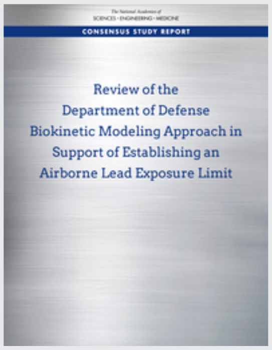

Review of the Department of Defense Biokinetic Modeling Approach in Support of Establishing an Airborne Lead Exposure Limit (2020)

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Review of the Department of Defense Biokinetic Modeling Approach in Support of Establishing an Airborne Lead Exposure Limit

Committee to Review DoD's Proposed Occupational Exposure Limits for Lead

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Consensus Study Reports published by the National Academies of Sciences, Engineering, and Medicine document the evidence-based consensus on the study's statement of task by an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and the committee's deliberations. Each report has been subjected to a rigorous and independent peer-review process and it represents the position of the National Academies on the statement of task.

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COMMITTEE TO REVIEW DOD'S PROPOSED OCCUPATIONAL EXPOSURE LIMITS FOR LEAD

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In the course of preparing its report, the committee held a public information-gathering session on June 13, 2019, to hear presentations from James Brown (U.S. Environmental Protection Agency), John Seibert (U.S. Department of Defense), Lisa Sweeney (UES, Inc.), and Kathleen Vork (California Environmental Protection Agency). Desmond Bannon (U.S. Department of Defense) served as the sponsor's point of contact during the study and facilitated responses to committee requests for written information.

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

G. Marius Clore, National Institutes of Health
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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **Mark Cullen**, Stanford University, and **Michael McCawley**, West Virginia University. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Acronyms and Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ACSL	Advanced Continuous Simulation Language
AF	absorption fraction
BLL	blood lead level
CV	coefficient of variation
DoD	U.S. Department of Defense
DOEHRS	Defense Occupational and Environmental and Health Readiness System
EPA	U.S. Environmental Protection Agency
GFR	glomerular filtration rate
GI	gastrointestinal
GSD	geometric standard deviation
ITC	inhalation transfer coefficient
MATLAB	Matrix Laboratory
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
Pb	lead
PBPK	physiologically-based pharmacokinetic
PEL	permissible exposure limit
RBC	red blood cell
TB	tracheo-bronchial
TLV	threshold limit value
TWA	time-weighted average
µg/dL	microgram per deciliter
$\mu g/m^3$	microgram per cubic meter

Contents

Summary

Military and civilian workers at the U.S. Department of Defense (DoD) can be exposed to airborne lead at firing ranges and in other occupational settings. In 1978, the Occupational Safety and Health Administration (OSHA) set the current permissible exposure limit for airborne lead at 50 µg/m^3. OSHA considers a blood lead level (BLL) of 40 µg/dL to be the upper acceptable limit to protect workers from adverse health effects. During the decades since OSHA set that limit, substantial scientific evidence pointed to a diversity of health effects associated with BLLs at less than 40 µg/dL. Based on that evidence and recommendations provided in 2013 by the National Research Council, DoD sought to identify BLLs lower than 40 µg/dL for worker removal and return to work. In addition, DoD sought to derive an airborne lead concentration corresponding to the BLL targeted by DoD management. That concentration is referred to as an occupational exposure limit (OEL), which is intended to represent the maximum contaminant concentration in the workplace that is intended to limit exposure concentrations and protect worker health.

DoD arranged for the use of a biokinetic model (also referred to as a physiologically-based pharmacokinetic [PBPK] model) to support the development of an OEL. Biokinetic modeling provides a mathematical technique for estimating absorption, distribution, metabolism, and excretion of chemicals, including particles and metals, in humans. Such models can be used to relate the amount of lead external exposure to the amount of lead found in the blood and other tissues at different points in time. DoD used a modified version of the O'Flaherty biokinetic model (referred to as the DoD-O'Flaherty model) to derive airborne concentrations of lead that correspond to BLLs for consideration by DoD management in establishing an updated OEL to replace the permissible exposure limit set by OSHA.

DoD requested that the National Academies establish an expert committee to evaluate whether the DoD-O'Flaherty model used to derive airborne lead concentrations from BLLs was appropriate. The committee was asked to consider whether an appropriate model was chosen, whether DoD's modifications to the model were appropriately justified, and whether the assumptions in and inputs to the model were reasonable. The committee was asked not to recommend specific OEL values.

As part of carrying out its task, the committee was asked to provide an overall summary conclusion on DoD's selected approach and the application of the approach for derivation of lead OEL values. It also was asked to address the following specific topics:

- Were the DoD-O'Flaherty model selection, parameterization, and validation appropriate, given the intended purpose—to develop OELs for DoD civilian and military workers?
- Were the inhalation rates used within the DoD-O'Flaherty model appropriate to represent DoD workers (military and civilian) who are occupationally exposed to lead?
- Were background levels of lead in air appropriately accounted for within the DoD-O'Flaherty model and representative of DoD workers who are occupationally exposed to lead?
- Is particle size variation appropriately accounted for within the DoD-O'Flaherty model and representative of lead absorption within the DoD workers (military and civilian) who are occupationally exposed to lead?

In its evaluation of model appropriateness, the committee considered questions posed in its Statement of Task and additional questions it selected from those commonly considered in reviews of PBPK model aspects. Elements of a biokinetic model that had the greatest impact on the predicted relationship between exposure concentrations of airborne lead and BLLs of adults received the greatest attention. The questions addressed by the committee were organized into four broad categories:

1. Was an appropriate model chosen?
2. Were structural modifications appropriately justified?
3. Were model assumptions and inputs reasonable?
4. Was the model application appropriate?

OVERALL CONCLUSION

The committee commends DoD for undertaking a very substantial, deliberative process to establish a lead exposure monitoring program intended to be more protective of its workers who are exposed to lead. The committee recognizes DoD's leadership in applying an innovative approach for establishing an OEL for lead using modern biokinetic modeling to develop quantitative relationships between occupational exposure and BLLs.

Overall, the committee found that the DoD-O'Flaherty modeling approach and application to support the development of an OEL for lead is appropriate. Specifically, an appropriate model was chosen, modifications to the model were appropriately justified, and the model assumptions and inputs were reasonable. The model was confirmed and shown to be sufficiently consistent with experimental data. The committee's conclusions resulting from its main considerations are summarized below. In addition, recommended ways in which DoD can improve the DoD-O'Flaherty model, its application, and documentation are also provided.

WAS AN APPROPRIATE MODEL CHOSEN?

DoD's evaluation of lead biokinetic models focused on the Leggett+ and O'Flaherty models, which are used to estimate BLLs resulting from exposure to lead in environmental media.[1] Both models met criteria for having appropriate compartments or processes for describing lead biokinetics, addressing the essential exposure routes, handling background lead exposure and occupational lead exposure, and calculating the corresponding lead dose-metric. The committee found that both the O'Flaherty and Leggett+ models described available BLLs with similar accuracy. Minor differences were cited by DoD as potential reasons for selecting one model over the other. However, the committee did not recognize that assessment as a basis for determining that either model would be inappropriate for use by DoD in developing a lead OEL.

Both the O'Flaherty model and Leggett+ model have been repeatedly utilized for more than a decade to calculate BLLs, with some modification by individuals using the model. Many of those applications have included separate reviews of the model's appropriateness.

DoD selected and modified the O'Flaherty model to support the development of a lead OEL. The O'Flaherty model has practical aspects that fit the purpose of DoD's modeling approach for supporting development of an OEL. For example, the model could be modified to facilitate probabilistic simulations of DoD worker populations. In addition, the model benefits from its treatment of birth date as a factor in historical exposures (e.g., dynamic background lead exposure).

The approach DoD used to select the model was reasonable and included consideration of the right models. The selection of the O'Flaherty model for use in developing an OEL for lead was appropriate and effectively justified.

[1]The Leggett+ model is a version of the Leggett model that was modified by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment.

WERE STRUCTURAL MODIFICATIONS TO THE MODEL JUSTIFIED?

DoD modified the O'Flaherty model code published in 2000 to run sensitivity analyses, Monte Carlo analyses, and other numerical simulations necessary to support the development of an OEL. The committee considered whether those changes might affect the representation of physiological compartments or processes that either alone or together impact lead biokinetics. The committee also considered changes made for supporting model operations, such as Monte Carlo analysis.

Model changes made by DoD in preparing the DoD-O'Flaherty model were justified appropriately. Changes made after publication of the O'Flaherty model in 2000, including those made by DoD, did not alter the model's representations of physiology or biochemical processes that would, in turn, affect representations of lead biokinetics relative to the model version described in 2000.

WERE THE MODEL ASSUMPTIONS AND INPUTS REASONABLE?

Model Consistency, Calibration, and Confirmation

As part of its Statement of Task, the committee was asked to consider whether the DoD-O'Flaherty model was appropriately validated. While the term validation is routinely used, DoD's efforts involved activities best described as model calibration and model confirmation. Calibration is the manipulation of parameter values for independent model variables to obtain a match between the observed and predicted dependent variables. Confirmation is the process of examining the consistency between model simulation results and observational/experimental data. The greater the number and diversity of confirmations that indicate consistency, the greater the likelihood the model accurately reflects the system under study.

To assess model calibration and confirmation, the committee focused on assessing whether the processes and results of selecting parameter values for calibration and confirmation were appropriate, whether appropriate data were used for model confirmation, and whether the consistency of the confirmation outcomes was adequate.

The calibration and confirmation of the DoD-O'Flaherty model were sufficient to conclude that, in general, the inputs and assumptions in the model were reasonable. The consistency of simulated BLLs between the DoD-O'Flaherty model and Leggett+ model provided additional evidence of the reasonableness of the model inputs and assumptions in the DoD-O'Flaherty model.

Though a comprehensive check of the correspondence between the code implementation and the external documentation of the DoD-O'Flaherty was not conducted by the committee, it performed several checks when questions arose about the code, particularly regarding the Monte Carlo analyses, and the committee found that the documentation faithfully reflected the implementation in the code. However a comprehensive error check of the model code is an important aspect of developing a biokinetic model for regulatory application.

DoD should conduct and document an error check of the DoD-O'Flaherty model to assure there are no mathematical errors or errors in the code and equations, and that the model reasonably reproduces the analytic results published in the 2019 model support document.

Particle Size Variation and Absorption Factor for Inhaled Lead

Particle size is an important variable in lead biokinetic modeling because it is an important determinant of the percentage of inhaled lead that is transferred to the blood, which is represented by the inhalation transfer coefficient (ITC).

Studies of airborne lead particle-size distributions, both in firing ranges and in other workplaces show particle diameters ranging from ultrafine size (< 0.1 μm) up to about 80 μm. However, definitive studies of the ITC for lead for a range of particle size distributions and activity levels have yet to be conducted. DoD assumed a point estimate of 30% for the ITC.

The approach used by DoD to assign an ITC value was reasonable, given the absence of definitive studies of the ITC and the wide range of airborne particle sizes expected in DoD occupational settings. However, DoD should consider evaluating the evidence of a wider band of ITCs, including the use of a local sensitivity analysis that is focused on examining the sensitivity of the model output to a higher deposition rate. Evidence supporting a role for tracheo-bronchial absorption of lead would be one factor that could influence the ITC. Strong evidence of a wider range of ITCs would justify inclusion of this factor in the Monte Carlo simulations used to establish the OEL.

An important part of relying on measurements of airborne lead concentrations to estimate BLLs is to use measurement methods that reliably sample the inhalable particle size fraction of airborne lead. The 37-mm plastic cassette is the typical sampling method used in the United States and many other countries for measuring airborne lead concentrations.

The typical 37-mm cassette-sampling device can result in airborne lead measurements that underreport total inhalable lead. DoD should verify that the sampling method used to implement the OEL utilizes a sampling device that measures total inhalable lead and does not suffer from the limitations of the typical 37-mm cassette sample.

Background Airborne Lead Concentrations

DoD updated the previous estimates of background air concentrations of lead used in the O'Flaherty model to reflect recent measurements that would better represent the airborne lead concentrations occurring during the lifetime of the DoD cohort. The updated background airborne lead concentrations used in the DoD-O'Flaherty model were obtained from the most recent U.S. Environmental Protection Agency (EPA) Integrated Science Assessment for Lead.

The use of airborne lead concentrations from that science assessment is appropriate, with the qualification that, according to EPA, the concentrations are heavily influenced by source monitors in the network. Source-oriented monitoring sites (e.g., next to airports used by aircraft that use leaded aviation fuel) are required near sources of lead emissions that contribute, or are expected to contribute, to ambient air lead concentrations that exceed National Ambient Air Quality Standards.

Therefore, measurements from source monitors may not reflect airborne lead concentrations experienced by DoD workers living and/or working at a distance from those sources. Conversely, they may better represent exposures for those that live in proximity to such sources. A more spatially and temporally informed approach was not available to DoD.

DoD made an additional adjustment, using a population modifier (EXPOSMOD), to background lead exposures to assure that total variability in BLLs was consistent with the BLL population variability reported in the scientific literature. The application of EXPOSMOD jointly to the oral (dietary) and inhalation components of exposure was appropriate. However, because the BLL distribution of the general population has changed over time, the correspondence between the model predictions and measured BLLs (both central tendency and geometric standard deviation [GSD]) are also variable.[2] Therefore, a single value for EXPOSMOD may not accurately represent all years considered in DoD's modeling approach.

Because dietary intake of lead tends to be the largest source of background lead exposure, estimates of the magnitude of dietary component can have a substantial effect on model estimates of non-occupational lead exposures. Previous versions of EPA's Air Quality Criteria for Lead may provide evidence of lower dietary lead concentrations prior to 1980 compared to those currently used in the model.

In general, background concentrations of airborne lead are appropriately accounted for in the DoD-O'Flaherty model. However, DoD should consider the evidence for a lower or declining BLL GSD and further consider if different values for EXPOSMOD over time may improve the model performance and accuracy of predictions for current and future OELs.

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[2]The modeled GSD is expected to directly influence the derived OELs.

In addition, DoD should consider reviewing the 1977 and 1986 EPA Air Quality Criteria for Lead to determine if using a lower dietary lead concentration for the pre-1980 background exposures would be more appropriate than those currently used in the DoD-O'Flaherty model.

Inhalation Rates

A key challenge for modeling DoD occupational lead exposure scenarios is to estimate long-term average daily lead intake via inhalation by using inhalation rates that adequately represent an expected range of activity patterns across the TriServices (U.S. Army, Navy, and Air Force). The committee considered two primary factors in evaluating the appropriateness of inhalation rates: (a) whether daily activity patterns were adequately represented, and (b) the strength of the underlying inhalation rate data for deriving distributions of inhalation rates. With respect to representing inhalation rates for daily activity patterns, DoD developed exposure scenarios that encompass activities of both typical workers and those who more likely engage in higher inhalation-rate activities. Under that approach, separate parameter values can be estimated for men and women. DoD intends for the DoD-O'Flaherty model to yield reasonable estimates of the relationship between exposure and BLLs to support the selection of an OEL intended to protect nearly all full-time military and civilian workers, including firing range personnel.

DoD's approach is reasonable for estimating inhalation rates of a general worker population and the use of gender specific inhalations rates is appropriate. The inclusion of the 95th percentile is reasonable to account for the higher activity patterns of some workers in the population.

The committee considered the strengths and limitations of the underlying inhalation rate data used to derive the inhalation rate distributions for derivation of the lead OEL. EPA's *Exposure Factors Handbook* was the primary source of data on inhalation rates. The handbook reports summary statistics (e.g., arithmetic mean, standard deviation, 95th percentile) grouped by age and gender. Overall, the data sources used to support inhalation rates for the model appear to be fit for purpose. The key studies are relatively current (published 2006 to 2009) and span survey years during the past 15 to 20 years. A major source of uncertainty of these data sources stems from the question of representativeness of the study populations (i.e., general worker populations) to the combination of military and civilian workers. It is conceivable that inhalation rates of military personnel are higher than average when they are engaged in strenuous activities. The extent to which the upper end of the distribution of inhalation rates proposed for derivation of the lead OEL adequately represents such high-end activity patterns of firing range personnel is unclear. This uncertainty may be offset to some degree by the inherent bias associated with the study protocols. Specifically, variability in inhalation rates measured during short periods is likely to be greater than variability in long-term average inhalation rates, which is the focus of DoD's modeling exercise. That may mean that the high-end estimate of the probability distribution (truncated at ± 2 standard deviations) from a study used to establish inhalation rates for the DoD analysis likely exaggerates long-term average daily inhalation rates for some military and civilian staff.

The data sources and general approach for developing the probability distributions of inhalation rates are reasonable. However, DoD should consider conducting additional Monte Carlo simulations at the candidate OELs using a distribution of inhalation rates (and cardiac outputs) representative of personnel with higher activity levels, such as those that might occur on a firing range. A comparison of the resulting BLL distributions to those used to derive the OELs should be used to determine the fraction or percentile of DoD workers in a higher activity group that would have BLLs below each target level. The analysis would illustrate the sensitivity of the model to inhalation rates in alternative exposure scenarios and the influence of uncertainty in the inhalation rate on outcomes. It would also help risk managers understand the level of protection afforded individuals with inhalation rates higher than those used to derive the candidate OELs.

Correlation Between Cardiac Output and Ventilation Rate

Ventilation rate and cardiac output are inherently correlated. The committee identified two potential issues related to the independence of cardiac output and ventilation rate in DoD's Monte Carlo analysis. First, if the Monte Carlo simulations included conditions where the expected ratio of inhalation rate to cardiac output was significantly violated, non-plausible physiological conditions could have arisen. The second issue has to do with the relationship between the inhalation rate and the glomerular filtration rate (GFR), which control the most significant rates of lead intake and elimination, respectively. The GFR is highly correlated with cardiac output, which is, in turn, highly correlated with inhalation rate. Changing inhalation rate, without corresponding physiologically accurate changes in cardiac output and GFRs, could establish unrealistic scenarios in which a lead dose rate increases but lead elimination through a correlated process decreases, instead of increasing. A main question is whether either issue would change the final distributions of BLLs for a given airborne lead concentration used to produce the final BLL distributions. The resulting BLL population distributions would then be in error. The committee notes that the coefficient of variation for the inhalation rate (0.2) may be small enough that perhaps there is little impact on the final BLL distribution from the ventilation rate-cardiac output correlation.

Varying cardiac output and ventilation rates may separately create non-physiological conditions in which a lead dose rate and renal clearance of lead do not increase and decrease together. DoD should explore the impact of correlated increases in ventilation rates and cardiac output on BLLs to determine if these parameters should be varied together, rather than independently, in the modeling of BLLs.

Model Documentation

Model documentation was spread among several documents, two technical reports, and the model code itself (which comprises many source-code files). This diversity of sources, style, and level of detail makes scrutiny of the mathematical and computational model rather burdensome. Though examination of the body of documentation permitted an evaluation of the model, it would have been highly desirable to have a single document that detailed the model structure, equations, parameters, and assumptions.

Documentation of the DoD-O'Flaherty model needs to be improved. DoD should prepare a support document for the DoD-O'Flaherty model in a manner similar to EPA's documentation of the Integrated Exposure Uptake Biokinetic Model. In addition, the support document for the DoD-O'Flaherty model should include:

- **An illustrative figure representing the compartmental structure, blood flows, and mass transfers.**
- **Information contained in DoD's response to the committee's information request of 2019.[3]**
- **Documentation of an error check of the DoD-O'Flaherty model code, and assurance that the model reasonably reproduces the analytic results published in the 2019 model support document.**
- **Strategies that would allow the DoD-O'Flaherty model to be usable in the future because the model relies on software that is no longer supported by the company that developed it.**

[3]On June 27, 2019, the committee submitted a written request to DoD for information on the DoD-O'Flaherty modeling approach. The information topics included the DoD-O'Flaherty model structure, changes DoD made to the 2000 version of the O'Flaherty model, the basis for DoD's estimated average removal duration for DoD workers, who exhibited elevated BLLs; DoD job activities that have the potential to result in lead exposure; modeled exposure scenarios; and approaches for selecting model parameters for the Monte Carlo analyses.

WAS THE APPLICATION OF THE MODEL APPROPRIATE?

In evaluating the overall approach and application of the DoD-O'Flaherty model for derivation of candidate OELs for lead, the committee considered the appropriateness of the model, the model assumptions and inputs, and several other factors.

In general, the committee agreed that the approach of using a biokinetic model to establish monitoring equivalent air concentrations representative of upper-bound BLLs is sound and well justified. The modeled population reasonably represented the worker population that DoD seeks to monitor and protect.

The assumptions and inputs to the model were largely considered appropriate. The approach considered variability in important exposure, physiological, and biokinetic parameters, including each in a Monte Carlo simulation producing likely distributions of resulting BLLs from which an OEL could be established. However, the committee observed that the results of the Monte Carlo analyses were not presented in a manner that gave the reader an appreciation for the prediction intervals or envelope. **The results of Monte Carlo analysis would be more useful to the reader if they included mean values of measures with prediction intervals based on model uncertainty and variability/error in the data used for parameterization.**

In carrying out its task, the committee's overall conclusion is that the DoD-O'Flaherty modeling approach and application to support the development of a lead OEL are appropriate. The committee's recommendations provide ways in which DoD can improve the DoD-O'Flaherty model, its application, and documentation.

1

Introduction

Human exposure to lead can cause adverse effects in the nervous, cardiovascular, renal, hematologic, immunologic, and reproductive systems. Lead exposure is also known to induce adverse developmental effects in utero.

The primary route of lead exposure in the workplace is through the inhalation of airborne particles containing lead. Worker exposure can be measured by sampling the air concentration of lead within the workers' breathing zone. In order to determine if workers inhale too much lead, industrial or occupational hygienists compare the measured worker exposures to an occupational exposure limit (OEL). The OEL is a general term for a maximum contaminant level in the workplace that is intended to limit exposure concentrations and protect worker health. (See Box 1-1.)

The Occupational Safety and Health Administration (OSHA) sets and enforces national standards for safety and health in the workplace. In carrying out its mission, OSHA sets 8-hour time-weighted-average (TWA) permissible exposure limits (PELs) as the highest concentration of a chemical to which a worker may be exposed (29 CFR 1910.1000).

In 1978, OSHA set the current PEL for airborne lead at 50 $\mu g/m^3$ (29 CFR 1910.1025) based on an assessment of studies that reported adverse health effects at different blood lead levels (BLLs). OSHA considers an average BLL of 40 μg/dL to be the upper acceptable limit to protect workers from adverse health effects.

PREVIOUS NATIONAL ACADEMIES REPORT ON POTENTIAL HEALTH RISKS TO U.S. DEPARTMENT OF DEFENSE FIRING-RANGE PERSONNEL FROM RECURRENT LEAD EXPOSURE

During the decades since the OSHA PEL was set, reviews of the scientific literature reported substantial evidence of a diversity of health effects associated with BLLs at less than 40 μg/dL (e.g., EPA [2006] and NTP [2012]). In light of the relationships between lead exposure and adverse health effects, the U.S. Department of Defense (DoD) asked the National Academies to evaluate potential health risks to firing-range personnel from recurrent lead exposure and determine whether the current OSHA exposure standard for lead adequately protects DoD firing-range workers. The committee established by the National Academies in response to DoD's request concluded that a BLL of less than 40 μg/dL (which is implicit in the OSHA standard) is not sufficiently protective of personnel who have repeated lead exposures on firing ranges (NRC 2013). That committee recommended that DoD review its guidelines and practices for protecting workers from lead exposure on firing ranges. That committee also recommended that DoD consider lowering the acceptable BLLs to more stringent levels that reduce the risk of adverse health effects in workers.

DOD'S INITIATIVE TO DEVELOP AIRBORNE LEAD OCCUPATIONAL EXPOSURE LIMITS

In response to that National Academies report, DoD pursued the development of lower allowable BLLs and lower OELs that would apply to all occupational exposures within DoD, not just firing ranges (Seibert 2019). DoD used a phased approach for developing an OEL for airborne lead (see Figure 1-1).

BOX 1-1 Occupational Exposure Limits (OELs)

OELs are set using toxicological data and epidemiologic health effects to define the level at which nearly all workers can be exposed without significant health effects (Jahn et al. 2015; Nims 1999; Ramachandran 2005). OELs are set by government agencies and nongovernmental organizations with the overall goal of ensuring a safe and healthful work environment (Friis 2016). An OEL is exceeded when the measured concentrations are statistically higher than the 95% upper confidence limit of the 95th percentile of airborne concentrations (Jahn et al. 2015).

OELs do not protect all workers (Perkins 1997) and the quality of OELs depends on the data and information used to set the limit (Jahn et al. 2015). The workers themselves can also affect whether OELs are protective. Physiologic changes within workers, such as pregnancy, will increase the likelihood that the OEL is not protective of the worker. Worker hobbies and non-occupational exposures also increase the likelihood that the OEL is not protective of the worker. Therefore, just having measured exposures lower than the OEL is not a guarantee that the health of workers is protected (Anna 2011). (See Box 3-1.)

As described in Sweeney (2019), the approach comprised revising the risk management options for measured BLLs in DoD occupational settings, developing airborne exposure levels that would be predictive of BLLs of concern, analyzing impacts on DoD's mission and costs associated with lowered BLLs, and selecting and implementing the OEL.

Based on its review of the literature on health effects at BLLs less than 40 µg/dL, a team assembled by the U.S. Army Public Health Command recommended replacing the OSHA BLL guidelines for worker removal and return to work with more stringent guidelines. The team also provided multiple management recommendations for various BLLs in the range of < 5 to > 80 µg/dl (USAPHC 2017).

As indicated in Figure 1-1, DoD's approach for developing an OEL for airborne lead involved deriving airborne lead concentrations for BLLs of interest to DoD management. The airborne concentrations were estimated by using a biokinetic model (also referred to as a physiologically-based pharmacokinetic model).[1] Biokinetic modeling provides a mathematical technique for estimating absorption, distribution, metabolism, and excretion of a chemical in humans. Such models can be used to relate the amount of lead exposure to the amount of lead found in the blood and other tissue at different points in time. The O'Flaherty biokinetic model was recommended for use in OEL development by DoD (Sweeney 2015). Sweeney (2019) describes, in general, how the O'Flaherty model was modified and presents the results of applying the DoD-O'Flaherty model in support of developing a lead OEL for DoD workers.

COMMITTEE'S STATEMENT OF TASK FOR THE REVIEW OF THE DOD-O'FLAHERTY MODEL

DoD requested that a National Academies committee be established to evaluate whether the DoD-O'Flaherty model used to derive airborne lead concentrations from BLLs, as described in Sweeney (2019), was appropriate (see Appendix A for the committee's Statement of Task). The committee also was asked to consider whether an appropriate model was chosen, whether modifications to the model were appropriately justified, and whether the assumptions in and inputs to the model were reasonable. The committee was asked not to recommend specific OEL values.

As part of carrying out its task, the committee was asked to provide an overall summary conclusion on DoD's selected approach and the application of the approach for derivation of lead OEL values. It also was asked to address the following specific topics:

- Were the DoD-O'Flaherty model selection, parameterization, and validation appropriate, given the intended purpose—to develop OELs for DoD civilian and military workers?

[1]In this report, the terms physiologically-based pharmacokinetic model and biokinetic model are interchangeable.

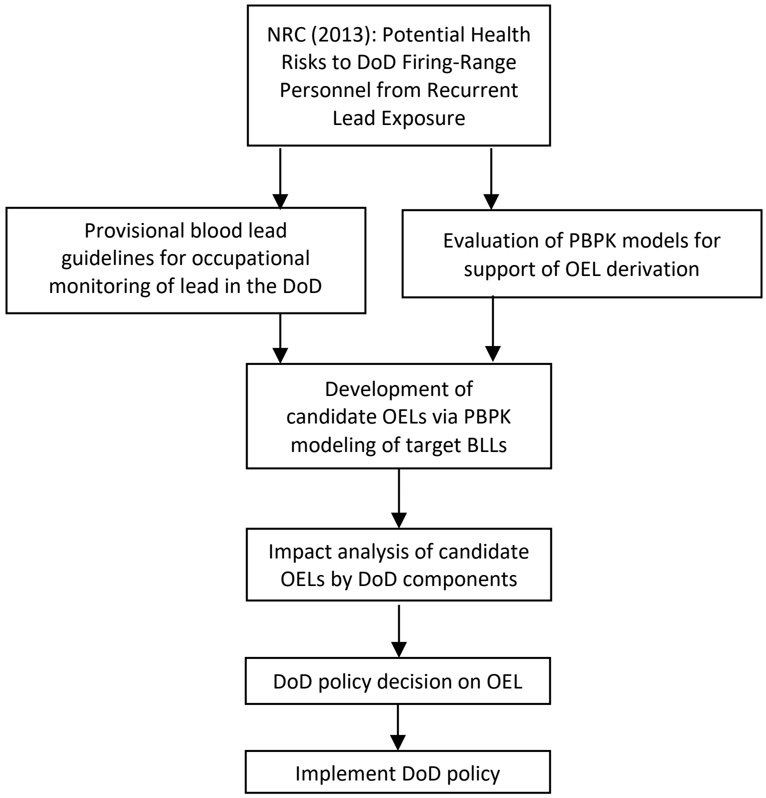

FIGURE 1-1 Outline of DoD's approach in the assessment and management of risks of DoD worker health from airborne lead exposure. NOTE: BLL = blood lead level; DoD = U.S. Department of Defense; NRC = National Research Council; OEL = occupational exposure limit; PBPK = physiologically-based pharmacokinetic. SOURCE: Adapted from Sweeney (2019).

- Were the inhalation rates used within the DoD-O'Flaherty model appropriate to represent DoD workers (military and civilian) who are occupationally exposed to lead?
- Were background levels of lead in air appropriately accounted for within the DoD-O'Flaherty model and representative of DoD workers who are occupationally exposed to lead?
- Is particle size variation appropriately accounted for within the DoD-O'Flaherty model and representative of lead absorption within the DoD workers (military and civilian) who are occupationally exposed to lead?

ORGANIZATION OF THE REPORT

In Chapter 2, the committee discusses the approach it used to address the elements of its task, as well as other relevant aspects. In doing so, the committee presents considerations for determining the appropriateness of DoD's selected approach and the application of that approach for derivation of airborne concentrations from BLLs. Chapter 3 presents the committee's evaluation of the specific items listed in its Statement of Task and other relevant aspects. The chapter also provides conclusions and recommendations stemming from the committee's evaluations.

2

Committee's Approach to Its Task

In response to the U.S. Department of Defense's (DoD's) request, the National Academies assembled a committee of eight members (biographical sketches of the members are presented in Appendix B). In the course of preparing its report, the committee held three meetings. Its June 2019 meeting included a public information-gathering session to hear presentations from representatives of DoD, the U.S. Environmental Protection Agency (EPA), and the California Environmental Protection Agency on issues relevant to DoD's efforts for developing an occupational exposure limit (OEL) and the use of the DoD-O'Flaherty model to support that activity. In addition, the committee considered relevant written material it received from DoD and other organizations.

It is important to note that the committee was not asked to, nor did it attempt to carry out, a comparative assessment of various modeling approaches to determine if the DoD-O'Flaherty model is the *best* model that could be used for developing an OEL for DoD workers. Consistent with its Statement of Task, the committee focused on evaluating whether DoD's selected modeling approach and the application of the approach were appropriate for deriving candidate lead OELs.

The committee did not perform a comprehensive evaluation of the DoD-O'Flaherty model framework, including the model code, equations, and model variables that define the model. In addition, the committee did not attempt to verify the ability of the model to reproduce results reported in Sweeney (2019), which presents model estimates of the workplace airborne lead concentrations that would correspond to maintaining personnel blood lead levels (BLLs) below various specified concentrations. While such activities are important aspects of developing a biokinetic model for regulatory application, the committee determined that such activities were not necessary to carry out its Statement of Task.

The DoD-O'Flaherty model is intended to derive TWA candidate OELs that would be used to maintain the BLL of the 95th percentile DoD employee below a specified BLL for a working lifetime. The committee did not consider how the model might be used for assessing short-term exposures (e.g., over 1 day or week), because that would be a use of the model that is separate from supporting the establishment of an OEL.

CONSIDERATIONS FOR DETERMINING MODEL APPROPRIATENESS

In its evaluation of model appropriateness, the committee considered questions posed in its Statement of Task and additional questions it selected from those commonly considered in reviews of physiologically-based pharmacokinetic models (see, e.g., Barton et al. 2007; Chiu et al. 2007; Clark et al. 2004; McLanahan et al. 2012). Selection of additional aspects for review supported a fuller assessment of model appropriateness by providing focus and detail to the broad questions posed by DoD. Additionally, the committee focused its evaluation on the elements of biokinetic modeling that may have the greatest impact on the predicted relationship between exposure concentrations of airborne lead and BLLs of adults. The questions addressed by the committee were organized into four broad categories, which were ordered to reflect DoD's model selection and development process. Presented in the order they are addressed in this report, the questions are:

- Was an appropriate model chosen?
- Were structural modifications appropriately justified?

- Were model assumptions and inputs reasonable?
- Was the model application appropriate?

The committee's final summary conclusions regarding the approach and application of the approach are built from the analyses of those four broad questions. In assessing whether specific aspects of DoD's modeling approach and its application were appropriate or reasonable, the committee often relied on its professional judgment, as it was not feasible to apply specific written standards.

COMMITTEE'S USE OF TERMS

In Sweeney (2015, 2019), the term "model parameter" is used to refer to the components of the model structure and the term "inputs" is used to refer to the parameter values, where some inputs are described as probability distributions for sets of parameters. The committee elected to clarify its charge to evaluate "parameterization" of the model by adopting definitions consistent with EPA's guidance (EPA 2001a; see Box 2-1). The committee used the term "model variable" when referring to a factor used in an equation, whereas "model parameter" is the value assigned to that variable. The committee focused its review on the appropriateness of the parameter values selected to represent point estimates and probability distributions.

The terms validation, verification, calibration, and evaluation are commonly used in reporting the outcomes from an assessment of biokinetic models, such as the DoD-O'Flaherty model. While terms such as verification and validation are routinely and even interchangeably used, these terms have specific meanings (Oreskes et al. 1994; see Box 2-1) and typically do not apply to the development and assessment of most biokinetic models. The committee found that DoD's efforts involved activities best described as model calibration and model confirmation, rather than verification and validation, which can rarely be established for models of open systems (EPA 2009a; Oreskes et al. 1994).

BOX 2-1 Definition of Terms

Calibration—manipulation of parameter values for independent model variables to obtain a match between the observed and predicted dependent variables.

Confirmation—the process of examining the consistency between model simulation results and observational/experimental data. The greater the number and diversity of confirmations that indicate consistency, the greater the likelihood that the model accurately reflects the system under study.

Model variable—a factor used in an equation that is part of the overall biokinetic model functionality.

Parameter value—the value used as an input to the model; for a model variable described by a single parameter (i.e., point estimate), the parameter value may represent the arithmetic mean or upper percentile of a distribution; for a variable described by a probability distribution, the value represents one of the distribution parameters, as described above, and is referred to as a model parameter.

3

Committee's Review of the DoD-O'Flaherty Model

WAS AN APPROPRIATE MODEL CHOSEN?

The U.S. Department of Defense (DoD) selected and modified the O'Flaherty model (O'Flaherty 1993) to support the development of a lead occupational exposure limit (OEL). The O'Flaherty model is one of several biokinetic models that are used to estimate blood lead levels (BLLs) resulting from exposure to lead in environmental media. For example, the U.S. Environmental Protection Agency (EPA) uses the Integrated Exposure Uptake Biokinetic model for lead in children (EPA 1994; White et al. 1998) and the agency is reviewing the All Ages Lead Model to assess childhood and adult lead exposures (EPA 2001b, 2019). Another biokinetic model is the Leggett+ model, which is a version of the Leggett model that was modified by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment to relate airborne lead exposures to BLLs among workers under various exposure conditions (Vork et al. 2013).

To determine if an appropriate model was chosen, the committee reviewed DoD's evaluation of existing lead biokinetic models, which focused on the Leggett+ and O'Flaherty models (Sweeney 2015). Information presented during the committee's public meeting in May 2019 and written material provided by DoD after the meeting were also considered. In its review, the committee focused on the appropriateness of the compartmental structure of the model and processes to represent various aspects of occupational exposure and dynamic background lead concentrations in the context of relating worker lead exposure to BLLs. Prior use of the model for contextually similar analyses and prior review of models was considered evidence of model appropriateness. No effort was made to discriminate between appropriate models and the best model.

The Integrated Exposure Uptake Biokinetic model describes the biokinetics of lead in children 7 and under. The committee agreed with Sweeney (2015) that the model is not useful for lead OEL development in an adult population. EPA's All-Ages Lead Model was under review and was not available for consideration by DoD for model selection. This model remains under review by a panel of the EPA Scientific Advisory Board and was not considered further by the committee.

The remaining models, O'Flaherty and Leggett+, both met criteria for having appropriate compartments or processes for describing lead biokinetics, addressing the essential exposure routes, handling background lead exposure and occupational lead exposure, and calculating the corresponding blood lead dosemetric. Reviewing the comparisons made in Sweeney (2015), the committee found that both the O'Flaherty and Leggett+ models described available BLLs with similar accuracy. Minor differences (such as, in predicting some BLLs for inhalation and lead in urine and bone) were cited in Sweeney (2015) as potential reasons for selecting one model over the other. However, the committee did not recognize that assessment as a basis for determining that either model would be inappropriate for use by DoD in developing a lead OEL.

Both the O'Flaherty model and the Leggett model have been repeatedly utilized for more than a decade to calculate BLLs, with some modification by individuals using the model, including government agencies, such as EPA and their contractors, and the California Department of Industrial Relations. Many of those applications have included separate reviews of the models' appropriateness (see, e.g., EPA 2006).

The O'Flaherty model has practical aspects that fit the purpose of DoD's modeling approach for supporting development of an OEL. For example, the model could be modified to facilitate probabilistic simulations of BLLs of DoD worker populations. In addition, the model benefits from its treatment of birth date as a factor in historical exposures (e.g., dynamic background lead exposure).

The committee considered the consistency between modeled and observed BLLs for workers and non-workers who were exposed to airborne lead, an important aspect of appropriateness. Adequate consistency was exhibited by the O'Flaherty model in estimating BLLs following community exposures to ambient lead concentrations (Azar et al. 1975) in the 1 to 10 μg/m^3 range of interest for DoD (see Figure 3-1).

The approach DoD used to select the model was reasonable and included consideration of the right models. The selection of the O'Flaherty model for use in developing an OEL for lead was appropriate and effectively justified.

WERE STRUCTURAL MODIFICATIONS TO THE MODEL JUSTIFIED?

Modifications of the O'Flaherty model were required to run sensitivity analyses, Monte Carlo analyses, and other simulations necessary to support the development of an OEL. DoD documented changes it had made to the model, and those made after preparation of the O'Flaherty model (O'Flaherty 2000) and before DoD's receipt of the model code. The committee considered whether changes might affect the representation of physiological compartments or processes that either alone or together impact lead biokinetics. The committee also considered changes made for supporting model operations, such as Monte Carlo analysis. Supplemental information provided to the committee by DoD documented all revisions to the model code (DoD 2019).

After reviewing the code changes provided in DoD's documentation, the committee agreed with DoD's summary statement that:

> Most of the changes were implemented to allow for the desired Monte Carlo simulations, including the selection of population-specific birth years and gender distributions. Other changes had been added (mostly by Gary Diamond) between the preparation of O'Flaherty (2000) and when DoD received Pb [lead] model code from Dr. Diamond in 2012. The other changes were to change the way two model parameters were computed: post-1975 background air concentrations of Lead and inhalation rate. (DoD 2019, p. 4)

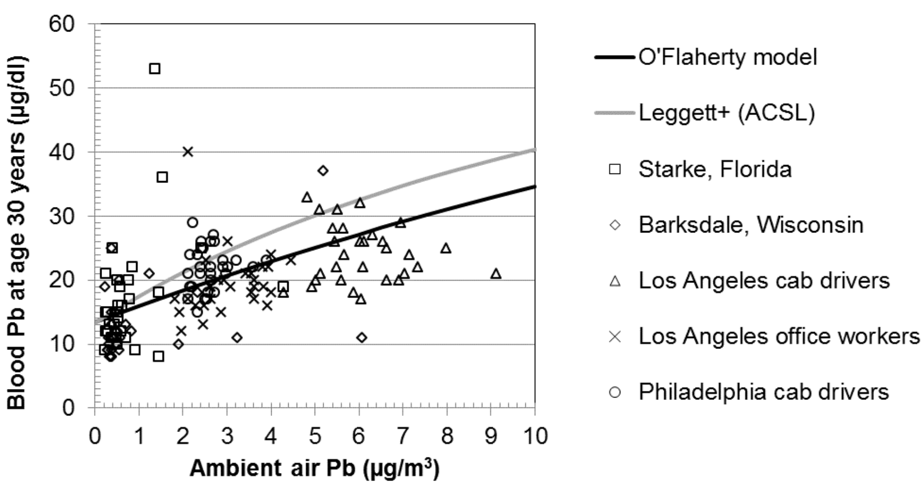

FIGURE 3-1 Simulations of 30-year exposure (from birth) to varying levels of ambient lead. NOTE: ACSL = Advanced Continuous Simulation Language; Pb = lead. SOURCES: Azar et al. (1975), as presented in Sweeney (2015, 2019).

Model changes made by DoD in preparing the DoD-O'Flaherty model were justified appropriately. Changes made after publication of the O'Flaherty model in 2000, including those made by DoD, did not alter the model's representations of physiology or biochemical process that would, in turn, affect representations of lead biokinetics relative to the model version described in 2000.

WERE THE MODEL ASSUMPTIONS AND INPUTS REASONABLE?

Assessment of a mathematical model is a multifaceted process that often attempts to answer the following questions:

1. Does the mathematical representation capture, to some appropriate degree, the underlying process to be simulated?
2. Does the model code faithfully represent the intended mathematics?
3. Do predictions from the computational model match known exact solutions in limiting cases?
4. Are model predictions consistent with relevant experimental measurements to some specified tolerance (calibration and confirmation)?
5. Do predictions from the computational model agree with results from comparable, independently developed models (consistency)?

The first two questions, listed above, were outside the scope of the committee's effort. However, the committee notes, as summarized below, the long-term use and multiple reviews of the O'Flaherty model, and general consistency with the Leggett+ model are evidence that the code likely represents the intended mathematics and that the mathematics, to some degree, properly reflects the important underlying processes being simulated.

The third question is impracticable to answer for a complex open-system model. Also, many practitioners of PBPK modeling do not find it useful to examine exact solutions in limiting cases (also referred to as edge cases).

The committee focused on the fourth and fifth questions: whether the processes and results of selecting parameter values for calibration and confirmation were appropriate, whether appropriate data were used for model confirmation, and whether the consistency of the confirmation outcomes was adequate.

Model Calibration, Confirmation, and Consistency

The procedure for model calibration (i.e., manipulation of the independent variables to obtain a match between the observed and predicted dependent variables) in the O'Flaherty model is described in O'Flaherty (1993) and Sweeney (2019). As mentioned above, Sweeney (2019) modified elements of the model structure and several model parameters to add Monte Carlo analysis functionality and incorporate findings from additional studies, but these changes necessitated minimal calibration of the model.

The Bayesian approach is an alternative to the model calibration strategy used by O'Flaherty (1993) and adopted by DoD. The Bayesian approach would provide several benefits:

- Evaluation of estimates of the distribution for each parameter, based on uncertainty in the underlying experimental data and the variability in the model parameter;
- Ability to easily update estimates for parameter distributions with data from other studies; and
- Estimation of parameter distributions over a hierarchy that can include population, study, and individual levels.

A considerable effort would be needed to conduct a Bayesian parameter estimation for this model in a proper manner. Each data set supporting the parameterization would need to be characterized in terms of an appropriate uncertainty model associated with each data point. However, only mean values of key data are usually available in the published literature, without the underlying primary data needed to obtain error estimates and conduct hierarchical analyses. The committee did not consider a Bayesian approach to be warranted for the DoD-O'Flaherty model because it had no evidence that the approach would or would not significantly change the candidate OELs established from the Monte Carlo simulations.

The O'Flaherty model (a version prior to DoD modifications) was confirmed through comparison of simulated and measured BLLs from 14 studies documented by Sweeney (2015, Table 1, 2019, Table B1). Figures 3-1 and 3-2 present two examples of such comparisons, where lead concentrations in whole blood are expressed as a function of inhaled concentrations. These results are important because airborne lead concentrations are in the region of interest for the DoD exposure scenarios.

The O'Flaherty model–simulated BLLs were similar to those of the Leggett+ model tested under specific conditions (Sweeney 2015). Agreement with the Leggett+ model, which is a lead biokinetic model independently developed by a regulatory agency, was viewed by the committee as additional evidence of the appropriateness of the O'Flaherty model. Consistency with another model of different formulation suggests, but does not prove, that the mathematical formulation is sound.

Overall, based on the range of comparisons conducted, Sweeney (2019) concluded that:

- The O'Flaherty model had an acceptable accuracy (model predictions were, on average, within a factor of two of the data, per IPCS 2010), and
- The O'Flaherty and independently developed Leggett+ model were similar in their ability to simulate BLLs.

The DoD-O'Flaherty model was not calibrated or confirmed for workers with specific biochemical or physiological vulnerabilities, for example, kidney disease, liver disease, or respiratory diseases that might significantly impact lead pharmacokinetics and resulting BLLs. Sweeney (2019) indicates in Section 2.3 that because the DoD-O'Flaherty modeling effort is intended to support the development of an OEL, it is appropriate to consider that an OEL is intended to protect nearly all workers, but is not an absolute guarantee of worker safety. The objective of protecting nearly all workers is consistent with the definition of Threshold Limit Values provided by the American Conference of Governmental Industrial Hygienists (ACGIH 2019; see Box 3-1). Sweeney also reported that the selection of the 95th percentile, which predicted BLL in healthy men and women following full-time, long-term lead exposure, was consistent with established occupational health practices (Sweeney 2019). The committee accepted that DoD's derivation of an OEL for lead was intended to provide a similar level of protection offered by threshold limit values (TLVs) (nearly all workers), and did not further consider whether the biokinetic model provided adequate protection to workers with specific vulnerabilities.

The calibration and confirmation of the DoD-O'Flaherty model were sufficient to conclude that, in general, the inputs and assumptions in the model were reasonable. **The consistency of simulated BLLs between the Leggett+ and O'Flaherty models provided additional indirect evidence of the reasonableness of the model inputs and assumptions in the DoD-O'Flaherty model.**

Though a comprehensive check of the correspondence between the code implementation and the external documentation of the DoD-O'Flaherty was not conducted by the committee, it performed several checks when questions arose about the code, particularly regarding the Monte Carlo analyses, and the committee found that the documentation faithfully reflected the implementation in the code. However a comprehensive error check of the model code is an important aspect of developing a biokinetic model for regulatory application.

DoD should conduct and document an error check of the DoD-O'Flaherty model to assure there are no mathematical errors or errors in the code and equations, and that the model reasonably reproduces the analytic results published in Sweeney (2019).

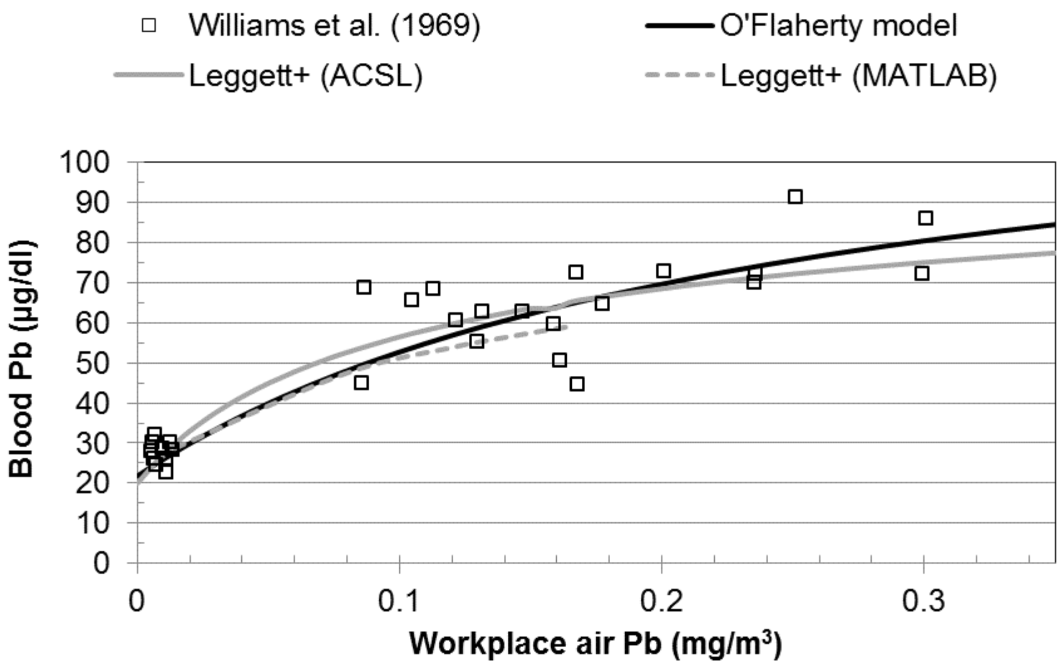

FIGURE 3-2 Comparison of model simulations to experimental data for workers in a lead-acid battery factory. NOTE: ACSL = Advanced Continuous Simulation Language; MATLAB = Matrix Laboratory; Pb = lead. SOURCES: Williams et al. (1969), as presented in Sweeney (2015, 2019).

BOX 3-1 Threshold Limit Values (TLVs)

The American Conference of Governmental Industrial Hygienists (ACGIH) is a charitable scientific organization that advances occupational and environmental health. One example of that effort is issuance of TLVs. According to ACGIH, TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects.

ACGIH recognizes that there will be considerable variation in the level of biological response to a particular chemical substance, regardless of the airborne concentration. Indeed, TLVs do not represent a fine line between a healthy versus unhealthy work environment or the point at which material impairment of health will occur. TLVs will not adequately protect all workers. Some individuals may experience discomfort or even more serious adverse health effects when exposed to a chemical substance at the TLV or even at concentrations below the TLV. There are numerous possible reasons for increased susceptibility to a chemical substance, including age, gender, genetic factors (predisposition), lifestyle choices (e.g., diet, smoking, abuse of alcohol and other drugs), medications, and pre-existing medical conditions (e.g., aggravation of asthma or cardiovascular disease). Some individuals may become more responsive to one or more chemical substances following previous exposures (e.g., sensitized workers). Susceptibility to the effects of chemical substances may be altered during different periods of fetal development and throughout an individual's reproductive lifetime. Some changes in susceptibility may also occur at different work levels (e.g., light versus heavy work) or at exercise—situations in which there is increased cardiopulmonary demand. Additionally, variations in temperature (e.g., extreme heat or cold) and relative humidity may alter an individual's response to a toxicant. The Documentation for any given TLV must be reviewed, keeping in mind that other factors may modify biological responses.

SOURCE: ACGIH (2020).

Particle Size Variation and Absorption Factor for Inhaled Lead

For the amount of airborne lead a person inhales, the fraction that is transferred to the person's blood is a key assumption in the DoD-O'Flaherty model. Inhalation of lead that is adsorbed to, or contained in, airborne particles is deposited in the airways and can be transferred to the blood via two pathways: directly from the alveolar region, and indirectly from the gastrointestinal (GI) tract, after deposited lead moves up the mucocilliary ladder and into the GI tract. In the DoD-O'Flaherty and Leggett+ models, the percentage of inhaled lead that is transferred to the blood is represented by the inhalation transfer coefficient (ITC). The ITC depends on the amount, size, and solubility of deposited lead particles and their location in the extra-thoracic, tracheo-bronchial (TB), and alveolar regions of the respiratory tract after deposition. The region-specific particle deposition fractions depend on particle size distribution and breathing rate. For particles that deposit in the upper airway—a function of particle size—and are later swallowed, conditions in the GI tract also influence the ITC. Particle size is, therefore, an important determinant of the ITC in lead biokinetic modeling and particle sizes can vary significantly in the occupational environment. Studies of airborne lead particles, both in firing ranges (e.g., Lach et al. 2015) and in other workplaces (e.g., Petito Boyce et al. 2017) show distributions of particle diameters ranging from ultrafine size (< 0.1 µm) up to about 80 µm.

In evaluating how DoD considered the substantial variability in particle size, the committee focused on how particle size was addressed in derivation of the ITC. This approach was selected because the committee determined it would not be feasible or practical for DoD to derive multiple OELs, each specific to the particle size and breathing rates for individual occupational settings.

A number of approaches have been used by researchers to estimate ITC values. However, definitive studies of the ITC for lead for a range of particle size distributions and activity levels have yet to be conducted. The earliest approach adopted by the Occupational Safety and Health Administration (OSHA) (Carelli et al. 1999; Froines et al. 1986; Hodgkins et al. 1990) has been to assume that the first 12.5 µg/m^3 of inhalation exposure is all submicron particles and 37% of the mass of that deposited fraction is absorbed systemically, while the remainder of the inhalation exposure is assumed to be larger particles that reach the GI tract, where 8% of the mass is absorbed.

Consider, for example, the airborne lead concentration of 72 µg/m^3, labeled as ISR TOX in Lach et al. (2015, Table 1). The ITC is obtained from a weighted average of the submicron concentration of 12.5 µg/m^3 and the concentration attributable to larger particles (72 to 12.5) µg/m^3:

$$\text{ITC} = (12.5/72) \times 0.37 + (59.5/72) \times 0.08 = 0.13 \text{ or } 13\% \qquad \text{(Equation 1)}$$

Several authors have criticized that approach for not using realistic assumptions of particle size distributions and for assigning fractions of submicron particles that were much less than assumed by OSHA (Froines et al. 1986). Other researchers (Vork 2013; Petito-Boyce 2017) used this equation:

$$\text{ITC} = [(\text{alveolar deposition fraction}) \times (\%\ \text{lung absorption})] + [(\text{ciliated and head region deposition fraction}) \times (\%\ \text{GI absorption})] \qquad \text{(Equation 2)}$$

Vork (2013) reviewed previously published literature on lead absorption by various routes and for different particle size distributions in several industries with differing lead operations that generate a range of particle sizes. Hursh et al. (1969) and Gross (1981) estimated values of about 35% for pulmonary absorption. GI absorption fractions reported in the literature varied widely (1% to 80%). According to Vork (2013, p. 28):

> This wide range occurs in part because absorption of lead from the gastrointestinal tract depends strongly on a variety of factors, including the level of minerals, fat, protein, and vitamin D present in

the intestines; the body's iron or zinc status; the amount of lead and the physical and chemical form administered; and the length of fasting. (Leggett 1993)

ITC values were calculated for four different industrial settings (two that generate finer particles and two that generate coarser particles) and five activity levels (resting, sitting, light work, moderate work, heavy work). Based on those previous studies and the calculations for the four industries (Liu et al. 1996; Park and Paik 2002; Spear et al. 1998a,b) and activity levels, Vork (2013) assumed a value of 30% absorption for GI absorption and 100% absorption for pulmonary absorption. The 30% GI absorption value represented a 24-hour TWA absorption of 30%, assuming 10 hours fasting (50% absorption fraction [AF]), 10 hours with liquids between meals (19% AF), 2 hours intake with solids (12% AF), and 2 hours in which no lead is swallowed (see Vork et al. 2013, p. 82). Those assumptions resulted in an ITC value of 30% using Equation 2 above. In summary, approximately 9.3% of the inhaled mass is assumed to be deposited in the alveolar region and distributed to blood with 100% efficiency, and 66.3% is removed by ciliary action or secretions, swallowed, and deposited in the GI tract, where 30% is distributed to blood (and 70% is excreted). The balance (i.e., 24.4%) is exhaled. Based on those assumptions, collectively, ITC is assumed to be 30%, rounding 29.2% to one significant figure.

Lach et al. (2015) measured airborne lead particle size distributions in firing ranges and found that 49% of the total inhaled lead is deposited in the entire respiratory tract, while 12% is deposited in the alveolar region (i.e., 37% is deposited in the extra-thoracic and TB regions).

Using the airborne lead concentration of 72 $\mu g/m^3$ from Lach et al. (2015) and Equation 2 an ITC value of $0.37 \times 30 + 0.12 \times 100 = 23.1\%$ is calculated. This is somewhat less than the ITC value of 30% assumed for the DoD-O'Flaherty model.

Petito-Boyce (2017) used an approach similar to Vork (2013) except that they assumed a value of 8% absorption for GI absorption and 100% absorption for pulmonary absorption. These assumptions were considered to be consistent with the O'Flaherty (1993) model.

Using the 72 $\mu g/m^3$ from Lach et al. (2014) and the Petito-Boyce (2017) method, the overall absorption percentage is $0.37 \times 8 + 0.12 \times 100 = 15\%$. This is considerably less than the ITC of 30% assumed for the DoD-O'Flaherty model.

Of the three methods described above, the method used by Vork (2013) seems to be the most defensible, because it is based on studies of pulmonary and GI tract absorption. In addition, the Multi-path Particle Dosimetry model (ARA 2012) that was used to estimate the proportion of inhaled lead particles that deposits in the head, ciliated regions of the lung, and the alveoli represents a range of activity levels. The method is also the most conservative in that the estimate used is higher than that resulting from the alternate methods.

Some evidence that chemicals (e.g., drugs) deposited in the TB region might be absorbed systemically is provided by Borghardt et al. (2015). If upon further evaluation the evidence is sufficiently supportive that deposited lead could also be absorbed, it may be appropriate to assume that some fraction of TB-deposited lead is absorbed at that location, instead of in the gut.

The approach used by DoD to assign an ITC value was reasonable, given the absence of definitive studies of the ITC and the wide range of airborne particle sizes expected in DoD occupational settings. However, DoD should consider evaluating the evidence of a wider band of ITCs, including the use of a local sensitivity analysis that is focused on examining the sensitivity of the model output to a higher deposition rate. Evidence supporting a role for TB absorption of lead would be one factor that could influence the ITC. Strong evidence of a wider range of ITCs would justify inclusion of this factor in the Monte Carlo simulations used to establish the OEL.

The use of a reliable method to sample the inhalable particle size fraction of airborne lead is an important aspect of estimating BLLs from airborne lead concentrations. The 37-mm plastic cassette is the typical sampling method used in the United States and many other countries for measuring airborne lead concentrations. A known limitation of the cassette sampler could provide airborne lead measurements that underreport total inhalable lead. In these devices, particles enter a narrow inlet and are collected on a filter medium in the cassette. The filter is weighed before and after sampling to determine the amount of particulate matter collected, prior to analysis for lead. However, a significant fraction of the particles entering the sampler are not collected on the filter because they are trapped on the walls of the cassette, and are thus unaccounted for (Ashley and Harper 2014; Vincent 1999).

The typical 37-mm cassette-sampling device can result in airborne lead measurements that underreport total inhalable lead. DoD should verify that the sampling method used to implement the OEL utilizes a sampling device that measures total inhalable lead and does not suffer from the limitations of the typical 37-mm cassette sample.

Background Concentrations of Airborne Lead

Sweeney (2019) updated the previous estimates of background concentrations of airborne lead used in O'Flaherty model to reflect recent measurements that would better represent the airborne lead concentrations occurring during the lifetime of the DoD worker cohort. The updated background concentrations of airborne lead used in the DoD-O'Flaherty model were obtained from the most recent EPA Integrated Science Assessment for Lead (EPA 2013). The background air concentrations in the model appear to match the observed data in the 2013 EPA report (see Figure 3-3).

The use of airborne lead concentrations from EPA (2013) is appropriate, with the qualification that the lead concentrations selected are approximately three to four times higher than general ambient concentrations in the post 1995 period because, according to EPA (2013), they are heavily influenced by source monitors in the network. Source-oriented monitoring sites are required near sources of lead emissions that contribute, or are expected to contribute, to ambient air lead concentrations that exceed National Ambient Air Quality Standards. An example of such a monitoring location is near airports used by aircraft that use leaded aviation fuel.

Therefore, measurements from source monitors may not reflect airborne lead concentrations experienced by DoD workers living and/or working at a distance from those sources. Conversely, they may better represent exposures for those that live in proximity to such sources. A more spatially and temporally informed approach may not have been available to DoD. The committee notes that, as indicated in Sweeney (2019) Section 4.1, the use of ambient lead concentrations from EPA (2013) resulted in BLL values that aligned more closely to the National Health and Nutrition Examination Survey 2009-2010 BLL data (CDC 2012) than those predicted using older air concentration data in the O'Flaherty model.

DoD made an additional adjustment to background lead exposures, using a population modifier (EXPOSMOD), so that total variability in BLLs was consistent with the BLL population variability reported by Maddaloni et al. (2005). This adjustment was intended to assure that total variability in simulated BLL, the product of variability in background exposure and variability in key physiological and biochemical processes, was properly represented in the exposure distributions used to select the upper bounds (e.g., 95th percentile) on BLL for OEL derivation. Variability in physiological and biochemical processes alone was found to be insufficient to describe the observed variability in BLLs (Maddaloni et al. 2005). The application of EXPOSMOD jointly to the oral (dietary) and inhalation components of exposure was appropriate because the objective was to assure variability in total exposure contributed to total variability in BLL. However, because the BLL distribution of the general population has changed over time, as reported by Maddaloni (2005) and EPA (2017), the correspondence between the model predictions and measured BLLs (both central tendency and geometric standard deviation [GSD]) are also variable. Therefore, a single value for EXPOSMOD may not accurately represent all years considered in DoD's modeling approach. The modeled GSD is expected to directly influence the derived OELs.

Because dietary intake of lead tends to be the largest source of background lead exposure, estimates of the magnitude of the dietary component can have a substantial effect on model estimates of non-occupational lead concentrations. Previous versions of EPA's Air Quality Criteria for Lead (EPA 1977, 1986) may provide evidence of lower dietary lead concentrations prior to 1980 compared to those currently used in the model.

In general, background concentrations of airborne lead are appropriately accounted for in the DoD-O'Flaherty model.

However, DoD should consider the evidence for a lower or declining BLL GSD and further consider if different values for EXPOSMOD over time may improve the model performance and accuracy of predictions for current and future OELs.

In addition, DoD should consider reviewing the 1977 and 1986 EPA Air Quality Criteria for Lead to determine if using a lower dietary lead concentration for the pre-1980 background exposures would be more appropriate than those currently used in the DoD-O'Flaherty model.

Inhalation Rates

A key challenge for modeling DoD occupational lead exposure scenarios is to estimate long-term average daily lead intake via inhalation by using inhalation rates that adequately represent an expected range of activity patterns across the TriServices. The committee considered two primary factors in evaluating the appropriateness of inhalation rates: (1) whether daily activity patterns were adequately represented, and (2) the strength of the underlying inhalation rate data for deriving distributions of inhalation rates.

With respect to representing inhalation rates for daily activity patterns, DoD elected to focus on exposure scenarios that encompass activities of both typical workers and those who more likely engage in higher inhalation-rate activities. That approach was properly fit for the purpose of developing an OEL intended to protect "nearly all" full-time military and civilian workers, including firing range personnel (Sweeney 2019, p. 3).

EPA's *Exposure Factors Handbook* (EPA, 2011) was the primary source of data on inhalation rates cited by Sweeney (2019). The handbook reports summary statistics (e.g., arithmetic mean, standard deviation, 95th percentile) grouped by age and gender. Table 3-1 lists the studies from EPA (2011) used in Sweeney (2019) to develop age and sex-dependent central tendency inhalation rates.

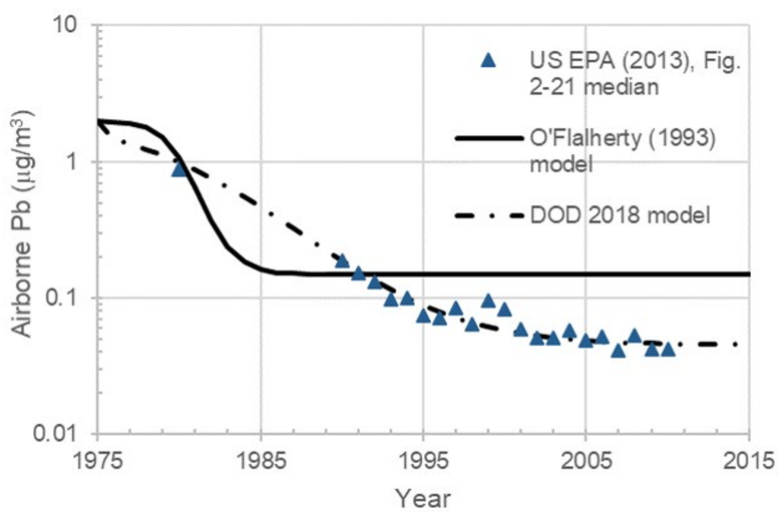

FIGURE 3-3 Background airborne lead concentrations in the United States. SOURCE: Sweeney (2019, p. 60).

TABLE 3-1 Studies Used in Sweeney (2019) to Develop Age and Sex-Dependent Central Tendency Inhalation Rates

Study	Table in EPA (2011)	Age Groups	Sample Size
Brochu et al. (2006)	6-5	All	2,210
Arcus-Arth and Blaisdell (2007)	6-11	< 11 years of age	Not specified
Stifelman et al. (2007)	6-13	All	Large
EPA (2009b)	6-16	All	Large

Sweeney (2019, pp. 54-55) evaluated the performance of the DoD-O'Flaherty model with the following inhalation rates:

- Central-tendency inhalation rate of about 18 m^3/day for men and about 14 m^3/day for women, and
- 95th percentile rate for men is 24.1 m^3/day for men and 18.7 m^3/day for women.

To interpolate inhalation rates between the age groups, Sweeney (2019) applied 6th order polynomial functions to describe the central tendency average daily inhalation rates as a function of age, using separate functions for males and females. Sweeney (2019) assumed that inter-individual variability in inhalation rates for each age group is described by a normal distribution. The coefficient of variation (CV) for each distribution was estimated directly from summary statistics (i.e., arithmetic mean and standard deviation or 95th percentile), and resulted in a weighted-average CV of 0.20. Gender related differences in inhalation rates were assumed to be negligible until age 11 so the averaged male-female data from Arcus-Arth and Blaisdell (2007) was used to reflect both males and females. To prevent inhalation-rate driven declines in BLL for 61 and older folks, inhalation rates for ages 51 to < 61 years were used as surrogates.

DoD's approach is reasonable for estimating inhalation rates of a general worker population and the use of gender specific inhalations rates is appropriate. The inclusion of the 95th percentile is reasonable to account for the higher activity patterns of some workers in the population.

The committee considered the strengths and limitations of the underlying inhalation rate data used to derive the inhalation rate distributions for derivation of the lead OEL (EPA 2011; Sweeney 2019). The observations, summarized in Table 3-2, formed the basis for the committee's determination of the appropriateness of the inhalation rates used to support the development of a lead OEL.

Overall, the data sources used to support inhalation rates for the model appear to be fit for purpose. The key studies listed in Table 3-1 are relatively current (published 2006 to 2009) and span survey years during the past 15 to 20 years. A major source of uncertainty of these data sources stems from the question of representativeness of the study populations (i.e., general worker populations) to the combination of military and civilian workers. It is conceivable that inhalation rates of military personnel are higher than average when they are engaged in strenuous activities. The extent to which the upper end of the distribution of inhalation rates proposed for derivation of the lead OEL adequately represents such high-end activity patterns of firing range personnel is unclear. This uncertainty may be offset to some degree by the inherent bias associated with the study protocols, as discussed in EPA (2011) (see Table 3-2, Item 9). Specifically, variability in inhalation rates measured during short periods is likely to be greater than variability in long-term average inhalation rates, which is the focus of DoD's modeling exercise. That may mean that the high-end estimate of the probability distribution (truncated at ± 2 standard deviations) from a study used to establish inhalation rates for the DoD analysis likely exaggerates long-term average daily inhalation rates for some military and civilian staff.

The data sources and general approach for developing the probability distributions of inhalation rates are reasonable. However, DoD should consider conducting additional Monte Carlo simulations at the candidate OELs using a distribution of inhalation rates (and cardiac outputs) representative of personnel with higher activity levels, such as those that might occur on a firing range. A comparison of the resulting BLL distributions to those used to derive the OELs should be used to determine the fraction or percentile of DoD workers in a higher activity group that would have BLLs below each target level. The analysis would illustrate the sensitivity of the model to inhalation rates in alternative exposure scenarios and the influence of uncertainty in the inhalation rate on outcomes. It would also help risk managers understand the level of protection afforded individuals with inhalation rates higher than those used to derive the candidate OELs.

TABLE 3-2 Key Elements of the Data Sources Used by DoD to Develop Age and Sex-Dependent Inhalation Rates

Item	Element	Description	Relevance to Parameterization
1		Results from the four studies listed in Table 3-1 are in general agreement; three studies provide data on adults.	↑ confidence
2	Consistency in Estimates Using Different Methods	Estimation techniques include reporting disappearance rates of oral doses of doubly labeled water (DLW) (^2H_2O for water output and $H_2{}^{18}O$ for water output plus carbon dioxide production rates) in urine, monitored by gas-isotope-ratio mass spectrometry for an aggregate period of more than 30,000 days. DLW data were complemented with indirect calorimetry and nutritional balance requirements (EPA 2011).	↑ confidence
3		Some researchers estimated inhalation rates using a metabolic method and energy intake data (EPA 2011, see pp. 6-8, Equation 6-2).	↑ confidence
4	Independent Review	EPA (2011, Table 6-3) assigns an overall confidence rating of *medium*, noting that the four key studies provide a larger data set than evaluations conducted prior to 2011, and that the cohorts are representative of a broad age range for the general U.S. population.	↑ confidence
5		Similar to values selected by DoD, mean values for adults range from 12.2 m^3/day (81 years and older) to 16.0 m^3/day (31 to < 51 years) and 95th percentile values for adults range from 15.7 m^3/day (81 years and older) to 21.4 m^3/day (31 to < 41 years) (EPA 2011).	↑ confidence
6	Comparability	California EPA used a higher inhalation rate, 26 m^3/day, for Leggett+ model (Vork et al. 2013), more similar to the 95th percentile than the mean. Based on a time-weighted average of 10 hours of moderate activity, 6 hours of light activity, and 8 hours of sedentary activity. The California Environmental Protection Agency states this may underestimate rates for workers with jobs involving strenuous activity, depending on "breathing patterns, lung morphology, and other factors" (Vork et al. 2013, p. 22).	↓ confidence
7		Industrial Hygiene module of the Defense Occupational and Environmental and Health Readiness System, September through November 2016, provides data on sex and birth year of individuals at DoD workplaces (by service) where lead hazards were identified.	↑ confidence
8	Relevance to Target Population	Data extracted from the Industrial Hygiene module appears to be most relevant to a target population that engages in a wide range of activities (i.e., military and civilian workers combined); it is unclear if even the upper percentiles of a distribution derived from these data are sufficiently representative of a distribution of inhalation rates for a receptor group that routinely engages in more strenuous activities (e.g., military at a firing range).	↓ confidence
9	Chronic Exposure	EPA (2011) notes that the 95th percentiles are highly uncertain and recommends caution if used to represent long-term exposures.	↓ confidence

Maximum Binding Capacity of Red Blood Cells for Lead

One of the key parameters influencing potential variability of observed BLLs is red blood cell (RBC) binding affinity and capacity (Sweeney 2019). Saturable binding of lead to RBC proteins contributes to an increase in the ratio of plasma-lead to whole-blood-lead with increasing exposure levels (e.g., Bergdahl et al. 1997, 1999). This relationship may have important health implications because plasma lead will continue to increase (and potentially distribute to the brain and other sensitive organs) at a linear rate above the saturation point for RBC protein binding.

The DoD-O'Flaherty model described RBC binding of lead with two terms, maximum binding capacity and half-saturation concentration. Point estimates for these variables were obtained from O'Flaherty (1993). To develop a probability distribution, Sweeney (2019, p. 6) states: "RBC binding (affinity and capacity) for lead and hematocrit were considered together, and the de Silva (1981) data on ratios of plasma-lead and RBC-lead concentrations in 103 human subjects were selected as appropriate surrogates for the combined variability of these parameters." Overall, the weighted coefficient of variation (CV) was 0.4 across the range of BLLs. A normal distribution for binding capacity was applied with this CV and truncation limits set at ± 2 standard deviations.

The approach DoD used to describe variability in RBC binding is reasonable, given that BLLs approaching the saturation point for RBC protein binding are unlikely for purposes of deriving the OEL.

Steady State and Periodicity

In deriving candidate OELs, DoD calibrated an ambient lead exposure concentration to which workers were assumed to be exposed by inhalation for 24 hours per day, 365 days per year during a working lifetime of at least 45 years, in addition to exposures to background concentrations of airborne lead. In contrast, OSHA (2011) considers an employee's working life to comprise 8 hours per day, 5 days per week, and 48 weeks per year for 45 years. To adjust the continuous ambient exposure scenario to reflect OSHA's standard workplace scenario, DoD applied an adjustment factor of 4.56 to the acceptable ambient lead concentration in the workplace: [4.56 = (24 hours/day × 365 days)/(8 hours/day × 5 days/week × 48 weeks)] (see Sweeney 2019, Section 3.1.7.1).

DoD's approach has the advantage of saving computing time, because much more time would be needed for simulating OSHA's exposure scenario with multiple periods of being on or off work. The committee considered the potential that the constant exposure scenario implemented by DoD may overpredict BLLs, and that the 48-week versus 52-week exposure may underpredict BLLs for some fraction of the worker population. In response to the committee's request for additional information, DoD (2019) reported that test simulations conducted during development of the final simulations showed no significant difference between BLLs obtained from the constant exposure scenario (168 hours/week) with adjustment for occupational exposure and the occupational exposure scenario of 40 hours per week. (A quantification of the difference was not provided.) DoD did not run model scenarios to compare results for exposure scenarios of 48 weeks versus 52 weeks. DoD (2019) noted that, at most, model estimates would need to be adjusted by 8% (i.e., 52/48), under the unlikely assumption that all 20 days of non-exposure occur consecutively. DoD further noted that a more likely percent difference would be within the rounding error of a candidate OEL designation of one significant figure.

DoD's exposure scenario approach is appropriate. DoD's use of an assumption of 48 weeks per year would theoretically result in an underprediction of no more than 8% and only if all 20 days off were taken consecutively, which is unlikely.

Gender Distribution of Exposed Worker Population

The distribution of men and women is a critical input into the Monte Carlo simulations because biokinetic differences between the genders produce lower BLLs for women for a given air lead exposure

(Sweeney 2019). Separate OELs would be necessary for populations that were 100% male or 100% female under these conditions. There are two potential issues with the selected male-female distribution. First, did the selected distribution adequately represent the gender distribution of DoD workers that the OEL is intended to protect? Secondly, will the gender distribution result in candidate OELs that are reasonably applicable to both men and women? DoD developed a gender distribution of 8% females and 92% males for lead-exposed workers exposed based on the industrial hygiene module of the Defense Occupational and Environmental and Health Readiness System (DOEHRS) (Sweeney 2019, Section 3.1.7.2). Because of the biokinetic differences between males (higher BLL) and females (lower BLL) for a given air lead exposure, an OEL based on this gender distribution would be somewhat lower compared to an OEL derived only for women. In contrast, such an OEL would be slightly higher compared to an OEL derived only for males. Under the conditions of DoD OEL derivation, which assumes no gender differences in susceptibility to lead, OELs derived using the DoD's selected gender distribution would be reasonably applicable to both genders.

The gender distribution selected by DoD based on 2016 information on lead exposed DoD workers documented in a DoD database is sufficiently representative of the worker population for developing candidate OELs.

Randomness in Birth Year

Within the DoD-O'Flaherty model, an individual's year of birth has a strong influence on BLLs through several factors:

- Amount of accumulated lead in the body owing to historical changes in exposures to background concentrations of airborne lead and the duration of potential occupational and background exposure;
- Body mass, and hence the associated mass of individual tissues;
- Rate of change of body mass; and
- Number of factors associated with the bone (a reservoir for lead), including the bone mass and rates of change of mass and remodeling.

To accommodate an inclusion of a distribution of birth dates representative of the DoD population, a model variable was introduced that allows sampling of birth years from a representative population distribution. The distribution for this variable was represented as a uniform distribution between 0 and 1. A value of 0 corresponded to selection of the earliest birth year in the distribution, whereas a value of 0.5 would correspond to selection of the median birth year in the distribution. The model was modified to allow for birth year to be calculated as a function of earliest birth year and a 6th-order polynomial equation. The distribution of birth year from lead-exposed U.S. Army personnel (military and civilians) was derived from the fall 2016 DOEHRS database and used to represent the overall DoD population of lead exposed workers (Sweeney 2019, Appendix D).

The use of the birth-year variable, assumed distribution of the variable, and associated equations result in an adequate representation of the historical exposure of population and their age-dependent pharmacokinetics. This approach also permitted the incorporation of data-driven year of birth distributions and specification of either individuals' ages or years of birth as inputs for simulations.

Sensitivity Analysis

As indicated in Sweeney (2019), the variables chosen for the Monte Carlo analyses were chosen based on a series of six local sensitivity analyses. In local sensitivity analyses, single variables are sequentially changed to determine their individual impact on model outcomes. Alternatively, global sensitivity analysis is an approach that decomposes the variance of the output of the model into fractions that can be attributed to inputs or sets of inputs. This helps to identify not just the individual parameter's sensitivities but also the affect and sensitivity from the interactions between the parameters.

As part of the sensitivity analysis, a rank correlation test was conducted to quantify the dependence of key model outputs to model variables, resulting in a set of correlation coefficients. The higher the absolute value of a coefficient, the stronger the relationship between the corresponding variable and output. Often a cut-off value is chosen, above which variables are deemed to be influential and those below as non-influential. The cut-off chosen for the DoD analysis (0.2) was reasonable in this context. The effective cut-off for including variables in the probabilistic analysis was ± 0.1 because model variables in the 0.1 to 0.2 range were included (DoD 2019).

The sensitivity analysis used to identify the most influential model parameters for Monte Carlo analysis was appropriately conducted. Although a more comprehensive and computationally costly approach (Global Sensitivity Analysis) could possibly have been used, the committee could not conclude that a global sensitivity analysis would have produced different results than those obtained by using a series of local sensitivity analyses.

Correlation Between Cardiac Output and Ventilation Rate

Ventilation rate and cardiac output are inherently correlated (e.g., see Figure 3-4). The committee identified two potential issues related to the independence of cardiac output and ventilation rate in the Monte Carlo analysis in Sweeney (2019). First, if the Monte Carlo simulations included conditions where the expected ratio of inhalation rate to cardiac output was significantly violated, non-plausible physiological conditions could have arisen. The second issue has to do with the relationship between the inhalation rate and the glomerular filtration rate (GFR), which control the most significant rates of lead intake and elimination, respectively. The GFR is highly correlated with cardiac output (Ackermann 1978), which is, in turn, highly correlated with inhalation rate. Changing inhalation rate, without corresponding physiologically accurate changes in cardiac output and GFRs, could establish unrealistic scenarios in which a lead dose rate increases but lead elimination through a correlated process decreases, instead of increasing. A main question is whether either issue would change the final distributions of BLLs for a given airborne lead concentration used to produce the final BLL distribution. The resulting BLL population distributions would then be in error. The committee notes that the inhalation rate CV (0.2) may be small enough that perhaps there is little impact on the final BLL distributions from the ventilation rate-cardiac output correlation.

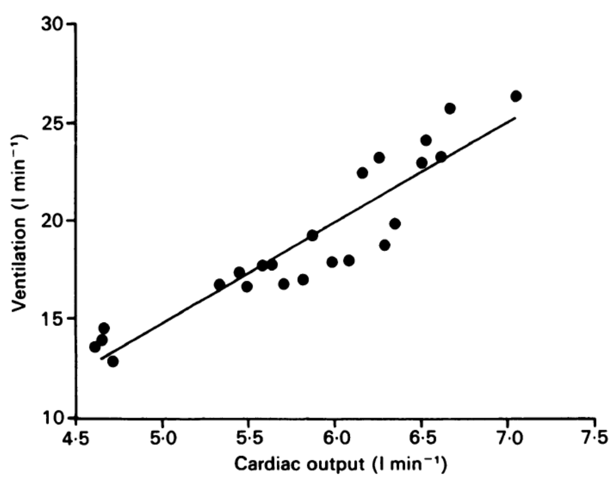

FIGURE 3-4 Regression of mean ventilation on mean cardiac output for exercise tests. NOTE: $R = 0.92$, $P < 10^{-5}$. SOURCE: Cummin et al. (1986). Reprinted with permission; copyright 1986, *Journal of Physiology*.

Varying cardiac output and ventilation rates may separately create unlikely physiological conditions in which a lead dose rate and renal clearance of lead do not increase and decrease together. DoD should explore the impact of correlated increases in ventilation rates and cardiac output on BLLs to determine if these parameters should be varied together, rather than independently, in the modeling of BLLs.

Glomerular Filtration Rate and Urinary Lead Elimination

Sweeney (2019, Appendix C) describes its GFR input distribution to Monte Carlo implementation as a normal distribution with a CV of 0.3 (30%). That appendix cites several previous Monte Carlo analyses for biokinetic modeling that use this CV as what appears to be a rounded default value. Other literature is supportive of this CV modeling estimate. For example, Peters et al. (2012) describe a population of healthy kidney donors across a wide age range (20-70 years) having a GFR CV in the range of 0.2. The CV in healthy adults engaging in active military duty may be even smaller than 0.2, given the more limited age range engaged in this activity. Thus, a CV of 0.3 appears to be a reasonable upper bound estimate for the variability in GFR for Monte Carlo analysis.

The committee explored a potential concern that underprediction of urinary lead concentrations by the DoD-O'Flaherty model (Sweeney 2019, Appendix B) was consistent with underestimation of lead excretion. The committee concluded that underrepresentation of urinary lead concentrations by the model was not evidence of underprediction or urinary elimination of lead. Measured urine lead concentrations (mass/volume) alone do not represent urinary elimination rates (mass/time) without the corresponding urine volumes or, over time, urine flow rates. Similarly, plots of biokinetic-simulated urinary lead concentrations are dependent on measured urine flowrates (volume/time, rarely available) to convert mass elimination rates (mass/time) to urine concentrations (mass/volume). Thus, there is uncertainty in the simulation of urine lead concentrations in the absence of urine flowrate data for the study cohort.

Variability in GFR was represented appropriately in the derivation of candidate OELs. Comparisons of modeled and measured urine concentrations were not necessarily informative about lead mass excretion. However, the ability of the DoD-O'Flaherty model to predict long-term, bone-lead concentrations and BLLs supports the conclusion that net lead elimination rates, dominated by urinary lead excretion rates, are not significantly under or over predicted by the biokinetic model. Uncertainty regarding these rates and differences across models are not expected to create a substantial modeling uncertainty with respect to model estimated relationships between BLLs and lead concentrations in inhaled air.

Characterization of DoD Worker Populations Exposed to Lead at the Candidate OELs

To inform occupational health managers, Sweeney (2019, Section 4.4) presented simulations to illustrate the predicted time series of BLLs in DoD workers resulting from exposures to various airborne lead concentrations. Figure 4 in Sweeney (2019) includes graphs of the predicted time course of BLLs in U.S. adult males born in 2000, using central tendency values for exposure to background concentrations of airborne lead or lead concentrations at various candidate OELs for 1920 hours of occupation exposure per year for 45 years. **To supplement those graphs, DoD should consider developing tables for workers born in 2000 that include the mean, median, interquartile range, and 95th percentile BLLs at various candidate OELs for:**

- **Men and women separately, and**
- **Various combinations of men and women that might comprise a future DoD workforce.**

In addition, DoD should consider developing data tables or graphs of predicted BLL time series of hypothetical cohorts of DoD workers who have been exposed to lead in the workplace in the past and would be exposed at various candidate OELs in future years. For example, tables or graphs could illustrate predicted BLL trends for cohorts of individuals whose ages are 28, 38, and 48 years old, and who were exposed only to background lead concentrations up to age 18, followed by lead exposure at 50 μg/m^3 during full-time work for 10, 20, or 30 years, respectively, and then exposure to lead in the workplace at a candidate OEL, beginning in 2020 until the end of their working years. Alternative cohorts could be constructed based on knowledge of past lead exposures in DoD workplaces.

Model Documentation

Model documentation was spread among several documents, including O'Flaherty (1993, 2000), two technical reports (Sweeney 2015, 2019), and the model code itself (which comprises many source-code files). This diversity of sources, style, and level of detail makes scrutiny of the mathematical and computational model rather burdensome. However, assuming results presented in the Sweeney documents, noted above, resulted from running the exact source code available, the computer code itself (not necessarily the comments within the body of the code) is the *ultimate truth* regarding the model implementation.

Though examination of the body of documentation permitted an evaluation of the model, it would have been highly desirable to have a single document that detailed the model structure, equations, parameters, and assumptions. An exemplar of such documentation is the *Technical Support Document: Parameters and Equations Used in the Integrated Exposure Uptake Biokinetic Model for Lead in Children* (EPA 1994).

In addition, as indicated in Sweeney (2019), DoD-O'Flaherty model simulations were conducted using acs1X model code (Advanced Continuous Simulation Language, AEgis Technologies Group, Inc). However, acslX software is no longer supported by AEgis Technologies. Strategies are needed that would allow the DoD-O'Flaherty model to be usable in the future.

Documentation of the DoD-O'Flaherty model needs to be improved. DoD should prepare a support document for the DoD-O'Flaherty model in a manner similar to EPA's documentation of the Integrated Exposure Uptake Biokinetic Model in EPA (1994). In addition, the support document for the DoD-O'Flaherty model should include:

- **An illustrative figure representing the compartmental structure, blood flows, and mass transfers.**
- **Information contained in DoD's response to the committee's information request (DoD 2019).**[1]
- **Documentation of an error check of the DoD-O'Flaherty model code, and assurance that the model reasonably reproduces the analytic results published in Sweeney (2019).**
- **Strategies that would allow the DoD-O'Flaherty model to be usable in the future.**

WAS THE APPLICATION OF THE MODEL APPROPRIATE?

In evaluating the overall approach and application of the DoD-O'Flaherty model for derivation of candidate OELs for lead, the committee considered the appropriateness of the model, the model assumptions and inputs, and several other factors.

In general, the committee agreed that the approach of using a biokinetic model to establish monitoring equivalent air concentrations representative of upper-bound BLLs is sound and well justified. The modeled population reasonably represented the worker population that DoD seeks to monitor and protect.

The assumptions and inputs to the model were largely considered appropriate. The approach considered variability in important exposure, physiological, and biokinetic parameters, including each in a Monte Carlo simulation producing likely distributions of resulting BLLs from which candidate OELs could be

[1]On June 27, 2019, the committee submitted a written request to DoD for information on the DoD-O'Flaherty modeling approach. The information topics included: the DoD-O'Flaherty model structure, changes DoD made to the 2000 version of the O'Flaherty model, the basis for DoD's estimated average removal duration for DoD workers, who exhibited elevated BLLs; DoD job activities that have the potential to result in lead exposure; modeled exposure scenarios; and approaches for selecting model parameters for the Monte Carlo analyses.

established. However, the committee observed that the results of the Monte Carlo analyses were not presented in a manner that gave the reader an appreciation for the prediction intervals or envelope. **The results of a Monte Carlo analysis would be more useful to the reader if they included mean values of measures with prediction intervals based on model uncertainty and variability/error in the data used for parameterization.**

As noted in Sweeney (2019), the OEL is intended to protect nearly all workers, but is not an absolute guarantee of worker safety. There was no specific indication that the modeling approach was designed to protect specific vulnerable groups, for example, those with altered patterns of particle deposition in their respiratory systems (chronic obstructive pulmonary disease) or reduced renal elimination (kidney disease). However, use of the upper 95th percentile BLL for establishing an OEL is consistent with the approach followed by ACGIH in setting TLVs for which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects. Also, in most cases, DoD's modeling assumptions would tend to err in favor of estimating higher BLLs for a given exposure, providing some additional reassurance.

SUMMARY CONCLUSION

The committee commends DoD for undertaking a very substantial, deliberative process to establish a lead exposure monitoring program intended to be more protective of its workers who are exposed to lead. The committee recognizes DoD's leadership in applying an innovative approach for establishing an OEL for lead using modern biokinetic modeling to develop quantitative relationships between occupational exposure and BLLs.

Overall, the committee found that the DoD-O'Flaherty modeling approach and application to support the development of an OEL for lead are appropriate. Specifically, an appropriate model was chosen, modifications to the model were appropriately justified, and the model assumptions and inputs were reasonable. The model was confirmed and shown to be sufficiently consistent with experimental data. The committee recommended several ways in which DoD can improve the DoD-O'Flaherty model, its application, and documentation.

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Appendix A

Statement of Task

An ad hoc committee will review the scientific and technical basis of the occupational exposure limits (OELs) for airborne lead developed by the U.S. Department of Defense (DoD). Specifically, the committee will evaluate whether the physiologically-based pharmacokinetic model (DoD-O'Flaherty model) used to derive airborne concentrations from blood lead levels was appropriate. Consideration will be given to whether an appropriate model was chosen, whether modifications to the model were appropriately justified, and whether the assumptions in and inputs to the model were reasonable. The committee will not recommend specific OEL values.

The committee will provide an overall summary conclusion on DoD's selected approach and the application of the approach for derivation of lead OEL values. The committee will address the following specific topics:

- Were the DoD-O'Flaherty model selection, parameterization, and validation appropriate, given the intended purpose—to develop OELs for DoD civilian and military workers?
- Were the inhalation rates used within the DoD-O'Flaherty model appropriate to represent DoD workers (military and civilian) who are occupationally exposed to lead?
- Were background levels of lead in air appropriately accounted for within the DoD-O'Flaherty model and representative of DoD workers who are occupationally exposed to lead?
- Is particle size variation appropriately accounted for within the DoD-O'Flaherty model and representative of lead absorption within DoD workers (military and civilian) who are occupationally exposed to lead?

Appendix B

Committee Member Biosketches

Justin G. Teeguarden (*Chair*) leads the Chemical Biology and Exposure Science Team and is the Chief Exposure Scientist for the Pacific Northwest National Laboratory (PNNL). He holds a joint faculty position with the Oregon State University (OSU) Department of Environmental and Molecular Toxicology, where he served as the director of the OSU–PNNL–Superfund Center Research Translation Core. Dr. Teeguarden also leads the Decoding the Molecular Universe Directorate Objective for the Earth and Biological Sciences Directorate of PNNL in addition to leading Defense Health Programs. He currently serves as the interim deputy director for Science for the PNNL Environmental and Molecular Sciences Laboratory. Recently, he helped build PNNL's growing computational metabolomics program, which has developed methods for identifying small organic molecules with computational derived libraries instead of libraries derived from authentic chemical standards. Dr. Teeguarden has more than 20 years of experience in computational and experimental exposure assessment in humans, animals, and cell culture systems. His particular focus has been the utilization of emerging technologies, novel experimental data, and computational methods for addressing public health challenges related to human exposure to chemicals. His experience includes developing pharmacokinetics models for volatile and non-volatile organics, trace metals, nanomaterials (particles), and receptor binding endocrine active compounds. These models were developed as tools for understanding the relationship between external exposure and internal exposures for purposes of comparing human exposure to those in toxicity test systems (such as rodents and cell culture systems). Dr. Teeguarden served on the National Academies Committee on incorporating 21st Century Science in Risk-Based Evaluations; Committee on Human and Environmental Exposure Science in the 21st Century; and Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. He currently serves on the U.S. Environmental Protection Agency's Board of Scientific Counselors Homeland Security Subcommittee. He has worked extensively with the Society of Toxicology and the Society for Risk Analysis to translate findings of fundamental science—particularly exposure and dosimetry information—into the risk and public health domains. Dr. Teeguarden received a PhD in toxicology from the University of Wisconsin–Madison, and is board certified in Toxicology. He is an Eagle Scout.

Jeffrey W. Fisher is a research toxicologist in the Division of Biochemical Toxicology of the U.S. Food and Drug Administration's National Center for Toxicological Research. Formerly, he was a professor in the Department of Environmental Health Science, College of Public Health, at the University of Georgia. He also worked at the Toxicology Laboratory of Wright Patterson Air Force Base, where he was principal investigator and senior scientist in the Toxics Hazards Division and technical advisor for the Operational Toxicology Branch. Dr. Fisher has 30 years of experience in physiological modeling. His career research interests are in the development and application of pharmacokinetic and biologically based mathematical models to ascertain health risks from environmental, occupational, and foodborne chemicals. His research activities included the development of a biokinetic model for nickel released from cardiovascular implanted devices. Dr. Fisher has served on several national panels and advisory boards for the U.S. Department of Defense, the Agency for Toxic Substances and Disease Registry, and the U.S. Environmental Protection Agency. He was a member of the National Academies Subcommittee on Acute Exposure Guideline Levels. Dr. Fisher received a PhD in zoology/toxicology from Miami University.

Gary L. Ginsberg is director of the Center for Environmental Health within the New York State Department of Health (NYS DoH) and has a clinical professor appointment at the Yale School of Public Health. His DoH duties include overseeing the administration and delivery of environmental health services across NYS, including public drinking water supplies, regulation of food establishments, prevention of childhood lead exposure, and protecting the public from waste site contamination and emerging contaminants. Previously, he was the state toxicologist at the Connecticut Department of Public Health. Dr. Ginsberg has published in the areas of toxicology and risk assessment including the development and evaluation of physiologically-based pharmacokinetic models for assessing risks from exposure to environmental agents, risks to children and other vulnerable populations, and risk/benefit analysis. He served on several National Academies committees, including the Committee on Use of Emerging Science for Environmental Health Decisions, Committee on Inorganic Arsenic, Committee on Improving Risk Analysis Approaches Used by the EPA, and Committee on Human Biomonitoring for Environmental Toxicants. Dr. Ginsberg received a PhD in toxicology from the University of Connecticut.

Philip E. Goodrum is a principal toxicologist at GSI Environmental Inc. Previously, he was a senior science advisor at Integral Consulting Inc. Dr. Goodrum has more than 25 years of experience in quantitative human health risk assessment, which includes statistical sampling methods, probabilistic risk assessment, and lead exposure modeling. He is also a board-certified toxicologist. Dr. Goodrum represents clients in negotiations with state and federal regulators, trustees, and stakeholder groups on issues related to data interpretation, statistical analysis, modeling, and risk characterization. He served on a number of national advisory committees that evaluated the scientific basis for changes in exposure factors and risk metrics for use in deriving risk-based action levels for lead in soil and water for residential, occupational, and recreational fishing exposure scenarios. For the U.S. Environmental Protection Agency, he served on the Peer Review Panel for Lead in Drinking Water, Clean Air Scientific Advisory Committee review panel for the National Ambient Air Quality Standards for lead, and Science Advisory Board's Ad Hoc All-Ages Lead Model Review Panel. Dr. Goodrum received a PhD in environmental engineering from the State University of New York College of Environmental Science and Forestry in Syracuse.

Sheryl A. Milz is a professor in the School of Population Health of the University of Toledo and is a certified industrial hygienist. Her research interests are in human exposure assessments, risk assessment, and environmental and occupational epidemiology. Before joining the University of Toledo, she was an industrial hygienist and safety and occupational manager at the Great Lakes Naval Hospital, where she evaluated firing ranges for lead exposure and ventilation requirements. Dr. Milz has been active in the American Industrial Hygiene Association and the American Conference of Governmental Industrial Hygienists. Dr. Milz served on the National Academies Committee on Potential Health Risks from Recurrent Lead Exposure to DOD Firing Range Personnel and she currently serves on the Committee on Toxicology. She received a PhD in public health sciences (industrial hygiene) from the University of Illinois at Chicago.

Roberta B. Ness (NAM) is a retired professor in the Division of Epidemiology and Disease Control, and was vice president for Innovation at The University of Texas Health Science Center at Houston. She holds the James W. Rockwell Professorship in Public Health. Dr. Ness was formerly dean of The University of Texas Health Science Center at Houston, School of Public Health. She was formerly chair of the Department of Epidemiology at the University of Pittsburgh Graduate School of Public Health, where she was a professor of epidemiology, medicine, and obstetrics & gynecology. Her research areas include innovation in science and women's health. One of her specific research topics includes lead exposure, attention deficit disorder, and delinquency. She is a member of the National Academy of Medicine. Her service on National Academies committees includes chair of the Committee on Blue Water Navy Vietnam and Agent Orange Exposure. She received an MD from Weil Medical College of Cornell University and an MPH in epidemiology from Columbia University.

Gurumurthy Ramachandran is a professor in the Department of Environmental Health and Engineering in the Johns Hopkins Bloomberg School of Public Health. He is also the director of the university's Education and Research Center for Occupational Safety and Health. His research focus areas include occupational exposure and health risk, as well as Bayesian applications in exposure assessment. Dr. Ramachandran developed occupational exposure assessment strategies for a variety of airborne contaminants; novel Bayesian statistical methods that synthesize exposure models, monitoring data, and probabilistic expert judgment; and mathematical methods for exposure modeling and analyzing occupational measurements. He served on the National Academies Committee on Making Best Use of the Agent Orange Exposure Reconstruction Model. Dr. Ramachandran received a PhD in environmental sciences and engineering from the University of North Carolina at Chapel Hill.

Brad Reisfeld is a professor in the Department of Chemical and Biological Engineering and in the School of Biomedical Engineering at Colorado State University (CSU). In addition, he leads CSU's Quantitative Systems Pharmacology and Toxicology Research Group. Dr. Reisfeld's primary research interests are in quantitative and computational pharmacology and toxicology, computational systems biology, pharmacokinetics, and pharmacodynamics. His work includes the use of pharmacokinetic modeling, pharmacodynamic modeling, and Bayesian and Monte Carlo analyses to aid in the assessment of risk associated with environmental pollutant exposure and in the optimization of drug regimens for infectious disease treatment. He is a Diplomate of the American Board of Toxicology, vice president of the Biological Modeling Specialty Section of the Society of Toxicology, and chair of the Systems Pharmacology Focus Group of the American Association of Pharmaceutical Sciences. Dr. Reisfeld received a PhD in chemical engineering from Northwestern University and was a postdoctoral fellow at the Johns Hopkins School of Medicine.