



Using the best science to inform health-protective measures for workers

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Overview

- Challenges with setting medical removal levels
 - Reconciling studies on the effects of lead exposure in the general population and in workers
 - Perspective from recent reviews of occupational standards and guidance
- Correlations between air lead and blood lead and influence on PELs
 - Observational vs. modeling approaches
 - Air lead/blood lead slope factors from the literature
- OEHHA (CA) model as the basis for PELs
- Lead particle size and implications for PELs
 - Influence of particle size on exposure
 - Regulatory definitions of respirable particles
 - New particle size study
- Conclusions

Challenges with Setting Medical Removal Levels

Studies of lead health effects in the general population in apparent conflict with studies on the effects of lead exposure in workers – Effects on key endpoints (CV, renal, and autonomous nervous systems) occur at much higher blood Pb levels in workers

- Higher statistical power in large epidemiological populations relative to smaller occupational cohorts? – **No**, not if consider meta analyses
 - Meyer-Baron and Seeber (2000): from an analysis of 22 studies, reported clear evidence of neurobehavioural deficits in workers w/ave. BL = 40 $\mu\text{g}/\text{dL}$
 - Araki et al (2000): reviewed 102 worker studies in which reduction in NCV occurred at ave. BL = 30 to 40 $\mu\text{g}/\text{dL}$
- Selection bias in worker studies – **Yes** (“Healthy worker” effect)
 - Health of employed people is generally better than that of the unemployed population because severely ill and disabled people are excluded from employment
 - General population studies usually do not exclude severely ill/disabled people

Challenges with Setting Medical Removal Levels

Studies of lead health effects in the general population in apparent conflict with studies on the effects of lead exposure in workers – Effects on key endpoints (CV, renal, and autonomous nervous systems) occur at much higher blood Pb levels in workers

- Study design deficiencies and/or ambiguous results – **Yes**, esp. for gen. pop. studies
 - Schwartz (1988): effects of BL (<20 µg/dL) on office BP but 24-hr ambulatory BP is now the measurement of choice, and no effect of BP on ambulatory BP (Staessen et al. in press)
 - Payton et al. (1994): cross sectional study; impaired kidney fn w/incr. BL; but does impaired fn cause reduced ability to clear lead?
 - Shih et al. (2007): decrements in cognitive function but only as indicated by bone lead, not BL
- Uncertainties in the lead exposure history, unaddressed confounders, insufficient quality control, and timing of lead exposure relative to onset of associated effects? – **Yes**, esp. for gen. pop. studies
 - Peters et al. (2012): effects of bone lead on CV disease in a population (aged 60-70+) where nutritional and activity patterns assoc. w/BP and mortality shift as a function of overall health status of the study subjects

Setting Medical Removal Levels – Perspectives from Recent Regulatory Reviews

- *De facto* MRLs
 - Safe Work Australia (SWA)
 - 30 µg/dL for females not of reproductive capacity and males
 - 20 µg/dL NOAEL for females not of reproductive capacity and males
 - 10 µg/dL removal level for females of reproductive capacity
 - Cal/OSHA and DoD
 - 1 test ≥30 µg/dL
 - 2 tests ≥20 µg/dL or the ave. of all tests during 6-mo. period ≥20 µg/dL
- Health-based blood lead values
 - ACGIH: BEI (Biological Exposure Index) = 20 µg/dL
 - “To reduce the risk of neurological and neurobehavioral effects and reproductive effects associated with lead exposure”
 - ANSES (France): BLV (Biological Limit Value) = 18 µg/dL
 - Developed “if the body of scientific evidence is sufficient to quantify a dose/response relationship with certainty”

Setting Medical Removal Levels – Perspectives from SWA

- Conducted an independent, evidence-based evaluation of health effects of lead
- Identified key epidemiological/toxicological studies relevant to setting **occupational** blood lead removal levels
- Identified key health endpoints: nervous system, increased blood pressure, heart rate variability, kidney dysfunction, and others
- Most adverse health endpoints associated w/ **average** blood lead levels >20 µg/dL; more evident at BLLs >30 µg/dL
- Very pragmatic approach, although separate MRL for women of reproductive capacity not workable in U.S.

Setting Medical Removal Levels – Perspectives from ACGIH

- Weight-of-evidence approach rather than restricting (as SWA did) to those studies relevant to setting blood lead removal levels – neuro, renal, CV, repro, genotox, carcinogenicity, etc., etc., etc.
- Comprehensive but still selective – didn't consider newer studies of neuro effects in adults (all pointing toward effects at $\sim 30 \mu\text{g}/\text{dL}$)
 - Postural sway
 - Peripheral nervous system effects (e.g., NCV)
 - Autonomic nervous system effects (e.g., heart rate variability)
- In effect gave studies equal weight, but not all studies are created equal
 - Failed to evaluate quality, reliability, design (via Klimisch scales) of individual studies – particularly imp. because of poor quality of studies where effects were demonstrated at $< 30 \mu\text{g}/\text{dL}$

Setting Medical Removal Levels – Perspectives from ANSES

- Key studies approach
- Identified two published studies in workers (Schwartz et al. 2001 and 2005) that indicated thresholds (LOAEL and NOAEL) in tests of neurological aptitude in Korean workers
 - Authors reported a LOAEL of 21 $\mu\text{g}/\text{dL}$
 - ANSES interpreted the results of the studies to indicate a NOAEL of 18 $\mu\text{g}/\text{dL}$
- But it was a questionable study
 - Very little persuasive epidemiological data to support the threshold identified in the study
 - Subtle effects on several neurological endpoints that may be reversible upon cessation of exposure
 - Subtle effects may not even be considered adverse

Setting Medical Removal Levels – Perspectives from Cal/OSHA

- Based on Kosnett et al. (2007) – “Recommendations for Medical Management of Adult Lead Exposure” (Table 1)
 - @20 – 29 $\mu\text{g}/\text{dL}$ BLL: remove from lead exposure if repeat BLL measured in 4 weeks remains ≥ 20 $\mu\text{g}/\text{dL}$
 - @30 – 39 $\mu\text{g}/\text{dL}$ BLL: remove from lead exposure
- Cal/OSHA says “lower the BLL at which workers must be removed from lead exposure to”:
 - Two BLLs at or above 20 $\mu\text{g}/\text{dL}$
 - One BLL at or above 30 $\mu\text{g}/\text{dL}$
- Also influencing were recent reviews
 - EHP: High blood pressure, decreased kidney function, low birth wt. at BL ≥ 10 $\mu\text{g}/\text{dL}$
 - NTP: Incr. BP, essential tremor at BL < 10 $\mu\text{g}/\text{dL}$; decr. kidney fn. and fetal growth at BL lower than 5 $\mu\text{g}/\text{dL}$
 - EPA: causal/likely causal relationships between BL and CV, neuro, and repro. effects

Setting Medical Removal Levels – Perspectives from DoD’s 2007 “Occupational Medical Examinations and Surveillance Manual”

- Based on Kosnett et al. (2007) – “Recommendations for Medical Management of Adult Lead Exposure” (Table 1)
 - @20 – 29 $\mu\text{g}/\text{dL}$ BLL: remove from lead exposure if repeat BLL measured in 4 weeks remains ≥ 20 $\mu\text{g}/\text{dL}$
 - @30 – 39 $\mu\text{g}/\text{dL}$ BLL: remove from lead exposure
- Table C4.T2 – “Blood Lead Laboratory Results and Health-Based Management Requirements and Guidelines”
 - @20 – 29 $\mu\text{g}/\text{dL}$ BLL: remove from lead exposure if repeat BLL testing is at or above 20 $\mu\text{g}/\text{dL}$
 - @30 – 39 $\mu\text{g}/\text{dL}$ BLL: remove from lead exposure if single test result is ≥ 30 $\mu\text{g}/\text{dL}$
- “The National Research Council has concluded that there is overwhelming evidence that the OSHA standard provides inadequate protection for DoD firing-range personnel and any other worker populations covered by the OSHA general industry standard.”

The Air Lead/Blood Lead Relationship

A highly variable correlation between air lead and blood lead makes development of a revised PEL a difficult proposition

- Air monitoring is an indirect method for determining exposure to lead as it only reflects **the amount of lead that is available to inhale** within the workers' breathing space and **does not represent actual exposure or body burden**
 - Area sampling doesn't reflect personal air lead concentrations
 - Different sampling methodologies would report different air concentrations for the same air sample
 - Respirator use mitigates air exposure
 - Hand-to-mouth behaviors influence exposure/body burden
- Quantifying the precise relationship between air lead concentrations and blood lead concentrations – expressed as “slope factors” – has been attempted many times with widely varying results

The Air Lead/Blood Lead Relationship

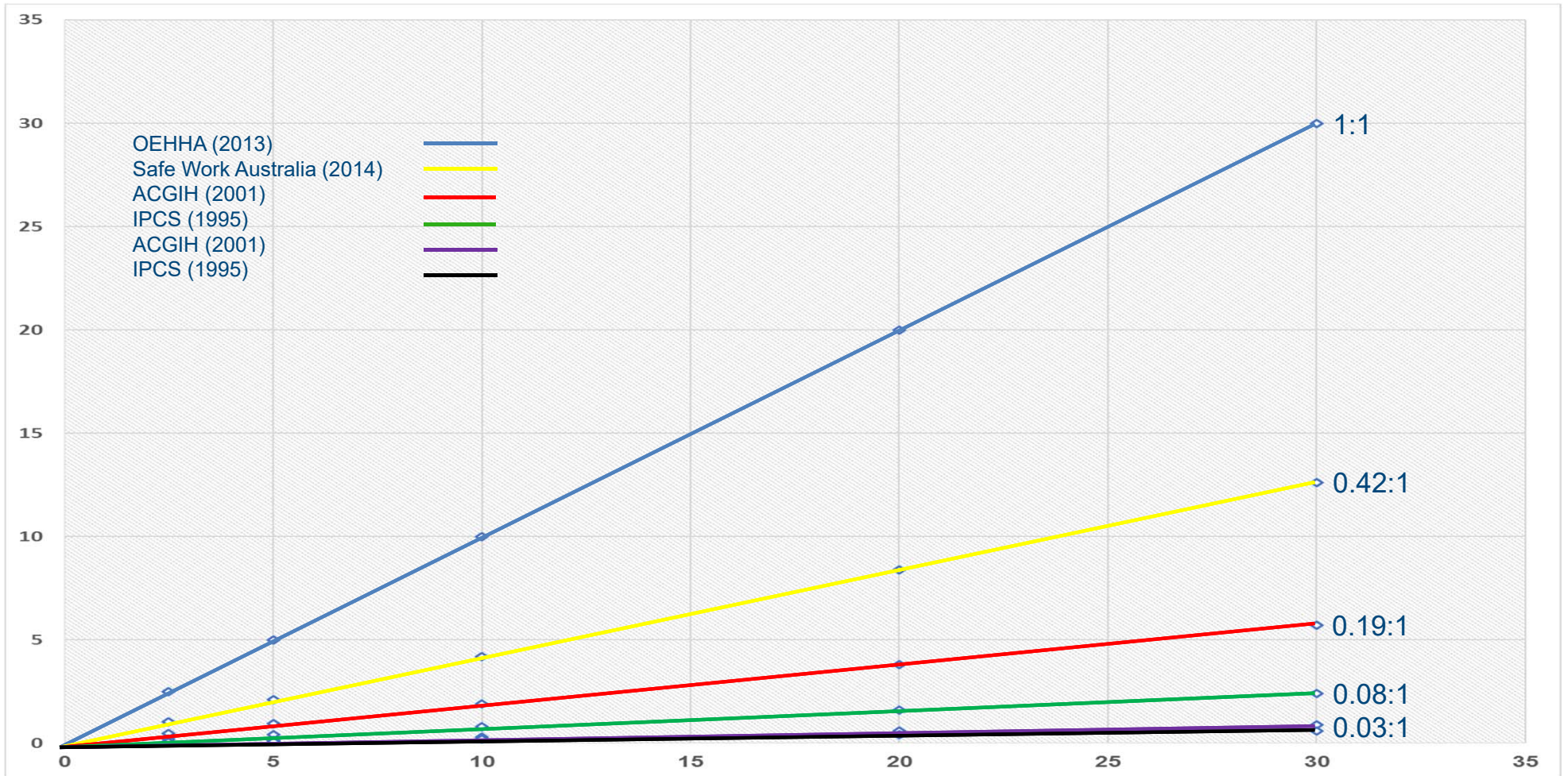
A highly variable correlation between air lead and blood lead makes development of a revised PEL a difficult proposition

- Slope factor = the change in blood lead (in $\mu\text{g}/\text{dL}$) for a change in air lead concentration of $1 \mu\text{g}/\text{m}^3$
- Two approaches
 - Observational (epidemiological) approach in which population blood leads are correlated with environmental ambient lead in air concentrations – many examples
 - Modeling approach – e.g., CA (OEHHA)
- Some slope factors were developed to model lead exposures not relevant for workers
 - For children: EPA's IEUBK model
 - For environmental exposures: O'Flaherty model
 - From food: European Food Safety Authority (EFSA) model

Blood Lead/Air Lead Slope Factors

Reference	Value ($\mu\text{g}/\text{dL}$ per $1 \mu\text{g}/\text{m}^3$)	Basis
IPCS (1995)	0.02 – 0.08	Based on a survey of the occupational literature Adopted to characterize occupational setting for the purposes of REACH registration in the EU
ACGIH (2001)	0.03 – 0.19	Based on a review of a number of occupational epidemiology studies
Safe Work Australia (2014)	0.42	Based on studies that encompassed a wide range of air Pb concentrations Recognized that slope factors for air lead concentrations lower than $50 \mu\text{g}/\text{m}^3$ could not be estimated because such concentrations were frequently beyond the range of the experimental data
OEHHA (2013)	1	Based on a modified version of the Leggett model

Blood Lead/Air Lead Slope Factors



Comments on OEHHA Model

The OEHHA model – the basis for revised PELs in California – should not be used as the basis for a revised PEL in Washington

- Model not validated or published in any peer-reviewed journal
 - Received a “private” review from a group selected by model authors
 - Industry provided peer review input in both the Cal/OSHA and in Prop 65 proceedings but OEHHA never updated to correct for the errors and deficiencies identified
- Model not endorsed for use in other regulatory deliberations
 - Not used in EPA's evaluation of the lead National Ambient Air Quality Standard
 - EPA used its Adult Lead Model (ALM) when developing lead dust standards for residences
 - EPA typically uses its IEUBK model as “the clearly preferred model” for assessing lead exposure at waste sites

Comments on OEHHA Model

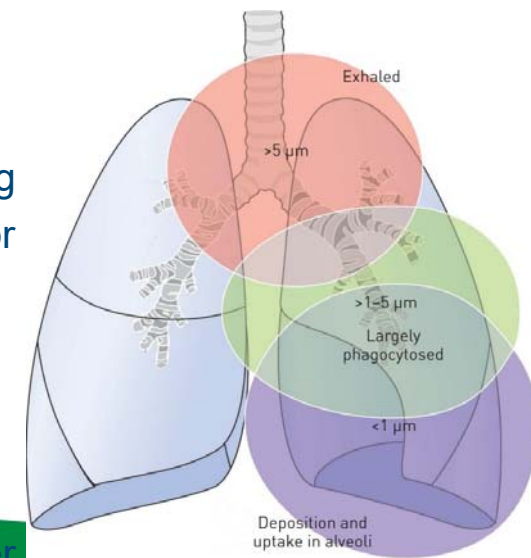
The OEHHA model – the basis for revised PELs in California – should not be used as the basis for a revised PEL in Washington

- Inappropriate particle size assumptions – assumes large particles that are typical of workplaces are absorbed when in fact they are cleared by nose-blowing or lung (mucociliary) clearance mechanisms
- Inhalation transfer coefficient (ITC) assumption errors – resulting in a model that predicts high blood lead at very low air lead concs.
- Used an outdated version of the MPPD (Multiple-Path Particle Dosimetry) model
- Mass-balance error – the amount of lead intake must equal the total amount of lead distributed to all tissue compartments
- Model based on empirical studies/data from older workplace studies – may not be a suitable basis for estimating exposures in current workers
 - Williams et al. (1969) – old battery factory worker study
 - Hammond et al. (1981) – hand-to-mouth lead transfer and personal working habits contributed to increased exposure
- Derived an extremely over-estimated air lead/blood lead slope (5- to 50-fold) compared to other estimates

Lead Air Standards and Particle Size

Any air standards should account for respirable particle size
– some background

- Particle size determines location of deposition in respiratory tract
 - $>20\ \mu\text{m}$ deposit in the upper airways w/v. limited penetration to deep lung
 - $<20\ \mu\text{m}$ but $>10\ \mu\text{m}$ capable of penetrating to tracheobronchial regions or deeper
 - $<10\ \mu\text{m}$ capable of deep lung penetration/deposition in alveoli
- Location of deposition influences absorption/exposure
 - In upper airways: expelled or enter GI track then follow kinetics of GI uptake
 - In tracheobronchial regions: subject to mucociliary clearance and transfer to GI
 - In alveoli: nearly complete dissolution/available for systemic uptake at nearly 100%.



Source: European Respiratory Journal
(<http://erj.ersjournals.com/content/44/3/765>)

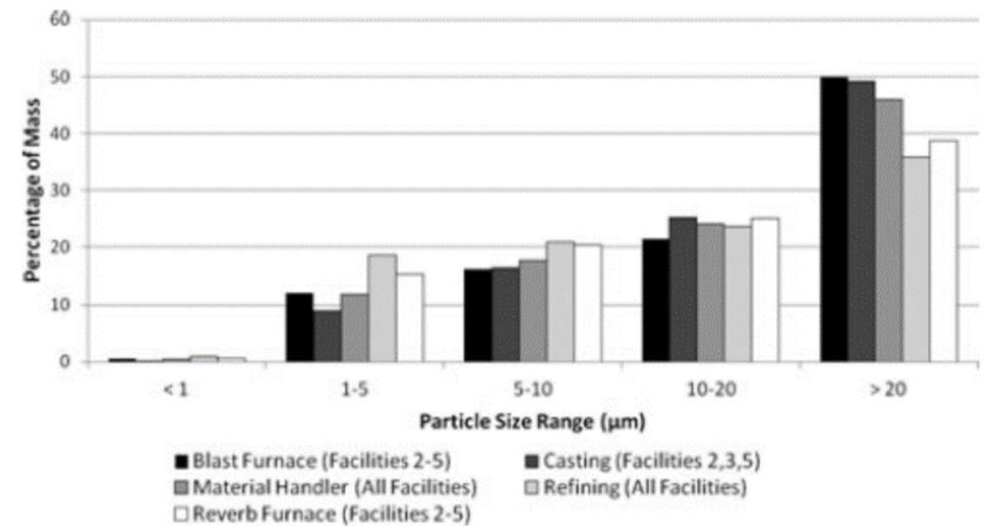
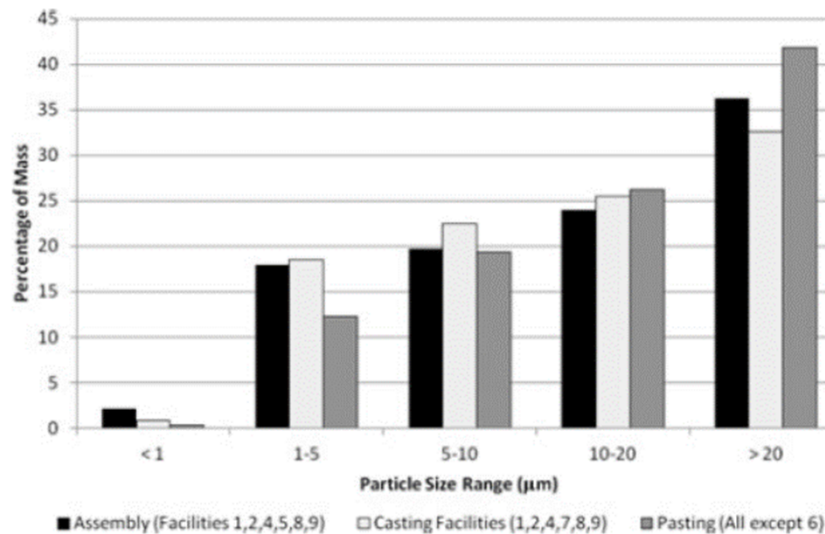
Lead Air Standards and Particle Size

Any air standards should account for respirable particle size – regulatory definitions of “respirable”

- New federal OSHA silica rule: **4 μm** , based on sampling technology
- EPA NAAQS for PM: 2 standards based on **10 and 2.5 μm**
- OEHHA model
 - “Our data indicate that while particle size distribution has a significant impact on the total fraction of inhaled lead deposited in the head and airways and on the fraction deposited in the alveoli, the fraction ultimately transferred to the blood does not vary greatly by particle size distribution.”
- New battery worker study (Petito Boyce 2017)
 - “These analyses indicated that the highest overall deposition in the respiratory tract was estimated for intermediate size particles (assuming an MMAD of **5 μm**). . .”
 - “The highest predicted deposition in the PU [pulmonary] region was calculated for a hypothetical modeled exposure to the smallest particles (assuming an MMAD of **1 μm** . . .)”
- Recommendation – per Silica Rule?

New Particle Size Study (Petito Boyce et al. 2017)

- First modern study to analyze actual workplace (BMFs and SSFs) lead-in-air data in the U.S.
- Larger particle size than was previously assumed
 - Reduce the degree to which workers absorb lead into the body/reduce exposure
 - Past modeling over-estimated and needs revisiting
 - Entered into the bibliography of WA reliance studies



Conclusions

- Several recent examples of MRL setting for WA-DOSH to use as a guide
- Air lead not as relevant to blood lead as some assume; quantifying this has yielded widely varying results
- OEHHA Model from California significantly flawed and should not be relied on the basis for any revised PEL
- PELs (if modified) should only address “respirable” particle sizes