 1920 h per year starting at age 18 years, based on targets of 5, 10, 15 or 20 µg/dl BLLs for the 95th percentile worker. The approach used here aimed to use the best available data and techniques. The use of Monte Carlo simulations rather than default or categorical uncertainty factors for interindividual variability exemplifies how that aim was implemented. The cOEL derivation also incorporates several conservative choices/assumptions (Table 2), as precautions against derivation of inadequately protective guidelines.

Table 2. Health-Protective Considerations Incorporated into the Derivation of the Airborne cOELs for Pb

Choice/Assumption	Why choice/assumption is health protective
Percentage of males in worker population was estimated from services with higher percentages of male Pb workers	Simulations indicated that older males have higher predicted BLL than women of the same age with the same exposure (Figure 2)
Age distributions of male and female were based on the service with the largest percentages of older workers	Simulations indicated that older workers have higher predicted BLL than younger workers of the same sex with the same exposure (Figure 2)
Four sets of starting values were used for Monte Carlo simulations, and the set yielding the highest BLLs was used to derive the guideline values	Simulations with different starting values for randomly generated numbers may lead to differing population results; the use of the set that yields the lowest BLL is a health-protective approach to addressing this uncertainty
Workers were assumed to have full-time occupational exposure to Pb full time from age 18 to at least age 63 (minimum) or beyond (based on current worker data)	Working lifetime assumption of 45 or more years equals or exceeds typical ranges (Vork et al., 2013)

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APPENDIX A

Health-Based Management Guidelines for Pb Exposure in the DOD

**Table A-1. Blood Lead Laboratory Results and Health-Based Management Guidelines
(Table C4.T2 of DOD, 2017; revised from a similar table from USAPHC, 2014)**

<u>BLL</u> <u>µg/dL</u>	<u>Short-term risks</u> (Lead exposure < 1 yr)	<u>Long-term risks</u> (Lead exposure ≥ 1 yr)	<u>Actions*</u>
<5	Studies have demonstrated adverse effects from lead exposure across populations, including on neurologic, reproductive, and renal functions and blood pressure, that occur at extremely low levels of exposure and appear not to have a threshold as reported by the Association of Occupational and Environmental Clinics, “Medical Management Guidelines for Lead-Exposed Adults” (Reference (s)).		<u>Supervisor/Personnel Management</u> • Ensure personnel are informed of potential health risks. • Consider reduction or avoidance of lead exposure for all workers. • Ensure personnel exposed to lead above the 30 µg/m³ AL are enrolled in medical surveillance. <u>Medical Management</u> • As part of health education and risk communication, recommend reduction or avoidance of lead exposure. • Educate on potential health risks. <u>Surveillance</u> • Coordinate with industrial hygiene, safety, and employee management. • Use current OSHA selection criteria (i.e., Action Level [AL] of 30 µg/m³ for 30 days per year). • Repeat BLL testing at least annually for individuals selected for BLL surveillance, and more frequently at the discretion of a medical provider.

5-9	• Possible spontaneous abortion • Possible postnatal developmental delay	Short-term risks plus: • Possible hypertension • Possible kidney dysfunction	<u>Supervisor/Personnel Management</u> • Ensure personnel are informed of potential health risks. • Consider reduction or avoidance of lead exposure for all workers. • Ensure personnel exposed to lead above the AL are enrolled in medical surveillance. <u>Medical Management</u> • As part of health education and risk communication, recommend reduction or avoidance of lead exposure. • Educate on potential health risks. <u>Surveillance</u> • Coordinate with industrial hygiene, safety, and employee management. • Use current OSHA selection criteria (i.e., AL of 30 µg/m³ for 30 days per year). <u>Surveillance</u> • Coordinate with industrial hygiene, safety, and employee management. • Use current OSHA selection criteria (i.e., AL of 30 µg/m³ for 30 days per year). • Repeat BLL testing at least annually for individuals selected for BLL surveillance, and more frequently at the discretion of a medical provider.
10-19	• Possible spontaneous abortion • Possible postnatal developmental delay • Reduced birth weight • >15 µg/dL adverse effects on sperm or semen	Short-term risks plus: • Hypertension and cardiovascular disease • Possible kidney dysfunction • Possible subclinical neurocognitive deficits	<u>Supervisor/Personnel Management</u> • Ensure personnel are informed of potential health risks. • Consider reduction or avoidance of lead exposure for all workers. • Ensure personnel exposed to lead above the AL are enrolled in medical surveillance. <u>Medical Management</u> • As part of health education and risk communication, recommend reduction or avoidance of lead exposure. • Educate on potential health risks. <u>Surveillance</u> • Coordinate with industrial hygiene, safety, and employee management. • Use current OSHA selection criteria (i.e., AL of 30 µg/m³ for 30 days per year.) • Repeat BLL testing every 3 months or more frequently at the discretion of a medical provider.
20-29	• Spontaneous abortion • Possible postnatal developmental delay	Short-term risks plus: • Hypertension and cardiovascular disease • Possible kidney dysfunction	<u>Supervisor/Personnel Management</u> • Ensure personnel are informed of potential health risks. • Remove from lead exposure if repeat BLL testing is at or above 20 µg/dl.

	• Reduced birth weight • Adverse effects on sperm or semen	• Possible clinical neuro-cognitive deficits	• Collaborate with occupational medicine to ensure employee is notified in writing within 5 working days of receiving results for any BLL of 20 µg/dL or above. • Return to lead work after 2 BLLs < 15 µg/dL 1 month apart. <u>Medical Management</u> • Notify supervisor/personnel management to remove from lead exposure if repeat BLL testing is at or above 20 µg/dL in 4 weeks. • Notify employee in writing within 5 working days of receiving results for any BLL of 20 µg/dL or above. • Educate on potential health risks. <u>Surveillance</u> • Perform monthly BLL testing. • Recommend to supervisor/personnel management return to lead work after 2 BLLs < 15 µg/dL 1 month apart. • When BLL has maintained at 15 µg/dL or below for 1 month and the worker is returned to lead work, repeat BLL testing every 3 months; more frequently at the discretion of a medical provider. • Surveillance frequency and management for each new BLL result will correspond to the directions in this table.
30-39	• Spontaneous abortion • Possible postnatal developmental delay • Reduced birth weight • Adverse effects on sperm or semen	Short-term risks plus: • Hypertension and cardiovascular disease • Possible kidney dysfunction • Possible clinical neuro-cognitive deficits • Possible nonspecific symptoms**	<u>Supervisor/Personnel Management</u> • Ensure personnel are informed of potential health risks. • Remove from lead exposure if single test result is ≥ 30 µg/dL. • Collaborate with occupational medicine to ensure employee is notified in writing within 5 working days of receiving results for any BLL of 20 µg/dL or above. • Return to lead work after 2 BLLs < 15 µg/dL 1 month apart. <u>Medical Management</u> • Notify supervisor/personnel management to remove from lead exposure. • Notify employee in writing within 5 working days of receiving results. • Educate on potential health risks. <u>Surveillance</u> • Perform monthly BLL testing. • Recommend return to lead work after 2 BLLs < 15 µg/dL 1 month apart. • When BLL has maintained at 15 µg/dL or below for 1 month and the worker is

			returned to lead work, repeat BLL testing every 3 months; more frequently at the discretion of a medical provider. • Surveillance frequency and management for each new BLL result will correspond to the directions in this table.
40-79	• Spontaneous abortion • Possible postnatal developmental delay • Reduced birth weight • Neurocognitive deficits • Sperm abnormalities • Adverse effects on sperm or semen	Short-term risks plus: • Hypertension and cardiovascular disease • Kidney dysfunction/neuropathy • Neurocognitive deficits • Subclinical peripheral neuropathy • Anemia • Colic • Possible gout • Nonspecific symptoms**	<u>Supervisor/Personnel Management</u> • Ensure personnel are informed of potential health risks. • Remove from lead exposure if single test result is ≥ 30 $\mu\text{g/dL}$. • Collaborate with occupational medicine to ensure employee is notified in writing within 5 working days of receiving results for any BLL of 20 $\mu\text{g/dL}$ or above. • Return to lead work after 2 BLLs < 15 $\mu\text{g/dL}$ 1 month apart. <u>Medical Management</u> • Notify supervisor/personnel management to remove from lead exposure. • Consider chelation therapy for BLL > 50 $\mu\text{g/dL}$ with significant symptoms or signs of lead toxicity. Notify employee in writing within 5 working days. • Educate on potential health risks. <u>Surveillance</u> • Perform monthly BLL testing. • Recommend return to lead work after 2 BLLs < 15 $\mu\text{g/dL}$ 1 month apart. • When BLL has maintained at 15 $\mu\text{g/dL}$ or below for 1 month and the worker is returned to lead work, repeat BLL testing every 3 months; more frequently at the discretion of a medical provider. • Surveillance frequency and management for each new BLL result will correspond to the directions in this table.
≥ 80	All of the short-term risks for BLLs between 5 and 79 $\mu\text{g/dL}$ plus: • Encephalopathy • Anemia • Colic	All of the short- and long-term risks for BLLs between 5 and 79 $\mu\text{g/dL}$	<u>Supervisor/Personnel Management</u> • Ensure personnel are informed of potential health risks. • Remove from lead exposure if single test result is ≥ 30 $\mu\text{g/dL}$. • Collaborate with occupational medicine to ensure employee is notified in writing within 5 working days of receiving results for any BLL of 20 $\mu\text{g/dL}$ or above. • Return to lead work after 2 BLLs < 15 $\mu\text{g/dL}$ 1 month apart. <u>Medical Management</u> • Notify supervisor/personnel management to remove from lead exposure. Refer for immediate/urgent medical evaluation.

-
- Educate on potential health risks.
 - Notify employee in writing within 5 working days of receiving results for any BLL of 20 µg/dL or above.
 - Probable chelation therapy.

Surveillance

- Perform monthly or more frequent BLL testing.
- Consider return to lead work after 2 BLLs < 15 µg/dL 1 month apart.
- When BLL has maintained at 15 µg/dL or below for 1 month and the worker is returned to lead work, repeat BLL testing every 3 months; more frequently at the discretion of a medical provider.
- Surveillance frequency and management for each new BLL result will correspond to the directions in this table.

* Consider more conservative management in the context of combined exposures to lead and other hazards (e.g., exposure to heavy metals increases the risk of noise induced hearing loss). Medical conditions that may be at increased risk from continued exposure include pregnancy, chronic renal dysfunction (serum creatinine > 1.5 milligrams per deciliter for men and >1.3 milligrams per deciliter for women, or proteinuria), hypertension, neurologic disorders, and cognitive dysfunction.

** Nonspecific symptoms may include headache, fatigue, sleep disturbance, anorexia, constipation, arthralgia, myalgia, and decreased libido.

APPENDIX B

Evaluation of Pharmacokinetic Models for the Disposition of Lead (Pb) in Humans, in Support of Application to Occupational Exposure Limit Derivation (adapted from Sweeney, 2015)

BACKGROUND

Overview of Pharmacokinetic Models for Pb in Adult Humans

Contemporary pharmacokinetic models for Pb were described in the 2006 Air Quality Criteria document for Pb (U.S. EPA, 2006); the 2013 Integrated Science Assessment noted that there have been few advances in this particular area since the 2006 document, and thus they were not extensively discussed therein (U.S. EPA, 2013). Three models were discussed in U.S. EPA (2006), the Integrated Exposure Uptake Biokinetic (IEUBK) model, the Leggett model, and the O’Flaherty model. U.S. EPA describes the O’Flaherty model as having fewer Pb-specific parameters, and being more physiologically-based in its description of Pb disposition than the Leggett model. All three models have been tested against individual human data, with the Leggett and O’Flaherty models having been tested against data from adults as well as children. The O’Flaherty model predicts slightly higher quasi-steady state BLL for a soil ingestion scenario tested by U.S. EPA (2006) (4.6 µg/dl for the O’Flaherty model vs. 4.1 µg/dl for the Leggett model for soil Pb of 1000 µg/g), suggesting that it is a modestly conservative model choice. Information regarding model parameter and input uncertainty and variability has not been incorporated into the Leggett model (U.S. EPA, 2006). While U.S. EPA (2006) notes that variability and uncertainty simulations have been conducted for the O’Flaherty model (Beck et al., 2001), the documentation in the Beck paper was limited, the code and other additional information was not available from Dr. Beck when this author (Dr. Sweeney) made inquiries previously (~2012), and Dr. O’Flaherty has retired and is not available for consultation. Because the IEUBK model is intended to describe the kinetics of Pb only in children age 7 or less (U.S. EPA 1994a, 1994b), rather than adults, to whom OELs are applicable, this model was not further considered. The Leggett model has been updated since the U.S. EPA assessment (2013) by Vork et al. (2013), Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (OEHHA, Cal EPA). This version of the Leggett model is referred to by Vork et al. (2013) and here as “Leggett+”.

O’Flaherty Model

The O’Flaherty (1993) model for Pb is a physiologically-based model, similar in many respects to those popularized for application to industrial chemicals by Mel Andersen and coworkers (e.g., Ramsey and Andersen, 1984). Distinctive features of the O’Flaherty model are (1) the incorporation of a detailed, age-dependent, physiological descriptions of bone growth and remodeling for trabecular and cortical bone of the skeleton and (2) the calendar-year dependent exposure parameters. Since its development, the model has been applied to evaluation of data from smelter workers (Fleming et al., 1999; Beck et al., 2001), impact of osteoporosis (O’Flaherty, 2000), determination of bioavailability (Polák et al., 1996), and the effects of microgravity-accelerated bone loss (Garcia et al., 2013).

The ACSL model code for the O’Flaherty human model (received from Dr. Gary Diamond, SRC) was consistent with the code provided in O’Flaherty (2000). Simulations were conducted using acslX (version 3.0.2.1, Aegis Technologies Group, Inc.). These two sets of model code had some discrepancies from the model description in O’Flaherty (1993). Specifically, the parameters “K” and “L” in O’Flaherty (1993) are called KAPPA and LAMBDA in the model code. The allometric exponent for bone growth (relating bone growth to body weight) is reported as 1.02 in O’Flaherty (1993), but as 1.188 in the provided model code and O’Flaherty (2000). The tissue:plasma partition coefficients in O’Flaherty (1993) were 100 for liver, kidney, and other well-perfused tissues and 20 for poorly perfused tissues other than bone. In contrast, the tissue:plasma partition coefficients in the model code received from Dr. Diamond and in O’Flaherty (2000) were 50 for liver, kidney and other well-perfused tissues, and 2 for poorly-perfused tissues other than bone. Autopsy data summarized by U.S. EPA (2006) indicated a skeletal muscle:liver ratio of 0.05, so the revised partition coefficients found in the code (Pb muscle: liver ratio of $2/50 = 0.04$) likely provide a better description of the soft tissue distribution of Pb than the O’Flaherty (1993) model (muscle: liver ratio of $20/100 = 0.2$). No communication of changes from original partition coefficients were discussed in subsequent publications of the O’Flaherty lead model (Beck et al., 2001; Fleming et al., 1999; O’Flaherty 1995, 1998, 2000; O’Flaherty et al., 1998; Polák et al., 1996), but the altered partition coefficient values were documented in a table of parameter values for the cynomolgus monkey (O’Flaherty et al., 1998) and in the code provided as a supplement to O’Flaherty (2000), as noted above. An Addendum at the conclusion of this appendix provides a summary of core parameters used in the cOEL derivations.

An aspect of the O’Flaherty model that contrasts to the Leggett/Leggett+ model was the way calendar years are incorporated in the description of exposures. Birth year is a potential risk factor for Pb toxicity due to the formerly higher environmental levels of lead due to uses that have since been curtailed (e.g., leaded gasoline), particularly in the U.S. and other developed nations; average BLL in children 1-5 years of age has decreased from 15.1 µg/dl to 1.51 µg/dl over the 30 year period from 1976-1980 to 2007-2008 (NTP, 2012). Calendar years are used to compute the background inhalation and ingestion (e.g., food and water) of Pb in the O’Flaherty model (O’Flaherty, 1993). Simulations were conducted to estimate 2009 BLLs (central tendency estimates) for women with different birth years, using the model parameter values of the O’Flaherty model (Figure B-1). Comparative data were derived from the CDC’s 2009-2010 NHANES database (CDC, 2012b), with the assumption that all blood samples were collected in 2009. Sample weights were used to derive a population-weighted average BLL for each age group; 38 to 67 samples were available for each age group. A single sample was excluded; this sample was from an 18-year old woman and contained 11.3 µg Pb/dl blood, the highest concentration reported among the 1528 samples from 18-47 year-old women. Exclusion of this apparent outlier reduced the estimated average blood concentration for 18-year-old women from 1.02 to 0.611 µg/dl. (Note: standard statistical tests for outliers are not valid for this non-random database due to oversampling of targeted subpopulations.) The model fairly consistently overpredicted the measured BLL. The discrepancy indices (the maximum of predicted value/measured value or measured value/predicted value) ranged from 1.0 (birth year 1988) to 2.3 (birth year 1971), with a geometric mean discrepancy index (GMDI) of 1.5. The agreement is well below the maximum discrepancy recommended by the IPCS (IPCS, 2010) for PBPK model use in risk assessment—IPCS recommends that, on average, the difference between the model

and the data should be no more than a factor of 2. In general, the agreement was better for birth years 1974-1991 (GMDI = 1.4) than birth years 1962-1973 (GMDI = 1.9).

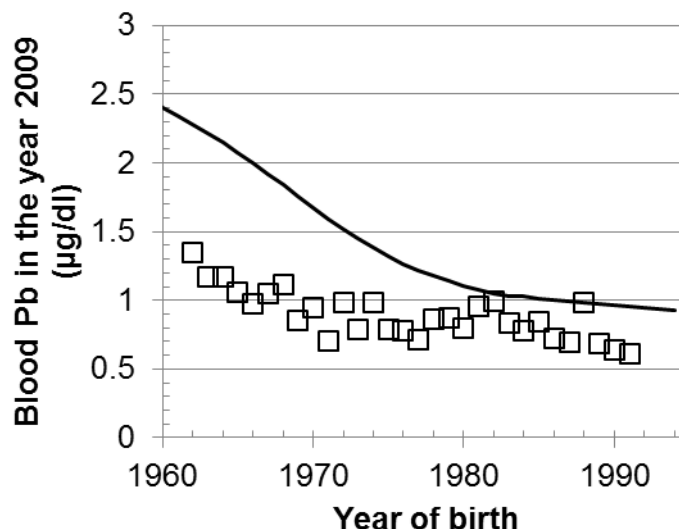


Figure B-1. Central tendency estimates of blood lead levels in the year 2009 for U.S. women born between 1960 and 1995, simulated using the O’Flaherty (2000) model (line), and compared to weighted average NHANES 2009-2010 data (CDC, 2012b) (symbols).

Leggett+ Model

The Leggett+ model was developed by Vork et al. (2013) as an update from the earlier ICRP/Leggett models. The ICRP/Leggett model (Leggett, 1993; Pounds and Leggett, 1998) was developed from models predominantly used in radiation protection, and is more commonly referred to as a “biokinetic” model rather than a “physiologically-based” model. The intercompartmental transfers in the ICRP/Leggett models are estimated primarily from empirical, chemical-specific data on transfer rates, rather than being based on physiological processes (such as blood flow) that can be measured (via appropriate markers) directly and adapted to specific, identified populations.

The Leggett+ model was developed from the Leggett/ICRP model explicitly for estimation of worker blood Pb levels. The strategy employed by Vork et al. (2013) was to adjust values of certain Leggett model parameters to improve fit to a subset of the available data (Hattis, 1981), and compare simulations, using the adjusted model parameter values, to other data sets.

PDF files containing the MATLAB model code for the Leggett+ model were downloaded from the Cal EPA website. The text in these files was used as the basis for an implementation of the Leggett+ model in acslX, prepared by the author of this report. Within this document, reproductions of simulations reported in Vork et al. (2013) will be denoted as “Leggett+ (MATLAB)”, while simulations conducted with the NAMRU Dayton implementation of the Leggett+ model in acslX will be denoted as “Leggett+ (ACSL).”

Discrepancies between the text and figures of Vork et al. (2013) and the provided model code (PDFs) and a lack of transparency were identified. In the text, Vork et al. (2013) stated that they “adjusted and tested bone, blood, and plasma (via urine) [parameters]” (p. 49). While the

“adjusted core model” blood and bone parameters are reported in the text (Table A-1, p. 56), the adjustment of the urinary clearance rate is not stated in the text. The adjustment value, “UCL = 0.25; % urine clearance setting” is noted in the model code (the “%” symbol marks the end of executable text in a line of MATLAB code), but no justification or other comments were provided. Figures show model-predicted concentrations in urine, but it was not clear from the publicly available code how these concentrations were derived. Mass balance equations for the urinary bladder were not a part of the Vork et al. (2013) model. The model includes a “urinary path” in the kidney and mass is transferred both from this urinary path and the diffusible plasma to a urinary bladder which is not a modeled compartment in Leggett+ (MATLAB). In Leggett+ (ACSL), a term was added to take the sum of these two transfer rates to the urinary bladder and divide by the urine output specified in the MATLAB code (urine volume = body weight $\times$ 24/100, where BW is in kg and urine volume is in liters/day.)

While the timing commands in the model code indicate that one year of simulation of “background” exposure (prior to elevated, occupational exposure) was used in at least some simulations, the depicted time courses for BLL and bone Pb in a worker exposed for 40 years (Vork et al., 2013 Figures 1, 2, and 3) appear to have a longer pre-employment simulation, perhaps 2 years. Pounds and Leggett (1998) report using simulations of 2000 days (~5.5 years) to achieve chronic, background pre-exposure levels for adults. The model code provides for the computation of initial adult Pb levels in various compartments, based on an initial BLL of 1.5 $\mu\text{g}/\text{dl}$. The basis for the proportions was not stated, and some compartments are initialized with no Pb. The basis may be the predicted distribution of lead at age 25 or 45 years after chronic life time exposure as predicted by the original Leggett model (Leggett, 1993, Table 3 therein). The proportions would be expected to be dose- and age-dependent (O’Flaherty, 1993). Considering how long it takes for new steady state levels to be achieved in the bone compartments (Vork et al., 2013, Figure 2 indicates that this process is incomplete after 40 years), the lack of information on how background distribution was estimated (at lower, current exposure levels) and the lack of information on how it was implemented for higher, historical exposures, lends uncertainty to the simulation of the calibration and validation data sets.

METHODS

Model simulations conducted for this report were performed using acslX (version 3.0.2.1, AEgis Technologies Group, Inc., Huntsville, AL) unless stated otherwise.

When experimental data were not available in tabular form, data in figures were converted from graphical to numerical format using Paint (Version 6.1, Microsoft Corporation). Several data sets used by O’Flaherty (1993) and Vork et al. (2013) were used to demonstrate model performance. O’Flaherty (1993) does not provide a clear distinction among data sets used for calibration (i.e., data used to derive estimates of parameter values) vs. validation (i.e., where comparisons of the model simulation and experimental data are used to “test” the model). Presumably, all presented data in O’Flaherty (1993) were used for “calibration”, and none were reserved for a separate “validation” step. In contrast, Vork et al. (2013) clearly indicated that a subset of the Hattis data (1981) (data for workers with BLL > 60 $\mu\text{g}/\text{dl}$ were excluded) were used for calibration, and the other data sets were used for validation. In this report, efforts to recreate the simulations conducted by the authors of the O’Flaherty (1993) paper and Vork et al. (2013) will be referred to as verification efforts. In addition to the data used in the development and

evaluation of the O’Flaherty and Leggett+ models, data identified from U.S. EPA (2013) were used to assess the accuracy of the model predictions.

RESULTS

Summary of Data and Model Output Used for Model Verification, Calibration, and Validation

Several data sets for the disposition of Pb in humans were used in the development of the two models under consideration, the Leggett+ model and its predecessors (Vork et al., 2013; Pounds and Leggett, 1998; Leggett, 1993) and the O’Flaherty (1993) model. In addition, relevant studies on the relationship between blood and plasma Pb levels were identified from U.S. EPA (2013). A general characterization of the study, the data, and how the data were used, as well as delineation of available model outputs and other relevant comments were summarized in Table 1 of Sweeney (2015), and in abbreviated form here in Table B-1.

Hattis (1981). Vork et al. (2013) used the Hattis (1981) data to recalibrate some of the parameters of the Leggett (1993) model as part of their development of the Leggett+ model, whereas O’Flaherty (1993) did not apparently use the Hattis (1981) data for model development or validation. While inspecting the Errata Sheet (October 2014) for Vork et al. (2013), discrepancies were found. These discrepancies occurred for individuals with equal duration of prestrike job tenure; the values for the final two columns were assumed to have been sorted incorrectly; by switching/rotating the paired values among the rows with equal job tenure (subjects 63, 73, and 474; 221 and 226; 45 and 47; 33, 34, and 39; and 8 and 15), the discrepancies could be eliminated. The corrected assignments of predicted post-strike BLL for Leggett+ (MATLAB) are presented in Sweeney 2015 Table 3 and were used for the analyses that follow.

Table B-1. Human Adult Pb Data and Model Output Used in Model Verification, Calibration, and Validation

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Hattis (1981)	BLL was measured in 66 ASARCO smelter workers (Glover, MO) prior to and during active employment, and prior to returning to work after a 9-month strike in 1976	For 47 workers, individual values of pre-employment BLL, prestrike job tenure, pre-strike BLL, and post-strike BLL were available.	None identified	Used for Leggett+ model calibration by Vork et al. (2013).	Leggett+ (MATLAB) post-strike BLL predictions reported in Vork et al. (2013) Table A-2 ("corrected", October 2014).	See Table 2 and 3 of Sweeney (2015) (correction of Vork et al. 2013, Table A-2), and Figure B2, and Figure B3 of this document (new simulations).
Manton and Cook (1984)	Samples were collected in Dallas, TX from 36 patients with neurological disease or symptoms. Occupation and source of Pb exposure were not characterized.	Serum Pb vs. blood Pb was plotted by the authors (Figure 2 of Manton and Cook, 1984	Used to establish the binding capacity and portioning between plasma and erythrocytes	One of two studies Vork et al. (2013) used to compare the plasma Pb vs. BLL relationship in the Leggett+ model	Leggett + (MATLAB) output was presented in Vork et al. (2013) Figure A-3.	See Sweeney (2015) Figures 4 and 5.
Manton and Malloy (1983)	Not determined for this evaluation.	Paired urinary Pb excretion and blood Pb, and urinary excretion and plasma Pb in a single adult male	One of the 3 studies used to determine parameters for Pb binding in blood.	None identified.	No O'Flaherty (1993) model output shown for urinary Pb excretion	Not used in the current evaluation. Original study not retrieved.
DeSilva (1981)	Blood was obtained from 103 subjects in the Melbourne, Australia area.	Paired plasma Pb and blood Pb concentrations in humans in O'Flaherty (1993), plasma and erythrocyte Pb in De Silva (1981).	One of the 3 studies used to determine parameters for Pb binding in blood	None identified.	O'Flaherty (1993) Figure 4	Not used in the current evaluation.
Rabinowitz et al. (1976)	Five healthy men in a hospital metabolic unit consumed known levels of dietary Pb.	Data for four subjects shown in O'Flaherty (1993)	Model calibration	Used by Leggett (1993) for model calibration.	Simulations for four individuals (O'Flaherty, 1993, Figure 11)	Modifications necessary to complete simulations were not undertaken.

Study name	Study description	Data description and availability	Use by O’Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O’Flaherty or Leggett+ only)	Comments
Hirata et al. (1995)	Blood and urine samples were collected from 5 Japanese Pb workers over a 15-month period.	A total of 75 sets of samples were obtained for Pb measurement in whole blood, plasma, and urine, 15 at high exposure, 60 at low exposure.	None	One of two studies used to compare the plasma Pb vs. BLL and urine vs. BLL relationships in the Leggett+ model to human observations.	Leggett+ (MATLAB) output in Vork et al. (2013), Figure A-3 and A-4	See Sweeney (2015) Figures 4-7
Schütz et al. (1996)	Human samples were collected to evaluate a new technique for measurement of Pb in human blood and plasma.	Blood and plasma Pb were measured in samples from 43 male Pb smelter workers and 7 controls.	None	None	Not applicable	See Sweeney (2015) Figure 5b
Hernández-Avila et al. (1998)	The relationship between plasma, blood, and bone levels was investigated in healthy individuals without occupational exposure.	Blood, plasma, tibia, and patella Pb levels were measured in 26 individuals with no known occupational exposure.	None	None	Not applicable	See Sweeney (2015) Figure 5b
Manton et al. (2001)	The relationship between serum and blood Pb was investigated in 73 Los Angeles women of child bearing age.	The subjects ranged in age from 16-47, with a mean age of 29 years, with an average number of 3 pregnancies.	None	None	Not applicable	See Sweeney (2015) Figure 5b
Lee (1982)	Blood and urine samples were collected from 234 male Pb workers.	In Lee (1982), the relationship of urine Pb to BLL was presented graphically for various ranges of BLL; urinary Pb was shown as mean $\pm$ 1 SD.	None	One of two studies used to compare urine Pb vs. BLL relationship in the Leggett+ model.	Leggett+ (MATLAB) output in Vork et al. (2013), Figure A-4	See Sweeney (2015) Figures 6 and 7
Williams et al. (1969)	Personal Pb samplers were worn by 30 Pb-exposed workers and 10 “controls”. One exposed worker withdrew from the study due to injury.	A scatter plot of BLL vs. Pb in air for 19 Pb-exposed workers and 10 controls was available in Williams et al. (1969).	Model calibration	Leggett+ model validation.	O’Flaherty (1993), Figure 7. Vork et al. (2013) Table B-8.	See Figure B4.

Study name	Study description	Data description and availability	Use by O’Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O’Flaherty or Leggett+ only)	Comments
Azar et al. (1975)	Personal air sampling devices were used. Participants were 30 subjects per location from 5 geographic locations. Blood Pb and urine Pb were measured.	Tabular data for all subjects, grouped by geographic location and occupational setting, were available in Azar et al. (1975).	Model calibration	None identified	O’Flaherty (1993) Figure 8.	See Figure B5.
Griffin et al. (1975)	Human volunteers were exposed ~23 hrs/day in an environmentally-controlled ward of a prison hospital, converted to serve as an exposure chamber. Blood was collected prior to, during, and after cessation of exposure to airborne Pb	Tabular data were available on ages, exposure dates, and individual blood Pb concentrations. Weekly average airborne Pb concentrations were also presented in tabular form.	None identified.	Vork et al. (2013) and Pounds and Leggett (1998); model validation.	Leggett+ (MATLAB) output in Vork et al. (2013) Table B-8.	See Figure B-6 and Sweeney (2015) Figures 11-12
Gross (1979)	Pb was ingested or inhaled under controlled conditions by human subjects in the “Kehoe” balance studies	BLL for 16 subjects available in O’Flaherty (1993), but exposure conditions not described	Model calibration	None identified	Simulated BLL of O’Flaherty (1993) available for the same 16 subjects for which data were presented in the same paper (Table 3)	The original study was not available.
Cools et al. (1976)	Male volunteers ingested Pb acetate in capsules or placebos. BLL was measured before and during the dosing period. Initial ingestion rate of 30 µg/day was adjusted once an individual’s BLL reached 40 µg/dl.	Group average BLL for 3 pre-exposure dates and 9 days during the 49 exposure period were presented graphically; range was shown for 3 means. Daily average Pb dose was also presented graphically in Cools et al. (1976).	Model calibration	None identified	O’Flaherty (1993), Figure 10	See Figure 13 and 14 of Sweeney (2015).

Study name	Study description	Data description and availability	Use by O’Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O’Flaherty or Leggett+ only)	Comments
Moore et al. (1977)	The relationship between household water used for drinking and food preparation and BLL in Scotland was evaluated.	A plot of mean BLL vs. water Pb for 9 intervals of water Pb was used as the source of data for the current evaluation.	Model calibration	None identified	O’Flaherty (1993), Figure 5.	Some uncertainty with respect to drinking water ingestion rate was identified attempting to reproduce the O’Flaherty (1993) simulations.
Sherlock et al. (1982)	The relationship between household water used for drinking and food preparation and BLL in women was evaluated in December, 1980.	Individual data could not be extracted due to the binned format for water and blood Pb ranges.	Model calibration	None identified	O’Flaherty (1993) Figure 6.	See Sweeney (2015), Figure 15.
Van de Vyver et al. (1988)	The relationship between blood Pb and Pb in the iliac crest was evaluated in samples collected via biopsy from 32 “at risk patients, including 21 lead workers”.	A scatter plot of bone Pb and BLL was presented in Van de Vyver et al. (1988).	Model calibration	None identified	O’Flaherty (1993) Figure 14	See Figure B7.
Nie et al. (2005)	Tibia and calcaneus bone Pb was measured in twice in 5 years in occupationally exposed workers; BLLs were also available for these workers. Data and simulations were conducted for a subset of 9 workers.	Blood Pb levels were only presented for one individual. Bone data (measured and simulated) were presented in tabular form for the 9 workers in the modeled subset.	None identified.	Model validation. Worker intake was estimated for multiple work periods based on BLL.	Simulations from the Leggett (1993) model and Nie’s adjusted model are presented in Nie et al. (2005). Leggett+ model predictions are reported for Subject #1 at 4 years after retirement. It is unclear why only one set of bone Pb measurements was predicted.	Given the small data set (2 measurements in one individual), these data were not used in our evaluation.

Unsuccessful attempts were made to verify the Leggett+ (MATLAB) post-strike BLL predictions using the Leggett+ (ACSL) model prior to achieving fairly similar values (Figure B-2). For example, in the first attempt, the initial distribution of the body burden of Pb was unaltered from that in the Leggett+ (MATLAB) code, and a long (20+ years) pre-exposure simulation period was assumed. With these assumptions, the Leggett+ (ACSL) model consistently overpredicted the Leggett+ (MATLAB) post-strike outputs reported in Vork et al. (2013) by an average of 1.5 µg/dl. The Leggett+ (ACSL) model predictions were better able to replicate the Leggett+ (MATLAB) outputs when the initial adult body burden was increased, based on the reported individual pre-employment BLL, and the pre-occupational exposure simulation (at background intake) was decreased to the 2 years (similar to Vork et al., 2013, Figures 1-3). The overprediction of the Leggett+ (MATLAB) post-strike outputs by the Leggett+ (ACSL) model was 0.3 ± 0.7 µg/dl. Subsequent to the conduct of these simulations, Dr. Vork provided modeling scripts (Personal communication to Lisa Sweeney, September 15, 2015) that indicated that the duration of the OEHHA pre-occupation exposure simulation was 1 year, rather than 2 years as estimated by NAMRU Dayton.

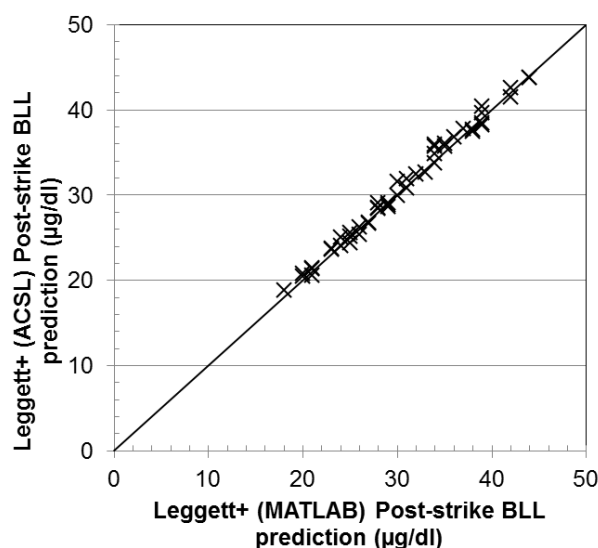


Figure B-2. Comparison of predictions of Hattis (1981) post-strike BLL for two versions of the Leggett+ model. × Pairs of model predictions. The plotted unity line (intercept = 0, slope = 1) represents where all of the paired model predictions would lie if there was perfect agreement between the two models.

To simulate the Hattis (1981) data with the O’Flaherty model, assumptions about the age of the subjects had to be made. Age at the time of the strike was assumed to be 30 years. Since the strike was known to have occurred in 1976, that made the 1946 the birth year for all subjects. To calibrate pre-employment BLL, the background ingestion of Pb in food (assumed constant throughout adulthood, including employment and the strike) for each individual was adjusted. The ambient air concentration for the employment period was then adjusted for each individual to match the pre-strike BLL. The resulting post-strike predictions were presented in Table 3 of Sweeney 2015.

The Leggett+ model, which was calibrated to the Hattis (1981) data, has slightly better agreement with the data than the O’Flaherty model in terms of average predictions and post-

strike value (1.9 ± 0.9 vs. 0.9 ± 0.9 $\mu\text{g/dl}$) (Sweeney, 2015). When the absolute value of the difference between the modeled and predicted values are considered, the gap narrows. The Leggett+ (MATLAB) model differs from the experimental data by 4.8 ± 0.5 $\mu\text{g/dl}$, while the O’Flaherty model differs from the experimental data by 5.2 ± 0.5 $\mu\text{g/dl}$. The agreement between the measured and predicted values of both the Leggett+ and O’Flaherty models are depicted graphically in Figure B-3. It is the judgment of the author of this report that the difference in the quality of fit between the models is small, but the fit to the Leggett+ model is marginally better.

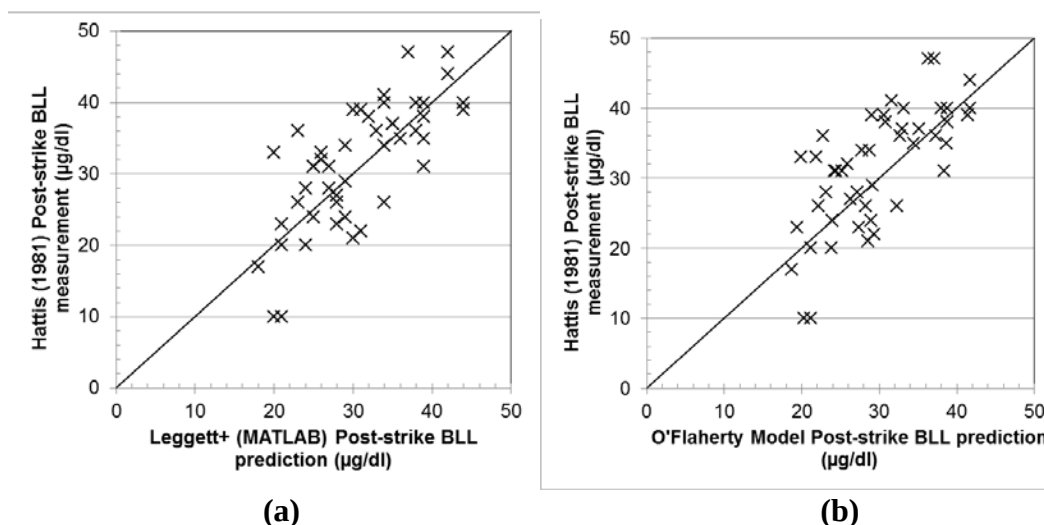


Figure B-3. Comparison of Hattis (1981) post-strike BLL measurements to predictions of the Leggett+ model (MATLAB) (a) and O’Flaherty model (b). The plotted unity line (intercept = 0, slope = 1) represents where all of the comparisons of experiment vs. model predictions would lie if there was perfect agreement between the model and data.

Manton and Cook (1984), Hirata et al. (1995), Lee (1982), Schütz et al. (1996), Hernández-Avila et al. (1998), and Manton et al. (2001). Data from Manton and Cook (1984), Hirata et al. (1995) and Lee (1982) were used by Vork et al (2013) as a basis with which to compare the Leggett+ (MATLAB) outputs for plasma Pb vs. BLL and urine Pb vs. BLL. More recent data from Schütz et al. (1996), Hernández-Avila et al. (1998), and Manton et al. (2001) (>90% extractable) were also considered to update and extend the analysis. The reader is referred to Sweeney (2015) for details.

Williams et al. (1969). The Williams et al. (1969) data were used by both Vork et al. (2013) and O’Flaherty (1993) for model validation. Our recreation of the O’Flaherty (1993) simulations (for a 30-year old worker with 10 years of elevated occupational Pb exposure) was evaluated by visual inspection, and determined to be consistent (not shown). Based on tabular data presented by Vork et al. (2013), Table B-3, a plot of BLL vs. workplace air Pb predictions for the Leggett+ (MATLAB) model could be constructed, and was incorporated into a figure depicting the O’Flaherty model and Leggett+ (ACSL) simulations, as well as our digitization of the Williams et al. (1969) data from the original paper (Figure 8). The Leggett+ (ACSL) simulations included two years of pre-occupational adult simulations with initial blood Pb at 20 $\mu\text{g/dl}$ and sufficient background exposure to maintain this level, followed by 20 years of occupational exposure, the occupational duration and beginning BLL specified by Vork et al. (2013) in their Table B-7.

Thus the assumptions about work duration differed in the two studies, but based on inspection of time course plots, 10 vs. 20 years of occupational exposure is unlikely to meaningfully affect predictions of BLL (e.g., Vork et al., 2013, Figure 1). The discrepancies between the pairs of digitized estimates were generally small (<2%). The NAMRU-D estimates for the control BLLs (Plastics Department workers) were closer to the published BLLs for these workers (Williams et al., 1969 mean of 28.2 $\mu\text{g}/\text{dl}$, matched by our data extraction, vs. 27.7 $\mu\text{g}/\text{dl}$ for Vork et al., 2013). In the Vork et al. (2013) evaluation, however, it should be noted that all subjects with $\text{BLL} > 60 \mu\text{g}/\text{dl}$ were excluded, leaving only 6 subjects with BLL elevated relative to the controls. This exclusion might be less of a concern if the 13 excluded subjects all had the highest estimated exposures as well, but this was not the case; 6 of the excluded subjects had workplace air exposures that were equal to or lower than that of the most highly-exposed “included” subject. Nonetheless, the models appear to have similar accuracy with respect to prediction of BLLs in this group of workers (Figure B-4).

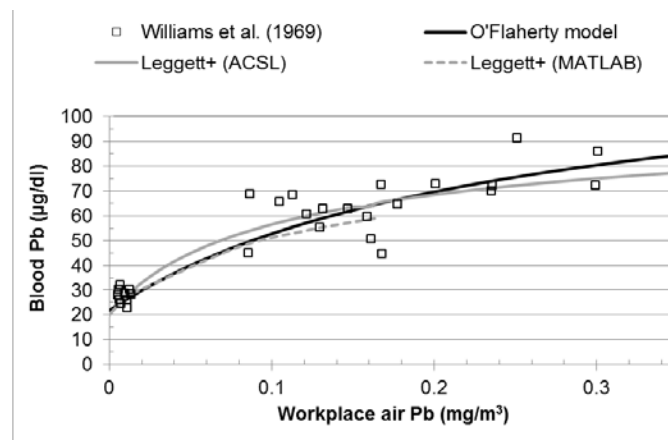


Figure B-4. Comparisons of model simulations to experimental data for workers in a lead-acid battery factory (Williams et al., 1969).

Azar et al. (1975). O’Flaherty (1993) considered the inhalation data of Azar et al. (1975) in developing her Pb model. The ACSL implementation of the Leggett+ model, calibrated for a background BLL of about 13 $\mu\text{g}/\text{dl}$, appears to fairly consistently overestimate the measured BLLs in the Azar et al. (1975) study, while the O’Flaherty model provides more accurate predictions (Figure B-5).

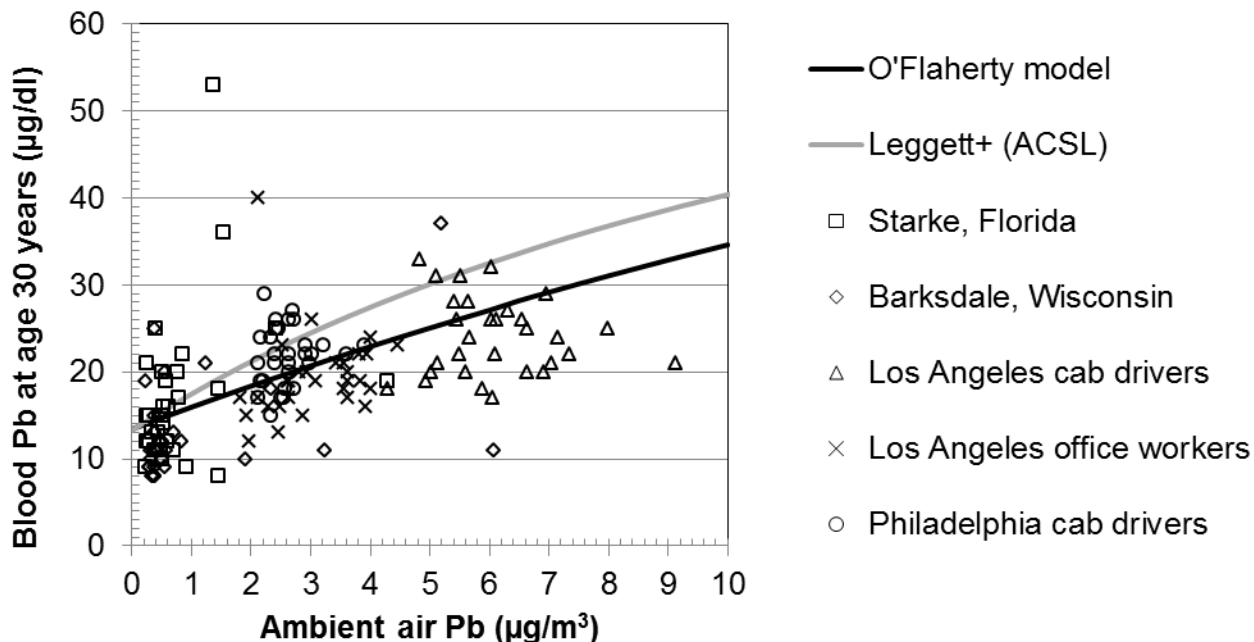


Figure B-5. Simulations of 30-year exposure (from birth) to varying levels of ambient air Pb (Azar et al., 1975).

Griffin et al. (1975). In the study conducted by Griffin et al. (1975), human volunteers (male prisoners) resided in a ward of the prison hospital that had been converted to an exposure chamber with sleeping space for 14. Vork et al. (2013) used pre-exposure blood levels to calibrate an individual's background exposure, and compared a simulated final blood concentration to a measured final value. Based on comparisons of the information in Vork et al. (2013) Table B-8, it appears that Vork et al. (2013) only used the last pre-exposure BLL to calibrate background exposures (typically, 2-3 measurements in a 2-3 week period prior to exposure were available). Also, it appears the final predicted BLL of Vork et al. (2013) was computed based on the total number of exposure days rather than the total number of exposure days prior to the last collected blood sample. In one case, the exposure period was 42 days, but the last BLL sample during exposure was collected 13 days earlier. More commonly the discrepancy was in the range of 3 days difference. For our simulations with the Leggett+ (ACSL) and O'Flaherty models, the background simulation considered all pre-exposure blood samples and the exposure simulation was conducted for precisely the number of days prior to the collection of the last blood sample. In the Leggett+ (MATLAB) model, the average measured less predicted BLL (based on total exposure days) was 0.83 µg/dl. In the Leggett+ (ACSL) model, the difference computed with only exposure days up to the last sample during exposure was 0.72 µg/dl. Using the O'Flaherty model, the difference was 3.55 µg/dl. The measured vs. simulated values for the Leggett+ (ACSL) and O'Flaherty models are summarized in Figure B-6. Vork et al. (2013) only considered the final BLL value during exposure when assessing the quality of the model fit. In Sweeney (2015), time course plots for all 12 individuals in each phase of the study were provided as Figures 11 and 12. In general, the models underpredict the data, the O'Flaherty model more so than the Leggett+ (ACSL) model.

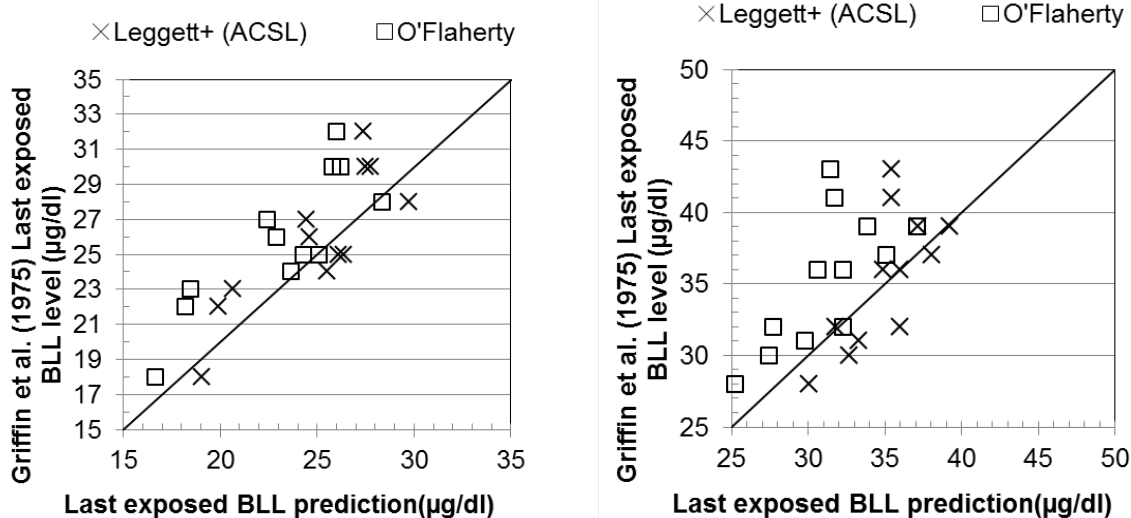


Figure B-6. Measured vs. predicted BLL at final blood sample during exposure for men exposed to 3.2 µg/m³ Pb for 53 to 123 days (left) or 10.9 µg/m³ Pb for 42 to 123 days (right) (Griffin et al., 1975). The plotted unity line (intercept = 0, slope = 1) represents where all of the comparisons of experiment vs. model predictions would lie if there was perfect agreement between the model and data.

Cools et al. (1976). The men in the Cools et al. (1976) study ingested Pb acetate with sucrose (or a sucrose placebo) in capsule form in a single-blind study. These data and the model simulations are described in Sweeney (2015). Based on these simulations, both models can adequately simulate the Cools et al. (1976) data.

Moore et al. (1977) and Sherlock et al. (1982). Both Moore et al. (1977) and Sherlock et al. (1982) investigated the relationship between various concentrations of Pb in drinking water and BLL. O'Flaherty (1993) used both of these studies in developing her model. Modeling efforts were described in Sweeney (2015).

Van de Vyver et al. (1988). O'Flaherty (1993) used the blood and bone (iliac crest) Pb data of Van de Vyver et al. (1988) in the development of her model. Individuals were assumed to have 30 years elevated occupational exposure to airborne Pb. In attempting to reproduce the O'Flaherty (1993) simulations, it was initially assumed that the predicted "bone" values were the model value of skeletal Pb (CSKEL). Upon further evaluation, it was found that using the trabecular bone Pb concentration (TCB, expressed in µg/L in the model) divided by bone density (DBONE, in the model) allowed the corresponding figure in O'Flaherty (1993) to be reproduced. For consistency, trabecular bone concentration in Leggett+ (ACSL) was also used as the metric of comparison (Figure B-7). Both models do good job of reproducing the bone vs. blood Pb relationship observed by Van de Vyver et al. (1988) in the 10-50 µg/dl BLL range, but the O'Flaherty model has better performance at higher BLLs.

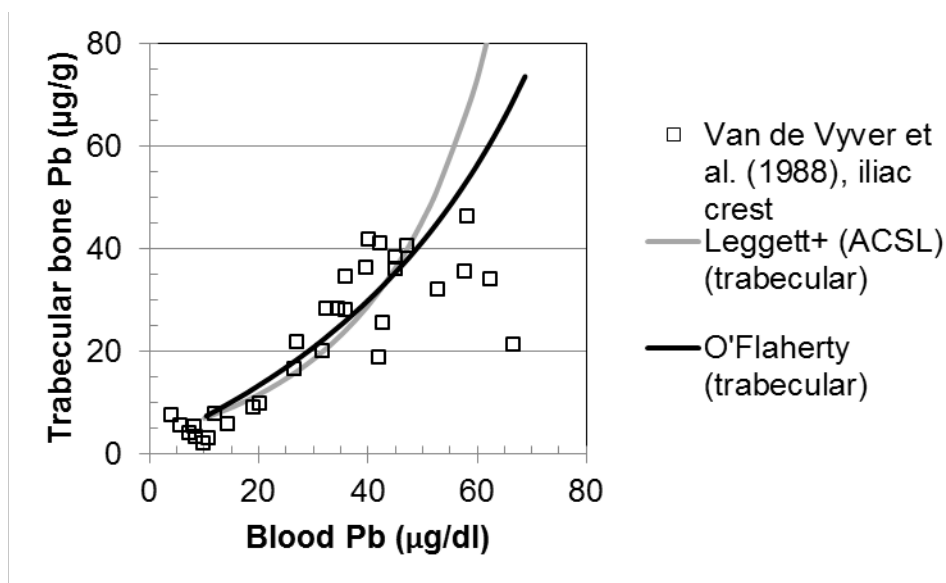


Figure B-7. Bone Pb vs. blood Pb in the Van de Vyver et al. (1988) study. O'Flaherty simulation is for a 50 year-old male, exposed for 30 years in the workplace; Leggett+ (ACSL) simulation is for 30 years of elevated adult exposure.

Mass Balance of Absorbed Pb

Vork et al. (2013) do not address the extent to which the Leggett+ model reproduces the observation on the excretion of absorbed Pb via various pathways. In the original Leggett model (Leggett, 1993), the relative rates of excretion by urinary vs. fecal pathways can be estimated from plot curves of excretion rates of injected Pb over time. After an initial distribution phase, the ratio of urinary to fecal excretion (determined by visual inspection) appears to be 2:1 (Leggett, 1993, upper panel of Figure 11). Simulations with the Leggett+ model (both ACSL and MATLAB versions) and O'Flaherty model are summarized in Table B-2. The urinary excretion rate for the Leggett+ model was computed using compartmental masses and transfer rates for the two pathways to the bladder. The urine:feces ratio in the Leggett+ model was closer to the inverse of the ratio in the original model, with fecal excretion occurring at a rate ~2.4-fold higher than the urinary excretion rate. The O'Flaherty model was used to simulate an adult born in 1970, with model-predicted excretion rates determined at age 45 (i.e., in 2015). The excretion rates add up to the default Pb absorption rate used in Vork, but the O'Flaherty model urine:feces split is 70%:30%, or ~2.3:1, a ratio similar to the original Leggett (1993) model.

Table B-2. Model-Predicted Steady State Pb Excretion Rates in Adults (absorbed Pb = 1.8 µg/dl)

Excretion rate (µg/day)	Leggett+ (ACSL)	Leggett+ (MATLAB)	O’Flaherty
Urine	0.42	0.42	1.23
Feces	1.03	0.99	0.53 ^a
Sweat	0.18	0.17	0
Other excreta	0.10	0.094	0
TOTAL	1.73	1.67	1.76

^aElimination from liver into feces; does not include unabsorbed, ingested Pb.

CONCLUSIONS

The Leggett+ model (Vork et al., 2013) and the O’Flaherty (1993) model for the disposition of Pb in humans demonstrated similar predictive ability with respect to available data on BLL. This finding is perhaps somewhat surprising given that these models were developed roughly 20 years apart and, for the most part, developed using different data sets. The Leggett+ model tends to do a slightly better job of predicting BLL after inhalation, with the O’Flaherty model doing a better job at predicting Pb in urine and bone. The revisions involved in updating the Leggett model to the Leggett+ model appear to have substantially diverted the excretion of absorbed Pb from the urine to the feces. This observation was originally determined using the ACSL version of the Leggett+ that we generated and was subsequently confirmed using the original MATLAB code.

A limitation of our analysis is that our attempts to recreate some of the Leggett+ (MATLAB) simulations with our Leggett+ (ACSL) model that we developed from the OEHHHA code were similar, but not identical. We believe this is primarily due to the use of slightly different assumptions, for example, with respect to simulating background (pre-employment) exposure. Our simulations of mass balance (excretion distribution of systemically absorbed Pb) using the original MATLAB code and ACSL+ version were within 7% of each other.

An important advantage of PBPK modeling (relative to more empirical modeling approaches) is their ability to simulate scenarios for which data are not available, with a reasonable expectation of accuracy. For example, in a physiologically based model, the modeler can incorporate new assumptions when pharmacokinetic data are not available. Examples could include the impact of a different exposure scenario (sporadic or intermittent vs. continuous and chronic) or the impact of physiological differences (e.g., kidney failure). In a non-physiological model, such modifications may be difficult or impossible, because of uncertainty regarding which parameters to modify, and by how much. In this regard, the O’Flaherty model would have to be considered superior to the Leggett+ model. U.S. EPA (2006) previously noted that the O’Flaherty model was more physiologically-based than the Leggett model. The modifications to the Leggett+ model made some moves toward being more physiologically realistic (removal of the blood binding threshold), but largely left the structure unaltered.

The observation that the Leggett+ model parameter changes produced (in our ACSL implementation) the redistribution of excreted Pb from the urine to the feces is of particular concern when it comes to possible population simulations (e.g., Monte Carlo simulation) and raises the question of the physiological consistency/realism of the updated parameters. The finding that prediction of urine concentrations by OEHHHA was not done in a physiologically

realistic way (the mass present in a kidney tissue region was used, rather than the transfer rate to the bladder) reinforces doubts about physiological realism of the optimized transfer parameters.

ADDENDUM

Several versions of the O’Flaherty PBPK model for Pb have been published and various modifications of the model code are available, with some inconsistencies among code and text, as noted in the “Background” section of this Appendix. Parameter values used in the cOEL derivation are summarized in the table below (**Table B-3**). This table is not complete, but addresses the core parameters.

Where male and female values of a parameter differ, these differences were previously addressed by scripts (.m or .cmd files) that assign simulation-specific values to a parameter. For the DOD application of the model, these gender-specific values were moved to the core of the basic model (.csl file). Logical expressions in the model are used to select FEMALE = 1 or 0, with MALE = 1- FEMALE. Where earlier model versions had, for example WCHILD = 23, the revised version has $WCHILD = MALE \times WCHILDM + FEMALE \times WCHILDF$, and likewise for other gender-specific parameters.

Table B-3. Selected Parameters from the O’Flaherty Model for Pb Carried Over to the DOD-O’Flaherty Modification Used for cOEL Derivation

Name	Value (units)	Description
AGEA	25 yr	Age at which bone growth ceases and remodeling becomes the sole bone formation process
WBIRTH	3.5 kg	Weight at birth
WCHILDM	23 kg	Maximum weight for early hyperbolic section of growth curve for male children
WCHILDF	22 kg	Maximum weight for early hyperbolic section of growth curve for female children
HALF	3 yr	Age at which weight is half of maximum weight for early hyperbolic section of growth curve for a male and/or a female child
WADULTM	50 kg	Maximum weight for later logistic section of growth curve for adult males
WADULTF	34 kg	Maximum weight for later logistic section of growth curve for adult females
KAPPA	600	Logistic constant kappa for age dependent changes in body weight
LAMDAM	0.0095 (1/(kg-yr))	Logistic constant lambda for age dependent changes in body weight for males
LAMDAF	0.017 (1/(kg-yr))	Logistic constant lambda for age dependent changes in body weight for females
QCC	1.241×10^5 L/yr/kg ^{0.74}	Body weight normalized for cardiac output in the adult
QLC	0.25	Fraction of the cardiac output going to the liver
QKC	0.17	Fraction of the cardiac output going to the kidney

Name	Value (units)	Description
QWC	0.44	Fraction of the cardiac output going to other well-perfused tissues
QBONEC	0.05	Fraction of the cardiac output going to bone
VBLC	0.067 L/kg body weight	Total blood volume
VLC	0.025 L/kg body weight	Liver volume in the adult
VKC	0.0085 L/kg body weight	Kidney volume in the adult
VLWPC	0.0576 L/kg body weight	Volume of blood in well-perfused tissues
VWC	0.16	Volume of well-perfused tissues
HCTAM	0.46	Hematocrit in adult male
HCTAF	0.41	Hematocrit in adult female
Bone Parameters		
D0	5.0×10^{-7} cm/day/ 0.5×10^{-4} cm	Permeability constant for diffusion within the bone
R0	5.0×10^{-7} cm/day/ 0.5×10^{-4} cm	Permeability constant for diffusion across the canaliculus-bone interface from bone to canaliculus
P0M	0.02 cm/day/ 0.5×10^{-4} cm	Permeability constant for an adult male
P0F	0.01 cm/day/ 0.5×10^{-4} cm	Permeability constant for an adult female
S	0.000126 cm ² /cm of canalicular length	Constant for surface area of canaliculi
RAD1	0.000027 cm	Radius of the first shell of bone in the canalicular (diffusion) region of deeper bone
RAD2	0.000052 cm	Radius of the second shell of bone in the canalicular (diffusion) region of deeper bone
RAD3	0.000079 cm	Radius of the third shell of bone in the canalicular (diffusion) region of deeper bone
RAD4	0.000106 cm	Radius of the fourth shell of bone in the canalicular (diffusion) region of deeper bone
RAD5	0.000133 cm	Radius of the fifth shell of bone in the canalicular (diffusion) region of deeper bone
RAD6	0.000150 cm	Radius of the sixth shell of bone in the canalicular (diffusion) region of deeper bone
RAD7	0.000187 cm	Radius of the seventh shell of bone in the canalicular (diffusion) region of deeper bone
RAD8	0.000214 cm	Radius of the eighth shell of bone in the canalicular (diffusion) region of deeper bone

Name	Value (units)	Description
Lead Parameters		
PL	50	Liver to plasma partition coefficient
PK	50	Kidney to plasma partition coefficient
PW	50	Well-perfused tissue to plasma partition coefficient
PP	2	Poorly-perfused tissue to plasma partition coefficient
LEAD	15000 L plasma cleared/L bone formed	Fractional clearance of lead from plasma into forming bone
BIND	2.7 mg/L of red cell volume	Maximum capacity of sites in red blood cells to bind lead
KBIND	0.0075 mg/L of red cell volume	Half-saturation concentration of lead for binding by sites in red blood cells
G	1.2	Linear parameter for unbound lead in red blood cells

APPENDIX C

Preliminary Analyses Toward Monte Carlo Implementation

SENSITIVITY ANALYSIS

Methods/Approach

Preliminary Sensitivity Analyses. Preliminary sensitivity analyses were conducted to identify the model parameters to be more closely scrutinized (for possible updating) and have their distributions characterized for subsequent Monte Carlo simulations. Three birth years were considered for each sex. For both sexes, 1952 and 1999 were considered, to address potential differences between individuals with higher historical exposures and lower contemporary exposures, at the ends of likely current-day occupationally exposed population. An additional year, 1966 for men and 1968 for women, was selected because for these birth years, 2017 blood level predictions (background exposure only) appeared to be the most sensitive to small changes in birth year (Figure C-1).

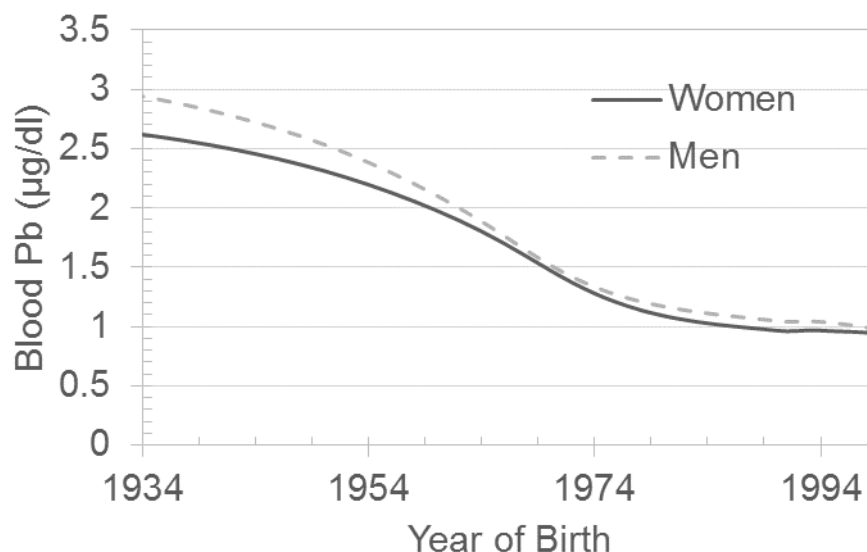


Figure C-1. Blood lead levels in 2017 predicted using the original O’Flaherty (1993) model, with only background exposure

The preliminary sensitivity analyses were conducted using the model essentially as prepared by Ellen O’Flaherty, with limited modifications incorporated by others (Gary Diamond and the current modeler, Lisa Sweeney) primarily for succeeding versions of ACSL and for specialized exposure scenarios. Sensitivity analyses were implemented using features built into the software. In this preliminary analysis, sensitivity analyses were conducted on the impact of altering the various “constants” in the model on the value on predicted PBB (the model’s designation for blood lead level) at a specified age. The constants frequently corresponded directly to a biochemical, physicochemical, or anatomical parameter (e.g., adult body weight), however, some parameters were computed using more complex, non-linear formulas. Some formulas for physiological/anatomical parameters were related to age directly (body weight,

glomerular filtration rate) or indirectly (tissue weights as a function of body weight). Some default exposure parameters in the O'Flaherty model were related to age (e.g., baby food/formula ingestion) or to calendar year (Pb in adult food supply and ambient air). The traditional approach to sensitivity analysis ($NSC = \% \text{ change in output per } \% \text{ change input value}$) for these physiological or exposure parameters defined by formulas, calendar year-dependence, etc. was augmented by expert judgment and additional simulations such as sensitivity analyses done directly (rather than through the acslX add-on), to add parameters to consideration for Monte Carlo analysis. For example, a percent change to year of birth is not meaningful given that other frames of reference besides the Common Era could be used. However, it is evident from model simulations with different values for year of birth (Figure C-1) that under conditions of background exposure to Pb, model predictions of final BLL are sensitive to this parameter. Parameters with $|NSC| > 0.2$ for at least one scenario were deemed potentially relevant to Monte Carlo variability analyses, and given further consideration.

Preliminary Sensitivity Analyses: Background/Community Exposure. A Monte Carlo simulation of variability in “background” blood levels was needed to assess whether or not pharmacokinetic variability and age-related alone (that is, in the absence of variability in exposure) could recapitulate the observed variation in BLL. To prepare for such simulations, sensitivity analyses were conducted in which no additional “ambient” (occupational) Pb exposure was assumed. Sensitivity analyses were conducted for 2017 BLLs for birth year 1999 (age 18), men with birth year 1966 (age 51), women with birth year 1968 (age 49), and birth year 1952 (age 65).

Preliminary Sensitivity Analyses: Occupational Exposure. For these sensitivity analyses, an additional ambient exposure was added for working years (age 18 and beyond), and simulations were conducted for lifetime exposure up to age 65 and physiological and anatomical parameters for a typical human. Test simulations were conducted with exposure during the working years implemented as intermittent (fraction of a day) at higher intensity, or continuous (24 h/day, 365 days/year) at a lower ambient air concentration with equivalent total exposure (concentration times duration). As the differences in final blood level were minimal, the simpler, computationally faster approach of continuous exposure was used for all subsequent occupational exposure simulations. Additional ambient exposures that would result in BLL of 10 $\mu\text{g/dl}$ (women and men) or 5 $\mu\text{g/dl}$ (women only) at age 65 were determined by iteratively testing a range of exposure concentrations until one that yielded the target BLL was identified. These concentrations are summarized in Table C-2 and used in the preliminary sensitivity analysis.

Table C-2. Additional Airborne Pb Concentrations Used in Preliminary Sensitivity Analyses of the Original O’Flaherty (1993) Model

Target blood concentration at age 65 years	Continuous additional ^a air concentration (CAMB) required to elevate BLL to target level (µg/m ³)					
	Women			Men		
	Born in 1952	Born in 1968	Born in 1999	Born in 1952	Born in 1966	Born in 1999
5 µg/dl	1.0	1.4	1.4	Not determined		
10 µg/dl	3.0	3.3	3.4	2.3	2.5	2.6

^aBackground air concentration for contemporary exposure were assumed equal to of 0.15 µg/m³ (O’Flaherty, 1993), the same as the proposed and prevailing primary National Ambient Air Quality Standard (U.S. EPA, 2016).

Results

Because of the large number of analyses and their preliminary nature, results are not reported in full detail. The sensitivity analyses of the revised and modified model (referred to as the DOD-O’Flaherty Model) are presented in the body of the report and are more germane to the issue of the derivation of the cOELs.

Parameters pertaining to historical exposure levels of Pb via food and air were found to influence predicted values of current or future BLL. These parameters were tentatively carried forward to the Monte Carlo simulations supporting cOEL development as a group, introducing a single parameter “EXPOSMOD” (“exposure modifier”) to multiply all background intakes for an individual. The need for and calibration of this parameter was addressed in Results—Population exposure variability assessment.

Similarly, BLL was found to be sensitive to inhalation rate and fractional uptake from the lungs. Inhalation rate consistently identified as sensitive across scenarios, was carried forward to variability considerations.

BLL was found to be sensitive to parameters contributing to the computation of glomerular filtration rate (GFR), a key parameter in calculating the excretion of Pb. This sensitivity was carried forward by introducing a proportionality coefficient to adjust GFR consistently across all ages for an individual.

Sensitivity of BLL to body weight (adult and child values, and curve-fitting parameters for age-dependence of body weight) was generally modest ($|NSC| < 0.3$), with greater influence for later birth years, and thus unlikely to be a key determinant of BLLs in 95th percentile individuals.

BLL was sensitive to parameters that determine the amount of Pb bound to red blood cells, specifically the hematocrit (HCTA), binding affinity (KBIND), and binding capacity (BIND). These parameters were carried forward to investigation of parameter variability, to be considered as a group, due to their interrelated nature.

PARAMETER VARIABILITY

Inhalation Rate

The same data sets that were used to derive age- and gender-specific central tendency values for inhalation rate, as summarized in U.S. EPA (2011) (see Appendix D), were also

consulted for determination of variability. Of the four data sets used for central tendency values, one did not have information on the standard deviation or 95th percentile values (Stifelman, 2007). The Brochu et al. (2006) data were reported as mean and standard deviation, so the coefficient of variation (CV) for each grouping was computed as standard deviation divided by the mean. For the remaining two data sets (Arcus-Arth and Blaisdell, 2007 and U.S. EPA, 2009), data were reported as mean and 95th percentile. The mean and 95th percentile values were converted to a CV estimate assuming a normal distribution; since the z value = 1.65 for the 95th percentile, $CV = (95^{\text{th}} \text{ percentile value} / \text{mean} - 1) / 1.65$. Data were weighted by age range covered (e.g., “1” age 1-<2 years, “5” for ages 6-<11 years) to compute the overall CV. Data were not combined across studies for specific age groups, and all study- and age-/gender- specific groups were considered. The weighted-average CV was 0.20. For Monte Carlo simulations, the parameter for modifying the inhalation rate was truncated at $\pm$ two standard deviations.

Fractional Uptake from Inhalation

Vork et al. (2013) considered the impact of particle sizes and activity levels (inhalation rate) on regional deposition using the ICRP Human Lung Model (ICRP, 1994), and the contributions of absorption in both the lung and the gut (from ciliary clearance, after deposition in the lung) to the total systemic absorption after inhalation (inhalation transfer coefficient—ITC). The ITCs for the workgroups (particle characteristics) and activity levels ranged from 29 to 31%. Because the variability was so small compared to other parameters of similar or greater sensitivity (e.g., inhalation rate), potential variability in this parameter was not carried forward to Monte Carlo simulations.

Glomerular Filtration Rate (GFR)

In the O’Flaherty model, glomerular filtration rate (GFR) was computed based on body weight (which has a gender-specific time course) and age. Variability in GFR (independent of age and body weight) has been incorporated in other PBPK modeling Monte Carlo analyses. Four papers from a collaborative research group (Wambaugh et al., 2015, Wetmore et al., 2012, 2015, Rotroff et al., 2010) used $CV = 0.3$ for the standardized GFR in 20-50 year olds, but either provided no justification, or ultimately referenced back to a paper which describes proprietary software with a parameter database, but no numbers from that database (Jamei et al., 2009). Wu et al. (2015) used a value of $CV = 0.05$ as the error of age-related GFR for females age 0-20 years. While Wu et al. (2015) compared their age-related GFR simulations to data compiled by Dewoskin and Thompson (2008), no details were evident in either paper for how a CV of 0.05 was determined from the data. Verner et al. (2015) characterized the variation in standardized GFR ratio in three studies of pregnant women, and determined a CV of 0.246. A secondary source (National Kidney Foundation, 2017) has described a “normal” GFR for adults as >90 ml/min/1.73 m² body surface area, with average GFR values of 116, 107, 99, 93, 85, and 75 for ages 20-29, 30-39, 40-49, 50-59, 60-69, and 70+ years. The National Institute of Diabetes and Digestive and Kidney Diseases (2017) reports that the prevalence of chronic kidney disease (CKD) in the U.S. is 14 percent. While not all who have CKD will have reduced GFR, those at Stage 2-5 will have $GFR < 90$ ml/min/1.73 m² body surface area. If a normal distribution of GFR is assumed, the 14th percentile value is assumed to be 90 ml/min/1.73 m², and the mean is assumed to be 116 ml/min/1.73 m² (the value for 20-29 year olds), the CV for GFR would be

0.21. Considering these precedents, a CV of 0.3 was adopted for GFR as a supportable, health protective assumption. For Monte Carlo simulations, the parameter for modifying the age-dependent filtration rate was truncated at $\pm$ two standard deviations.

Red Blood Cell Pb Binding

Red blood cell (RBC) Pb binding affinity, RBC binding capacity (normalized to RBC volume), and hematocrit were found to be sensitive parameters in the model. DeSilva (1981) determined plasma/red blood cell concentration ratios of Pb in 103 human subjects (60% of whom were Pb workers). The CV of the plasma/red blood cell concentration ratio was assumed to be an appropriate surrogate for the combined variability of the total Pb binding capacity and affinity. The plasma/RBC Pb ratios CVs were consistent across the range of erythrocyte Pb concentrations. Overall, the weighted CV was 0.40, and the CV for the lowest concentrations of Pb (up to 39 $\mu\text{g Pb/dl}$ in erythrocytes), the range most relevant to contemporary exposure, was likewise 0.40. Variability in hematocrit has previously been reported to be low (CV = 0.030 for males, 0.032 for females; Borel et al., 1991), so the RBC Pb binding variability was attributed to variability binding capacity (sites per RBC volume) (“BIND” in the model), and assigned a CV of 0.40. For Monte Carlo simulations, the range of values for binding capacity was truncated at $\pm$ two standard deviations.

Exposure Modifier (“EXPOSMOD”)

In simulation of BLLs for female NHANES III participants, it was determined that physiological and pharmacokinetic parameters alone could not explain the observed variability in BLLs, and therefore additional variability in exposure was necessary to recapitulate population BLL variability. A lognormal distribution was assumed, and lower limit was set to 0.01. The variability for this parameter was derived as described in the main text.

APPENDIX D

Development and Refinement of Parameter Inputs

INHALATION RATE

The inhalation rate to be used in the modeling was a topic discussed by the DOD subject matter experts involved in preparations for the modeling activity described in this report. The ability of the O'Flaherty model to reproduce BLL simulations of various scenarios described in data sets used in the original model development and additional simulations, including worker inhalation exposures has previously been documented (Sweeney, 2015) and was summarized in Appendix B. In that model, a 25- year old man would have a body weight of 73.8 kg and inhalation rate of 14.6 m³/day. For comparison, OEHHA (Vork et al., 2013) assumed a breathing rate of 26 m³/day based on 10 h of moderate activity, 6 h of light activity, and 8 hrs of sedentary activity. The recommended long-term inhalation rate for males and females combined is 15.7 m³/day, with a 95th percentile value of 21.3 m³/day for ages 21 to <31 years in the Exposure Factors Handbook (EFH; U.S. EPA, 2011). It seems unlikely that an “average” worker’s inhalation rate would exceed the population 95th percentile values, as would be the case under the OEHHA assumption. The approach used in this effort was to use datasets described in the EFH, but to derive separate values for males and females.

Data used to develop the age and sex-dependent central tendency inhalation rates were taken from tables in the EFH (U.S. EPA, 2011) for normal weight males and females. We used the same age bins (e.g., birth to <1 month old, 1 to <3 months old) as U.S. EPA (2011) and took the unweighted averages of central tendency estimates for Brochu et al. (2006) (EFH Table 6-5), Arcus-Arth and Blaisdell (2007) for age <11 years old (EFH Table 6-11), Stifelman (2007) (EFH Table 6-13), and U.S. EPA (2009) (EFH Table 6-16). Arcus-Arth and Blaisdell (2007) only presented data for males and females combined. However, looking at the Brochu et al. (2006) data in EFH Table 6-5, the female/male inhalation rate ratios ranged from 0.93 to 0.96 for all age bins <11 years old, but decreased to 0.76 to 0.81 for age 11 and up. Thus, it was assumed that sex related differences were small for age <11, and the Arcus-Arth and Blaisdell (2007) data for this range could be used in the current, sex-specific analyses for males and females with minimal error. Using the same approach as U.S. EPA used when developing central tendency estimates for males and females combined, the unweighted average inhalation rates from the applicable studies were used to compute an average inhalation rate for each age bin. To develop a lifetime description of the inhalation rate, the midpoint of each age bin was used, and trendlines (6th order polynomials) were fit to the breathing rate vs. age data. Initially, all data points as derived from the unweighted averaging were used to develop the age-dependent inhalation rates. However, it was noted that the inhalation rates steadily decline in the older age bins (age 61 and higher). Simulations with age-related declines in inhalation rate were tested in the O'Flaherty model, and found to lead to a prediction of declining BLL with age; in test simulations with additional Pb exposure such that blood Pb levels would exceed 10 µg/dl with extended exposure, the blood Pb levels would decline approximately 1 µg/dl after age 55. Such an occurrence would be problematic for OELs derived based on final Pb levels. Furthermore, it is reasonable to suppose that the age-related decrease observed may be due to lower activity levels, which might not accurately describe the working population in this age range. Thus, the inhalation rates for ages 51 to <61 years were used as surrogates for workers ages ≥ 61 years. The data and the 6th order polynomials are shown in Figure D-1. The inhalation rates for average adult males are

approximately 18 m³/day, which is greater than the rate used by O’Flaherty (~15 m³/day), but lower than that used by OEHHA (26 m³/day). The inclusion of variability (discussed in Appendix C) results in 95th percentile inhalation rates of 24.1 m³/day for men and 18.7 m³/day for women, so the 95th percentile rate for men in the current simulation is slightly less than the central tendency value used by OEHHA in Vork et al. (2013).

$$\begin{aligned} \text{Inhalation rate (male; m}^3\text{/day)} = & -1.026 \times 10^{-9} \times \text{age}^6 + 3.032 \times 10^{-7} \times \text{age}^5 - \\ & 3.634 \times 10^{-5} \times \text{age}^4 + 2.302 \times 10^{-4} \times \text{age}^3 - 0.08329 \times \text{age}^2 + 1.653 \times \text{age} + \\ & 4.378 \quad (r^2 = 0.9868) \end{aligned} \quad (1)$$

$$\begin{aligned} \text{Inhalation rate (female; m}^3\text{/day)} = & -2.791 \times 10^{-9} \times \text{age}^6 + 7.860 \times 10^{-7} \times \text{age}^5 - \\ & 8.618 \times 10^{-5} \times \text{age}^4 + 4.662 \times 10^{-3} \times \text{age}^3 - 0.1304 \times \text{age}^2 + 1.795 \times \text{age} + \\ & 4.192 \quad (r^2 = 0.9868) \end{aligned} \quad (2)$$

where “age” is in years.

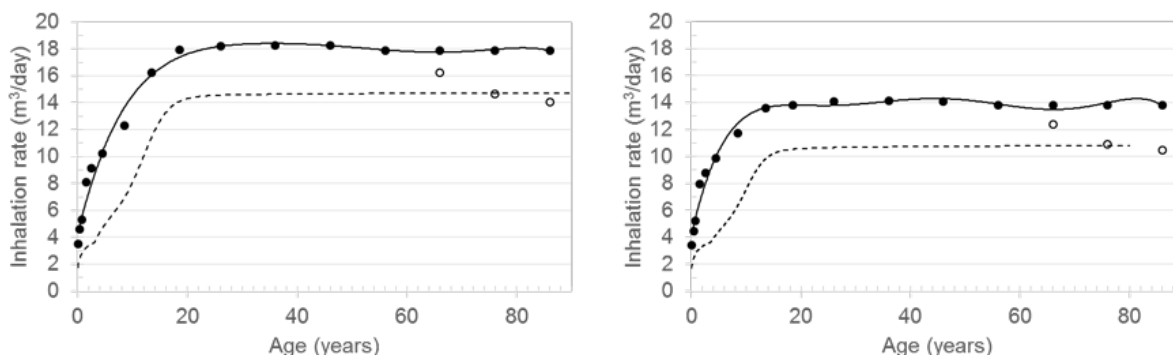


Figure D-1. Age-dependent inhalation rates. Filled circles (data from U.S. EPA, 2011) were used to develop the 6th-order polynomial equations (solid lines) implemented into the model. Open circles represent inhalation rates derived from the same sets used to derive the inhalation rate estimates for ages <61 years old, but not used to develop worker inhalation rates. Dashed lines represent the rates used in the original O’Flaherty (1993) model. For details and equations for the trendlines, see text. (Left) males, (Right) females.

GENDER AND AGE DISTRIBUTIONS FOR WORKS EXPOSED TO Pb IN THE DOD

Summary of DOEHRs-IH and DMDC Data

Data that served as the basis of the age and gender distribution for workers exposed to Pb in the DOD were developed based on queries of the industrial hygiene (IH) module of the Defense Occupational and Environmental and Health Readiness System (DOEHRs) in September through November of 2016. Queries were developed to capture Air Force-specific data by Eddie Lenos and Edward Lafferty (Wright Patterson AFB, OH), and filters revised to capture only Army data, compiled by Monica Ahuna Williams (Army Public Health Center, Aberdeen Proving Ground, MD), or only Navy Data, compiled by Leslie Crowder (Navy and Marine Corps Public Health Center, Portsmouth, VA). The data provided indicated the sex and year of birth of individuals at DOD workplaces (by service) where Pb hazards were identified. The extracted DOEHRs-IH data did not distinguish between military and civilians. A small number of records were excluded from the frequency distribution analyses due to lack of information on sex or birthdate or improbable birthdates. For example, system defaults may have

replaced blank dates with the year 1901 (found with much greater frequency than 1902), and some improbable recent dates (e.g., 2005) may have been the date the employee started in the shop, rather than a birthdate.

Data on Active Duty military personnel and DOD civilians were obtained from the Defense Manpower Data Center (DMDC) in September 2016 by Laurie Cummings (Office of the Assistant Secretary of Defense, Energy, Installations, and Environment). These data reflected manpower as of July 31, 2016 per the Active Duty Master Personnel File.

Per DMDC, 2,044,203 military and DOD civilians were distributed among the services/programs as follows: Army, 36%; Air Force, 24%; Navy 25%; Marines, 11%; and other DOD (civilians only), 4%. In contrast, in DOEHRS-IH, out of 52,625 Pb-exposed individuals, the distribution was Army, 23%; Air Force, 67%; and Navy, 10% (see Table D-1 for numbers of Pb-exposed workers in each service). DMDC data are known to be complete, whereas the DOEHRS-IH data may not be. Thus, while it is possible that the Air Force truly has a much larger fraction of the Pb-exposed DOD military and civilian worker population than the other services, it might not be the case. Based on this concern, the age and sex distributions for Pb-exposed workers in DOEHRS were not combined directly across services, due to potentially unrepresentative weighting. Birth-year distributions reported for Pb-exposed workers in the Army in DOEHRS-IH were selected to serve as the basis for derivation of the DOD-specific cOELs due to their clear relevance (a DOD subpopulation) and a moderate degree of conservatism, as described below, in order to be health protective.

Table D-1. Pb-Exposed DOD Workers in DOEHRS-IH (Fall 2016)

Branch	Male	Female	Male:female ratio
Air Force	30,897	4294	7.20
Army	11,164	1053	10.6
Navy	4830	387	12.5

As described in Appendix C (Figure C-1), the O’Flaherty model predicts that among individuals with only background exposure, older individuals will have higher blood Pb levels. Birth year distributions for Pb-exposed civilians and military for each of the three services were compared (Figure D-2, Figure D-3) to identify which of the three branches had the “oldest” Pb-exposed workers. As can be seen in Figure D-2, the Army consistently has a larger fraction of its Pb exposed men in earlier birth years with the exception the very earliest birth years (less than earliest 1%), where the Navy has a slightly higher proportion of Pb exposed men. Since the cOELs are to be derived to protect the 95 percentile (with full-time exposure assumed), a modest underestimate of age for the oldest ~0.7% was presumed unlikely to impact the cOEL. Similarly, the Pb-exposed Army women were older than their Navy and Air Force counterparts for most percentiles. Looking at the lowest percentiles, i.e, below 4 percent, the Navy population appears somewhat older (larger number of early birth years). It should be kept in mind, however, that only 387 Navy women were identified as Pb-exposed, so the Navy data in the right hand panel of Figure D-2 correspond to 19 women. Furthermore, Pb-exposed women in the DOD are outnumbered by the men (Table D-1), tend to be younger than the men (Table D-2), and for men and women of the same birth year, women are predicted to have lower background blood Pb levels (Figure C-1). Thus while the lower end of the age distribution for women is uncertain, it is unlikely to have a significant impact on the 95th percentile cOEL given men’s greater numbers, age, and predicted pharmacokinetic differences.

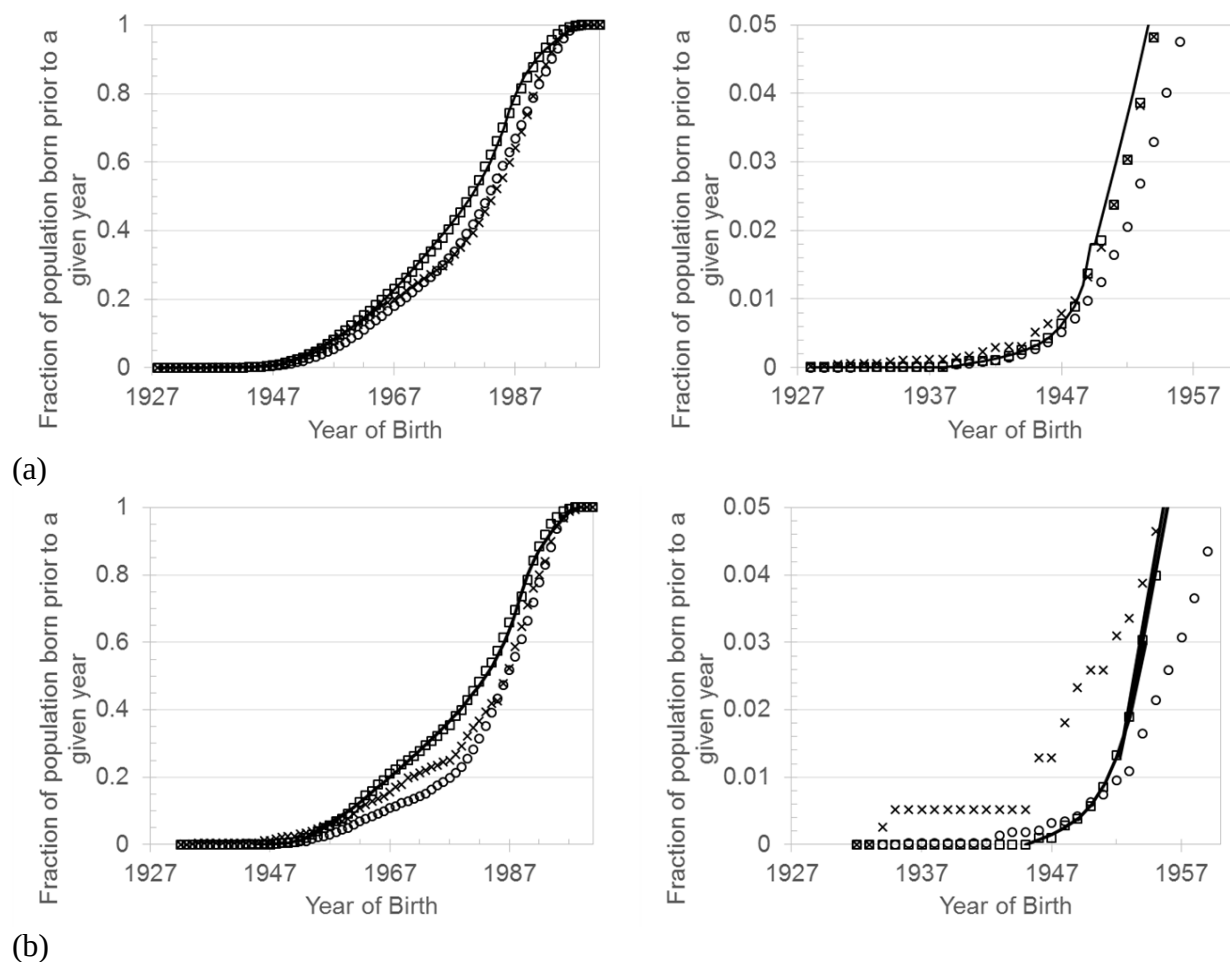


Figure D-2. Cumulative distribution of birth years for Pb-exposed DOD workers in DOEHRs-IH (Fall 2016)—full distributions (left) and detailed few of lower percentiles (right). (a) Men ($n = 30897$, 11164 and 4830, for Air Force, Army, and Navy, respectively), (b) women ($n = 4294$, 1053, and 387, for Air Force, Army, and Navy, respectively). Symbols: $\circ$ = Air Force, $\square$ = Army, $\times$ = Navy. Solid line = best fit 6th-order polynomial equation fit to Army data (see text for details).

Table D-2. Birth Years Corresponding to the Median or Oldest 5% of Pb-Exposed DOD Workers in Different Branches (data from DOEHRS-IH, Fall 2016)

Subpopulation	Metric	Air Force	Army	Navy
Men	5 th Percentile	1955	1953	1953
	Median	1981	1978	1982
Women	5 th Percentile	1958	1954	1954
	Median	1985	1981	1985

As indicated in Table D-1, the male: female ratios of Pb-exposed workers tracked in DOEHRS-IH differed among the services. A population with 8 percent women (intermediate between Navy and Army percentages, but less than Air Force) was chosen for the Monte Carlo simulations with a target BLL of 10 µg/dl because it is conservative (health protective) for two reasons. As previously noted, the O’Flaherty model predicts that when men and women have the same birth year and same historical (background) Pb exposure, men will have slightly higher BLLs than women (Figure C-1) and the men in the Pb-exposed group tended to be older than the women (Table D-2). Thus, the Pb-exposed men are at greater risk than women on the basis of pharmacokinetic differences and the age distribution of these cohorts, so inclusion of more men in the simulation should result in more health-protective cOELs.

To use the population birth year distribution data in the Pb PBPK model, a model parameter with a defined distribution shape (e.g., normal, lognormal, triangular, uniform) pertinent to the data must be incorporated into the model. Because the population’s birth year cumulative fractions can be described as a parameter with uniform distribution between 0 and 1, the model was modified to allow birth year calculation as a function of earliest birth year and a 6th-order polynomial equation. The equation relates year of birth to the (randomly generated) cumulative fraction of the population of concern with birth years prior to the individual’s birth date. For example, if YOBFrac = 0, the birth year would be the earliest birth year, and if YOBFrac = 0.5, the computed birth year should correspond to the median birth year. Distributions were developed for two subpopulations of interest: men and women. In the pharmacokinetic model, slightly different parameter sets have been used to describe the disposition of Pb in men vs. women. Since the values of model inputs are linked to gender, year of birth distributions must also be linked to gender.

Cumulative year of birth distributions were summarized graphically, including the outputs of the best-fit equations, in Figure D-2. The best-fit equations for the subpopulations are provided below, along with the quality of fit. The form, 6th-order polynomial, was selected among the options provided in Microsoft Excel based on visual inspection of possible fits and maximum flexibility among the family of nth-order polynomials. Inspecting the fits of the 6th-order polynomials, special attention was paid to the fit at lower fractions (the oldest population), as accurate (but health protective) description of that fraction of the population is key to derivation of scientifically-defensible cOEL. The 6th-order polynomial equations fit to the full range of data tended to err in prediction of early birth years (not shown). To compensate, the ranges were divided into two overlapping subsets, each of which was fit to a 6th order polynomial equation. The lower end of the equation was forced through YOBFrac = 0, and the upper range was forced through an intercept selected based on inspection of the data. For women, the transition point between lower and upper ranges was YOBFrac = 0.03 (for curve fit, lower range: YOBFrac = 0 to 0.04, upper range = 0.008 to 1) and for men, the transition point was at

YOBFRAC = 0.018 (for curve fit, lower range: YOBFRAC = 0 to 0.03, upper range = 0.008 to 1).

In Figure D-2 and the following equations, y = years older than earliest year of birth for the subpopulation, x = cumulative fraction of the subpopulation below the year of birth.

$$\begin{aligned} \text{All women, YOBFRAC} \leq 0.03 \text{ (} r^2 = 0.9942 \text{): years above baseline} = \\ 1570.1 \times \text{YOBFRAC} - 1.8139 \times 10^5 \times \text{YOBFRAC}^2 + 1.2921 \times 10^7 \times \\ \text{YOBFRAC}^3 - 5.0964 \times 10^8 \times \text{YOBFRAC}^4 + 1.0167 \times 10^{10} \times \text{YOBFRAC}^5 - \\ 7.9586 \times 10^{10} \times \text{YOBFRAC}^6 \end{aligned} \quad (3)$$

$$\begin{aligned} \text{All women, YOBFRAC} > 0.03 \text{ (} r^2 = 0.9991 \text{): years above baseline} = \\ 5.79 + 114.85 \times \text{YOBFRAC} - 300.28 \times \text{YOBFRAC}^2 + 939.11 \times \text{YOBFRAC}^3 - \\ 1649.2 \times \text{YOBFRAC}^4 + 1328.5 \times \text{YOBFRAC}^5 - 386.69 \times \text{YOBFRAC}^6 \end{aligned} \quad (4)$$

$$\begin{aligned} \text{All men, YOBFRAC} \leq 0.018 \text{ (} r^2 = 0.9927 \text{): years above baseline} = \\ 3963 \times \text{YOBFRAC} - 7.878 \times 10^5 \times \text{YOBFRAC}^2 + 9.174 \times 10^7 \times \\ \text{YOBFRAC}^3 - 5.954 \times 10^9 \times \text{YOBFRAC}^4 + 1.985 \times 10^{11} \times \text{YOBFRAC}^5 - \\ 2.628 \times 10^{12} \times \text{YOBFRAC}^6 \end{aligned} \quad (5)$$

$$\begin{aligned} \text{All men, YOBFRAC} > 0.018 \text{ (} r^2 = 0.9987 \text{): years above baseline} = \\ 8.9 + 157.2 \times \text{YOBFRAC} - 537.54 \times \text{YOBFRAC}^2 + 1419 \times \text{YOBFRAC}^3 - \\ 2009.2 \times \text{YOBFRAC}^4 + 1330.9 \times \text{YOBFRAC}^5 - 309.72 \times \text{YOBFRAC}^6 \end{aligned} \quad (6)$$

Age Distribution of Women age 20-49 Years in the 1990 Census (Byerly and Dearsdorf, 1995)

Similar to the age distributions required for DOD workers, to compare BLL variability in a subset of NHANES III participants (Maddaloni et al., 2005), census data on age distribution of women ages 20-49 years old in 1990 (Byerly and Deardorff, 1995) were fit to a third order polynomial.

$$\begin{aligned} \text{Women, (} r^2 = 0.99996 \text{): years above baseline} = 42.894 \times \text{YOBFRAC} - 29.165 \times \\ \text{YOBFRAC}^2 + 42.894 \times \text{YOBFRAC}^3 \end{aligned} \quad (7)$$

BACKGROUND LEVELS OF Pb IN AMBIENT AIR

The description of background levels of Pb in air was updated based on data in U.S. EPA (2013). Data on the median air concentration of Pb at sites reporting to the U.S. EPA Air Quality System Database (both non-source and source-oriented monitors) were taken from the text (1980) and Figure 2-21 of U.S. EPA (2013). The data in Figure 2-21 were digitized using WebPlotDigitizer (Version 4.1, released January 8, 2018, <https://apps.automeris.io/wpd/>, accessed May 14, 2018).

In the O'Flaherty (1993) model, the change in background air levels of Pb was described as follows: a constant background level (CAIR1 = 0.002 mg/m³) was assumed for all dates preceding 1975. For dates in 1975 and later, the concentration in air (AIR) was described as AIR = CAIR1 - (CAIR1 - CAIR2) × TIMES, with CAIR2 = 0.00015 mg/m³ and TIMES = exp(year - 1975) / (exp(5) + exp(year - 1975)), where exp(x) = e^x. In the updated description modified time-adjustment factor was incorporated with TIMES = [exp(year - 1975)]^{SF2} / (exp(SF1) + [exp(year - 1975)]^{SF2}) where SF1 (shape factor 1) and SF2 (shape factor 2) were adjusted to match new data.

This format allows the previous simulations to be replicated (with $SF1 = 5.0$, $SF2 = 1.0$, and $CAIR2 = 0.00015 \text{ mg/m}^3$) while allowing greater flexibility to capture trends that could not have been anticipated when the model was originally developed. Based on U.S. EPA (2013), an updated value for $CAIR2$ was identified as 0.000045 mg/m^3 . The shape factors were tuned by visual inspection to approximate the U.S. EPA (2013) data, with values of $SF1 = 1.2$ and $SF2 = 0.25$ providing a very good fit to the U.S. EPA (2013) median data (Figure D-3). The overall quality of the fit (discrepancy index) was quantified as the geometric mean of the discrepancy quotient for each point, defined as the maximum of modeled value/experimental value or the experimental value over the modeled value. As such, perfect agreement between the model and data would return a discrepancy index of 1. For the 2018 model, the maximum discrepancy quotient for the 22 points was 1.57 and the overall discrepancy index was 1.12, indicating that model-predicted air concentrations were typically within 12% of the U.S. EPA median. By contrast, the O'Flaherty (1993) model had similar accuracy for 1980 and 1990-1992, but for the entire U.S. EPA (2013) median air concentration data set, the discrepancy index was 2.11.

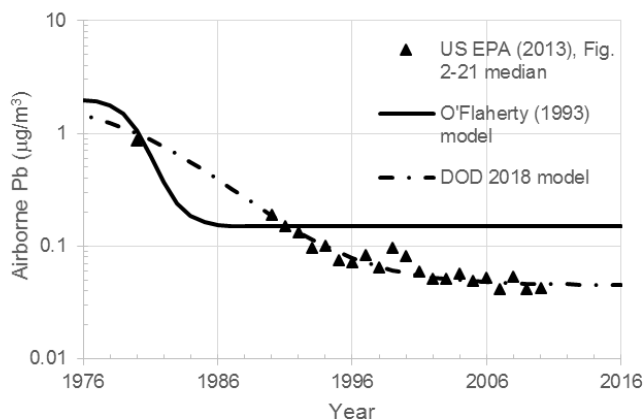


Figure D-3. Background air Pb concentrations in the U.S. ▲ = Medians from U.S. EPA (2013), Figure 2-21. Solid line: O'Flaherty (1993) model. Dashed-dotted line: DOD 2018 model.

LIST OF ABBREVIATIONS AND ACRONYMS

ACGIH	American Conference of Governmental Industrial Hygienists
AL	action level
BLL	blood lead level
CAIR	environmental air concentration
CAIR1	pre-1975 background air concentration
CAIR2	current background air concentration
Cal OSHA	California Department of Industrial Relations Division of Occupational Safety
CAMB	ambient air concentration
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Health
cOEL	candidate occupational exposure limit
CV	coefficient of variation
DMDC	Defense Manpower Data Center
DOD	Department of Defense
DOEHRS	Defense Occupational and Environmental Health Readiness System
EFH	Exposure Factors Handbook
EPA	Environmental Protection Agency
EXPOSMOD	exposure modifier
GFR	glomerular filtration rate
GMDI	geometric mean discrepancy index
GSD	geometric standard deviation
ICRP	International Commission on Radiological Protection
IEUBK	Integrated Exposure Uptake Biokinetic
IH	industrial hygiene
IPCS	International Programme on Chemical Safety
ITC	inhalation transfer coefficient
NAMRU Dayton	Naval Medical Research Unit Dayton
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council

NSC	normalized sensitivity coefficient
NTP	National Toxicology Program
OASD-EIE	Office of the Assistant Secretary of Defense for Energy, Installations, and the Environment
OEHHA	Office of Environmental Health Hazard Assessment
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PBBfinal	final blood Pb concentrations
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
RBC	red blood cell
SD	standard deviation
SF	shape factor
TSTC	Tri Service Toxicology Consortium
TSOMWG	Tri Service Occupational Medicine Working Group
TSIHWG	Tri Service Industrial Hygiene Working Group
TWA	time-weighted average
USAPHC	U.S. Army Public Health Command