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Lead remediation and changes in human lead exposure: some physiological and biokinetic dimensions☆

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Abstract

This paper presents a qualitative and quantitative analysis of the various aspects of lead remediation effectiveness with particular reference to human health risk assessment. One of the key elements of lead remediation efforts at such sites as those under the Superfund program deals with populations at elevated exposure and toxicity risk in the proximity of, or at, the site of remediation, especially remediation workers, workers at other tasks on sites that were remediated down to some action level of lead concentration in soils, and groups at risk in nearby communities. A second element has to do with how one measures or models lead exposure changes with special reference to baseline and post-remediation conditions. Various biomarkers of lead exposure can be employed, but their use requires detailed knowledge of what results using each means. The most commonly used approach is measurement of blood lead (Pb-B). Recognized limitations in the use of Pb-B has led to the use of predictive Pb exposure models, which are less vulnerable to the many behavioral, physiological, and environmental parameters that can distort isolated or 'single shot' Pb-B testings. A third aspect covered in this paper presents various physiological factors that affect the methods by which one evaluates Pb remediation effectiveness. Finally, this article offers an integrated look at how lead remediation actions directed at one lead source or pathway affect the total lead exposure picture for human populations at elevated lead exposure and toxicity risk.

Keywords: Lead remediation; Blood lead; Clean-up

1. Introduction

Much work has been researched and written about for the stable lead (Pb) exposures of human populations, especially those at high risk for both exposures and poisoning (NAS/NRC, 1993; USCDC, 1991; USATSDR, 1988; USEPA, 1986; Mushak, 1998a, 1993, 1992). In fact, much of what we quantitatively comprehend about dose–response relationships and environmental marker–biomarker relationships arise from both the body levels and biokinetics of Pb that are at 'steady-state,' or more properly in whole-body terms, near steady-state (Mushak, 1993). Lead contamination as a regulatory issue is increasingly one of Pb remediation and any likely reduction in exposure and toxicity risks following such remediation. The message from science and health research makes

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it compellingly clear: Pb in various contact media needs to be reduced or eliminated. That typically translates to remediation of Pb in such media as soils and dusts at Superfund sites and paint Pb in deteriorated housing or other sites where public agencies have regulatory or intervention oversight.

Such agencies are directly interested and involved in what happens in human Pb exposures when long-existing environmental Pb concentrations in and around waste sites and adjacent communities are disturbed with Pb remediation activities. In that connection, ongoing and/or post-remediation action can theoretically cause lower or higher exposures. The questions to be addressed in this article are: Who is exposed? How do they differ in their Pb exposures physiologically and toxicokinetically? How best do we record these differences in populations and their respective Pb exposures? How do we translate such changes to effectiveness of Pb remediation? Addressing these core questions requires attention to other issues that are also addressed here: What other changes in environmental Pb levels, in addition to site Pb remediations, are occurring? What is the temporal nature of such Pb remediations in terms of total populations impacted over time?

2. Populations affected by soil Pb remediation effectiveness

Lead remediation at Superfund and other hazardous sites clearly affects, albeit in various ways, at least three categories of individuals: those who are conducting the remediating, those who are working at some industrial activity on remediated sites, e.g. the 'brownfields' sites, or those with proximity to the activities as residents, to particularly include infants and toddlers. The extent to which we can identify generic or specific risks for each group varies considerably.

2.1. Lead remediation (clean-up) workers

These individuals can potentially sustain increased exposures from remediation activities requiring disturbance and transitory mobilization of soils, dusts and sediments. Such persons can have their Pb exposures on-site, where levels being encountered are highest, or off-site, where overall exposures may be lower but still potentially in excess of background Pb risks. Remediation exposures are presumably only transitory for any given on-site or off-site residential remediation work periods and such remediation work would typically be done within a worker protection plan as part of some overall remediation design that must be approved by the agency providing oversight on any clean-up. On the other hand, compliance by workers with these paper protocols can be problematic. In addition, long-term employment of experienced workers at multiple sites over time extends the total time interval of exposure.

Of the three categories of individuals identified above, we know the least about the quantitative extent of such Pb exposures in remediation workers. We therefore can only draw precautionary conclusions about the need to control transitory exposures without easily quantifying that exposure. Furthermore, the US Supreme Court in 1991 held, in the Johnson Controls case (Automobile Workers v. Johnson Controls, Inc., 499 US 187:89–1215 (1991)) that gender discrimination cannot be employed to protect the fetus.

Therefore, women of childbearing age could not be automatically prevented from working in areas of industrial facilities where there might be exposures to Pb, particularly if such exclusion resulted in such women being denied better paying positions within the meaning of Title VII of the 1964 Civil Rights Act. The Court in that case concluded that sex discrimination and attendant economic discrimination in the workplace, based on added health hazards to the fetuses of pregnant women and the principal basis for industrial operations excluding such women over most of the 20th Century, was illegal. One could therefore potentially find women of childbearing age working at Pb remediation sites. This likelihood permits us to define women of childbearing age as those most at risk during Pb remediation work in and around some particular site.

2.2. Non-resident adult workers at remediated sites

Remediated industrial or commercial sites can eventually produce Pb exposures which are higher

than what workers employed thereon had encountered previously, depending on the methods by which one arrives at some permissible site soil or dust Pb levels. In addition, unlike the case for clean-up workers where exposures are too variable for limited empirical or predictive modeling assessment, Pb exposures are more stable over time and therefore more amenable to attempts at quantification, either empirically or by use of steady-state predictive modeling.

Such workers therefore have invited more attention from regulators and others than has the clean-up worker category (USEPA, 1996a; Bowers and Cohen, 1998). Such workers are also a major focus for discussion in this article, particularly those women workers of childbearing age and older male and female workers whose prior occupational histories were linked to the acquisition of high body Pb burdens in their bones. To date, EPA has viewed the Pb problem of post-remediation site workers as one of potentially pregnant women (or likely to get pregnant in the future) at such sites transmitting exposure and toxicity risks to the fetus (USEPA, 1996a). That is certainly appropriate in terms of fetuses being a highly vulnerable population during any type of elevated Pb exposures, but it is equally true that the women themselves are at added risk (Mushak, 1998a; Silbergeld, 1991; Gulson et al., 1997). Similarly, older women approaching or in menopause have endogenous Pb circulating in the blood compartment, especially if they had high Pb exposures in prior employment (Silbergeld et al., 1988). Also, older men with similar high Pb occupational histories will retain elevated blood lead (Pb-B) values going into site employment.

2.3. Residents of communities with Pb remediation sites

Residents in and around Pb remediation sites, notably Superfund sites, are mainly affected in terms of Pb-B changes post-remediation. Given usual work practices controlling soil/dust Pb mobility during removal, exposure alterations at this stage are minimal. Among residents who are most impacted from exposure changes arising from Pb remediation efforts, infants and toddlers are of special concern in those cases where remediation is of soils and dusts on a household exposure unit basis. Older children who are mobile enough to come into contact with Pb outside the home would be affected by reduced exposures of remediated environmental media outside the residence.

3. Biomonitoring Pb exposure changes in remediation

Assessments of changes in Pb exposures take place in the larger context of human health risk assessment, with its focus on quantification of biological markers of either exposure or early effect. Of these markers, those of Pb exposure are, for all practical purposes, the ones having widest use (see below).

There are three approaches to monitoring Pb exposure changes in site soil and dust Pb remediations. One can carry out Pb-B screening within some systematic protocol during the clean-up activities. Secondly, one can model Pb exposures predicted during clean-up activities using inputs to these models that include measured levels of Pb in those dusts and soils. Finally, one can use a combination of modeling and screening, for example through use of a pre-work Pb-B measurement with subsequent estimates of likely exposures being modeled rather than measured.

Pb-B is the common biomarker of Pb exposure. However, to use this marker effectively and correctly, one must be aware of its characteristics (NAS/NRC, 1993; USCDC, 1991; USEPA, 1986; Mushak, 1992, 1993). Pb-B in the young child is relatively labile, and can rise or fall relatively quickly. With aging, and certainly by adulthood, the stability of the measure with moderate Pb intake increases or decreases is more (e.g. Delves et al., 1984). Part of this stabilization with age is that the bone Pb pool becomes much larger and an increasingly more unstable contributor to total Pb-B than external Pb inputs (Mushak, 1998a; Delves et al., 1984; Manton, 1985; Gulson et al., 1995; Smith et al., 1995).

The degree of Pb-B variability over time even within the young child band of 0–5 years of age can vary greatly, depending on the degree of ongoing Pb exposure. Unlike the case with older

children or adults, bones of the very young are constantly being remodeled, with Pb entering and departing younger children's bones more rapidly and with more dependence on ongoing exposure, compared to the cumulative deposition of Pb in bones underway by older childhood. This is seen in the calculations and discussions of O'Flaherty (1993, 1995, 1998) where mobile bone Pb in the very young can wash out into blood at varying rate as a function of the extent of exposure changes (typically downward). This process affects one biokinetic measurement of Pb-B mobility, the biological half-life or half-time. This parameter has been discussed in detail elsewhere (Mushak, 1998a).

The typical mean-life of Pb-B under certain conditions and exposure histories is held to be, on average, approximately 30 days (NAS/NRC, 1993; Chamberlain, 1985; Rabinowitz et al., 1976). Across groups of children, that average describes a wide range, from several days to values well in excess of 30 days (Otto et al., 1985; Gulson et al., 1995; Manton et al., 2000; Succop et al., 1987). One complexity largely unrecognized by those only superficially familiar with the topic is that half-lives for Pb-B will vary with the age of the individual, the body burden of the individual and the presence of more than one biokinetic compartment. In general, the fast component of body Pb burden, even in workers with heavy occupational exposures, is still measurable as being approximately 30 days. However, one or more separate bone compartments define slower biokinetic compartments. These differentiated compartments are discussed by Nilsson et al. (1991), Schütz et al. (1987), O'Flaherty et al. (1982), Hryhorczuk et al. (1985), Kang et al. (1983). Teasing out the presence of multiple biokinetic compartments and their estimable half-lives is made more feasible by the use of more data points through longitudinal investigations, as noted elsewhere by this writer (Mushak, 1989), especially for relatively large bone Pb burdens acquired by adult workers.

In children, and certainly for those in the 0–5 year age band, there are for all practical purposes no easily discerned multicompartmental kinetic depictions of body Pb burden. Rather, as calculated and shown quantitatively by O'Flaherty (1993, 1995, 1998), Pb-B and soft tissue Pb is linked with a small and highly mobile bone Pb compartment in the very young. The half-life of Pb-B within this linkage, however, will vary and even vary considerably with the size of this mobile child bone Pb pool (Otto et al., 1985; Succop et al., 1987; Gulson et al., 1999; Manton et al., 2000). This pool is generated within infancy and toddlerhood and then diminished with older childhood, followed finally by a largely unidirectional (upward) increase with age.

The above characterization is the obvious explanation for the findings by different researchers that half-life values of Pb-B in the very young range beyond merely 30 days or so and can even be up to several years in length (Otto et al., 1985; Succop et al., 1987; Gulson et al., 1999; Manton et al., 2000). Put simply, the greater the transitory accumulation of Pb in the mobile mineral matrix of very young children's bones, the longer the bone Pb wash-out period and the longer the half-life of the Pb-B in that time interval between 2 and 3 years and that older childhood age period when there is the onset of long-term bone Pb sequestering that continues through much of adulthood.

The first inkling that Pb-B half-life values are variable and can range well beyond 30 days was reported in a 1985 paper by Otto et al. (1985). They showed that when the Pb-B values of a group of children first measured as pre-schoolers were statistically compared to the 5-year follow-up Pb-B levels, a high rank order in Pb-B was preserved, although absolute Pb-B values had actually declined. A high original Pb-B ranking was linked to an equally high Pb-B ranking 5 years later. This was consistent with a slow kinetic contributor to Pb-B of these children over the years. Succop et al. (1987) reported that pre-school children exposed at high Pb levels in inner-city Cincinnati had a mean half-life in Pb-B of approximately 10 months. Aschengrau et al. (1994), in following declines of age-adjusted Pb-B levels in children in soil Pb-remediated Boston housing, noted that after 2 years post-remediation a half-life from starting Pb-B was still not reached. In newborn infants followed up to 6 months of age, Gulson et al. (1999) measured a half-life of Pb-B of 91 days,

about twice that of their mothers. A recent report by Manton et al. (2000) estimated half-lives for Pb-B in inner-city, lead-exposed children of up to several years. In summary, when very young children have high Pb exposures by their peak expression of that exposure, approximately 2–3 years of age, the decline of that peak exposure to 50% (definition of half-life) will take more time than if the original mobile bone level was less.

One obvious factor not to be ignored in assessing these reports is that of the degree of continuing exposure when children get older. To get a meaningful half-life in a child's Pb-B, it is assumed that with aging the level of Pb intake has been reduced enough to allow Pb-B to decline at least 50%. If ongoing exposure is sufficient to thwart achieving this 50% decline in the short-term, then the linkage of Pb-B to bone Pb or other endogenous Pb source in the very young in any estimations of Pb-B half-life is more complicated.

Finally, the differences in Pb mobility, adults versus children, means that one can collect a single Pb-B for adult Pb exposure scenarios and have a better picture of ongoing exposure than is the case for children, where single-shot Pb-B surveys can yield erratic results owing to such factors as public attention, caregiver concerns, etc. (Mushak, 1998a).

4. Biokinetic modeling of Pb exposure changes in remediation

4.1. The USEPA's Pb exposure models

EPA employs several biokinetic models at Superfund sites for application to various exposure populations (USEPA, 1994, 1996a). The Integrated Exposure-Uptake Biokinetic (IEUBK) model applies to children from early infancy to 84 months of age (USEPA, 1994). It is a steady-state model with both compartment and physiologically based-pharmacokinetic (PB-PK) features and contains a number of features that permit its use for group exposure modeling, via a batch run computational module, and the generation of descriptive and inferential statistics by use of a statistical module. The IEUBK model also is open-ended and, as noted elsewhere (Mushak, 1993, 1998a), it can predict the future in terms of land use and child demographic changes and, in a sense it can reconstruct the past, using available background or remote, preindustrial historical environmental data to reconstruct children's exposures.

There are two current forms of adult Pb exposure modeling, viewed as being useful in such exposure scenarios as those of workers employed on remediated sites or even doing on-site or off-site Pb remediations of such environmental media as soils and dusts. One of these, recently introduced as an interim modeling methodology until more sophisticated methodology is available (USEPA, 1996a), is the Adult Lead Model (ALM). The ALM is basically an equation model with some probabilistic estimating added via use of a geometric standard deviation and other simple parameters. It attempts to combine a background Pb-B level in non-resident adults (i.e. on-site workers after remediation), with such parameters for soil and dust Pb as the amount of daily media ingestion, the Pb uptake rate from such media and the biokinetic slope factor (a numerical expression which links daily absorbed Pb to a blood level in the adult, and in the case of pregnant women, to the fetus). From such estimating, one can derive, in theory, remediation goals and ceilings to maternal Pb-B levels that also provide fetal protection.

The EPA all-ages lead model (AALM) now under active development is unlike the simple equation model, being a PB-PK model. It is intended to address lifespan Pb exposures of populations impacted by such Pb sources as Superfund sites. A version for peer review is currently being prepared by the EPA contractor. The assessment of relatively short-term Pb exposures as would occur during remediation can really only be handled via the PB-PK methodology of the AALM, since the steady-state models such as the ALM are really not applicable.

Extant PB-PK models are viewed as increasingly useful, including the published versions of O'Flaherty (1993, 1995, 1998) and Leggett (Pounds and Leggett, 1983; Leggett, 1993). They do have their own limits, however. First, the level of validation has been limited. Secondly, the current versions are in a computational form which is limited as to the incorporation of probabilistically estimated out-

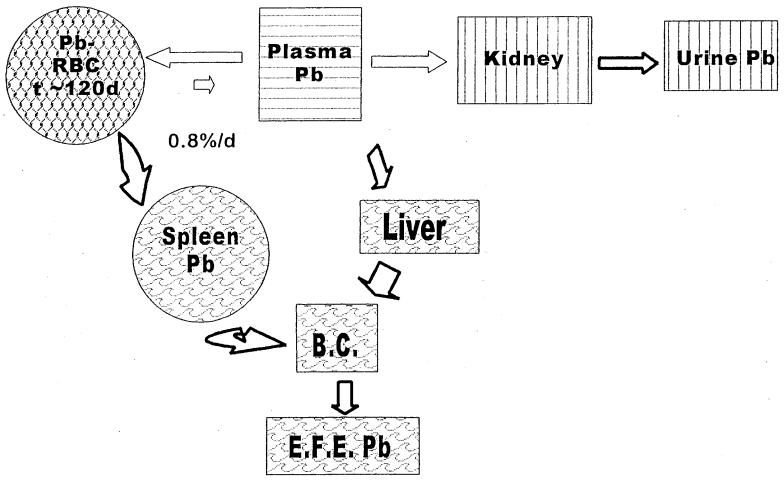

Fig. 1. Disposition of erythrocyte lead with normal cell turnover rate at low to moderate lead exposures. RBC, red blood cells; B.C., biliary clearance; E.F.E., endogenous fecal excretion.

put ranges rather than their current derivations of point estimates as outputs.

5. Physiological aspects of Pb biokinetics and exposure changes

There are two physiological issues associated with human Pb exposures and changes in those exposures. Related to these physiological factors are several environmental issues with which this physiology interacts. The first physiological factor is the behavior of Pb in the blood compartment relative to movement within it and movement into and out of the circulation. This includes subsequent distribution to tissues and organs and then excretion. The second is the role of skeletal Pb accumulation and release biokinetics in affecting both the measurement and predictive modeling of changes in Pb-B with some level of remediation. A comprehension of these factors is required to fully evaluate the relative effectiveness of remediation of Pb, particularly within various population groups at high risk.

Two environmental issues that interact with lead physiology are especially important, in that they have a bearing on the long-term positive impact of lead remediation, particularly with regard to populations of children. The first has to do with the full characterization of all lead sources that increase Pb exposures before and during lead remediation. The second concerns the most appropriate statistical methodology for quantifying remediation effectiveness. For example, when lead remediation of residences is being carried out, are any declines in Pb-B due just to soil/dust Pb remediation? When doing statistical assessments of exposure changes post-remediation, are the best analyses being done? As noted elsewhere (USEPA, 1996b), soil Pb may impart its contribution to children's Pb-B not via its direct ingestion but as a source of leaded dust adhering to children's hands, followed by ingestion. Since the source of that pathway dust is obviously soil, any statistical methodology which ignores dust's intermediacy greatly underestimates the total soil Pb input to Pb-B. The second has to do with the nature of the lead biokinetic profiles of children moving in and out of permanently remediated residential units and their yards. This is also an especially important matter when quantifying the overall benefits to human health in terms of avoided Pb toxicity management costs. These issues are discussed after the physiological and biokinetic discussions.

5.1. Lead in the blood compartment

A generalized depiction of Pb in the blood compartment is contained in Fig. 1, as part of a

larger depiction of the pathway for erythrocyte degradation in humans. It is generally accepted that Pb in whole blood is distributed unevenly between the erythrocytes and plasma or serum, with the former binding virtually all of the total Pb-B content (Baloh, 1974; Bruenger et al., 1973; Manton et al., 2000; Manton and Cook, 1979; Ong and Lee, 1980). The first observation of this traces back to the early 20th Century (Schmidt, 1908). Serum and plasma differ little in Pb content, harboring approximately 1% of the total amount in blood, 99% being erythrocyte-bound. This equilibrium distribution increases somewhat towards plasma in a curvilinear manner with increases in Pb-B above approximately 25–40 μg/dl (DeSilva, 1981; Manton and Cook, 1984) and is dependent to some extent on the fasting state of the individual (Manton and Cook, 1984).

The plasma Pb content even in high exposures is quite low, complicating accurate and precise measurement (Mushak, 1998a; Everson and Patterson, 1980; Manton and Cook, 1984). A further difficulty in using this medium as an exposure biomarker is the high potential for artifactual transfer of Pb from the dominant subcompartment depository of Pb-B, the erythrocytes, to plasma. This writer previously reported some comparative contamination examples of this hazard (Mushak, 1998a). Plasma is the component of whole blood that is the conduit for lead transport to tissues and would perhaps show a more proximate dose–response relationship, but this biological and biokinetic feature is obscured by the methodological artifact of hemolytic lead release and contamination and the sensitivity requirements of methods for the much lower levels (Mushak, 1998a).

Lead in the human erythrocyte has long been held as being largely bound to hemoglobin (85%), particularly Hb-A_1 and Hb-A_2 (Moore, 1988). The balance is bound to membrane sites. Lead has been assumed to be bound mainly to albumin (70%) and other biomolecular sites in plasma (Moore, 1988). Recent studies and observed kinetic behavior of Pb in blood, however, have implicated other major sites of erythrocyte Pb binding, one being the cytosolic vestigial heme synthesis pathway enzyme in the cell, δ-aminolevulinic acid dehydratase (δ-ALAD; Bergdahl et al., 1997; Gercken and Barnes, 1991), and perhaps, at high Pb levels, a Pb-binding protein that resembles metal-inducible metallothionein (Lolin and O'Gorman, 1988). This new view of how lead is stored in blood cells, if widely confirmed, has a number of implications for lead binding in diverse populations, especially those populations in which δ-ALAD or other erythropoietic proteins of genetic polymorphism are affected.

5.2. Genetic polymorphism in δ-ALAD and Pb–blood interactions

Various authors have described the impact of ALAD genetic polymorphism on lead–blood interactions (e.g. Astrin et al., 1987; Wetmur, 1994). Hematology in human populations has a number of genetic determinants, and the genetic polymorphism for various components of the human blood compartments has the potential to affect not only the binding of Pb in blood, but the associated dose–response relationships for Pb owing to such alterations. At the least, these genetic correlates enhance the variability of Pb-B between subjects with the same overall external Pb contact.

Genetic polymorphism within and between populations exposed to Pb is an intrinsic factor in Pb exposure and toxicity and affects in its own way in vivo impacts of changes in the external Pb exposure setting. The focus here is on ALAD. The enzyme shows genetic polymorphism in certain human populations. The gene encoding δ-ALAD is localized on chromosome 9q34 and is expressed as two codominant gene alleles, ALAD1 and ALAD2 (Astrin et al., 1987). Expression of these two alleles produces three ALAD isozyme phenotypes: ALAD 1–1 (normal), ALAD 1–2 (heterozygote variant), and the relatively uncommon ALAD 2–2 homozygote variant. The gene frequencies are 0.9 and 0.1 for ALAD1 and ALAD2 alleles, respectively.

Distribution of the isozyme ALAD variants differs with racial makeup of the population (Astrin et al., 1987; Wetmur, 1994). Caucasians show approximately 80% of ALAD 1–1, 18–19% ALAD 1–2, and 1–2% of the homozygotic isozyme 2–2. Afrocentric populations show little of the variant allele expression, while those of Asian

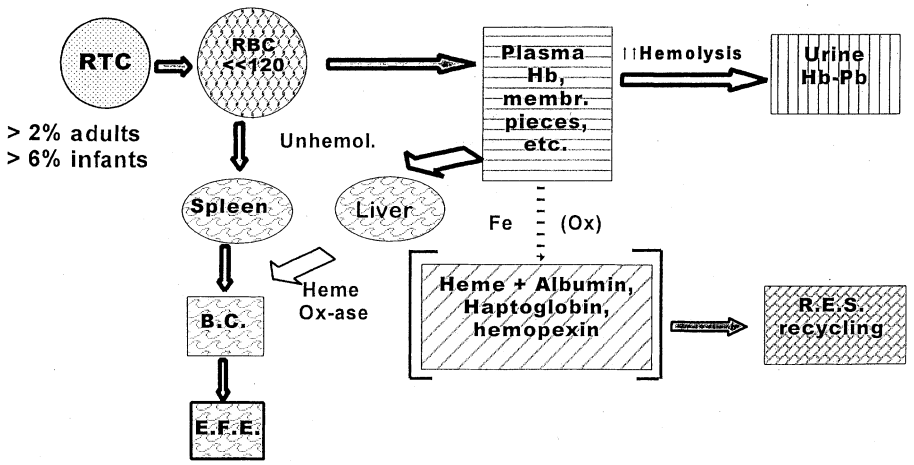

Fig. 2. Disposition of erythrocyte lead with altered cell turnover due to toxic hemolysis at high lead exposures, above 50–60 μg/dl. RTC, reticulocytes; B.C., biliary clearance; E.F.E., endogenous fecal excretion; R.E.S., reticuloendothelial system.

descent appear intermediate in the fractions of isozyme variants. Genetic polymorphism expressed as ALAD isozyme variants has been claimed to be linked to differential binding in the erythrocyte and such binding differences would be significant to Pb–blood interaction, lead body burden toxicokinetics, and expressions of Pb toxicity. First, epidemiological data suggest that children (Astrin et al., 1987; Wetmur, 1994) and adults (Smith et al., 1995; Ziemsen et al., 1986) with the ALAD2 variant have higher Pb-B levels, and Pb workers with the variant accumulate higher bone Pb in their bones with age (Smith et al., 1995). Secondly, differences in Pb–ALAD isozyme variant interactions appear to influence the severity of toxic effects, but in inconsistent ways (Schwartz et al., 1995; Smith et al., 1995). At present, the relationship among ALAD allele distributions, Pb-B and bone Pb remains ill-defined.

5.3. Erythrocyte degradation and its Pb disposition

Fig. 1 indicates that the human erythrocyte lifetime is approximately 120 days, corresponding to a daily turnover of 0.8%/day. That particular turnover rate is in the absence of marked hemolysis, which serves to greatly disturb hematopoiesis and distribution of Pb. The erythrocyte is degraded in the spleen, with degradation products and presumably bound Pb being released with its binding substrate. Depending on the extent of binding to ALAD versus hemoglobin, Pb will mainly exit via biliary clearance and endogenous fecal excretion or enter the plasma compartment to some degree. Eventually, of course, some of the plasma Pb will itself enter the biliary tract (Klaassen, 1976; Klaassen et al., 1981). It is not clear the extent to which individuals with the 1:2 or 2:2 isozyme variant have their erythrocyte Pb burdens follow this partitioning of 99:1 accepted in lead biokinetics. If Pb is bound more tightly, then the erythrocyte burden of Pb when released may go a different disposition pathway in the spleen. Little is known of this possibility.

Fig. 2 depicts how the presence of a toxic hemolysis from very high Pb-B levels can affect erythrocyte Pb distribution. First, the normal turnover of erythrocytes is disturbed with cell destruction resulting in release of cell contents for altered metabolic processing. Simultaneously, reticulocytes (RTCs) increase in count, RTC Pb having a relatively unknown partitioning with serum or plasma. Plasma in the presence of a toxic hemolysis hematologically inherits erythrocyte degradation products, only part of which can be effectively dealt with by the cell degradation pathway. Hemoglobin enters plasma and eventually appears in urine. The spleen becomes stressed with its work

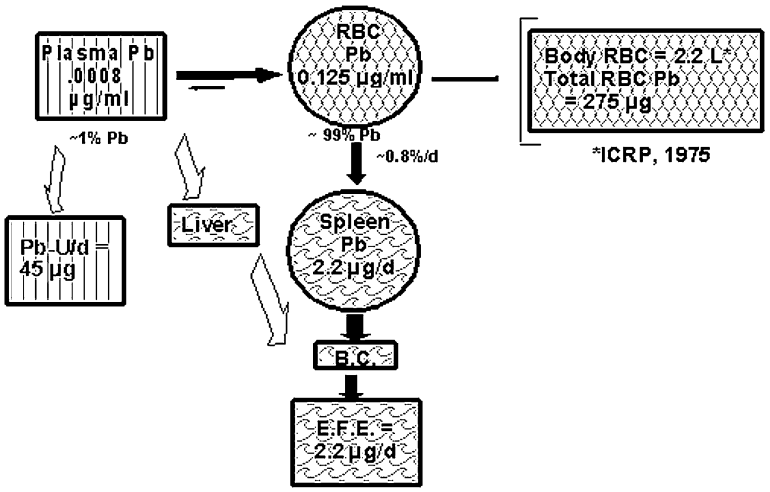

Fig. 3. Quantitative estimate of lead excreted from erythrocyte turnover at a Pb-B of 50 μg/dl. ICRP, International Commission on Radiation Protection; B.C., Biliary Clearance; E.F.E., Endogenous Fecal Excretion.

of processing cell debris and splenomegaly or spleen swelling occurs. In all likelihood, excess Pb compared to usual hematopoiesis enters both urine and the biliary tract.

A question of considerable interest to this topic is that of relative disposition of Pb via erythrocyte degradation vs. glomerular filtration and biliary clearance via plasma. The estimate associated with a daily cell Pb release at a steady-state adult Pb-B of 50 μg/dl is shown in Fig. 3 as 2.2 μg/d for adult males. This value is calculated from: (a) the 1975 ICRP Reference Man estimate of 2.2 l of packed erythrocytes; (b) the corresponding total erythrocyte Pb content in these cells of 2750 μg at a whole blood level of 50 μg/dl; and (c) a daily erythrocyte turnover rate of 0.8% (1250 μg Pb/l cells × 2.2 l × 0.008/d = 2.2 μg/d). At a Pb-B of 50 μg/dl, the daily urine Pb excretion is 45 μg/d, extrapolating from data of Chamberlain (1985). Hence, the relative amount of body Pb being excreted via cell degradation and release of its Pb content versus daily excretion via the urine is approximately 5%. In terms of total Pb excretion, via urine and endogenous fecal excretion of that fraction passing through the biliary tract, i.e. 68 μg/d, the erythrocyte daily contribution from erythrocyte degradation amounts to approximately 3%.

Chamberlain (1985), using adult volunteers injected with Pb-203, noted that endogenous fecal excretion via the biliary tract is 50% that of urinary excretion. Such experiments, however, are not at steady-state conditions and are only perhaps a crude depiction thereof. Klaassen (1976) reported biliary excretion of metals in a number of species but noted, for obvious reasons, difficulties with human data. A better method than radioisotopic tracer studies is needed. An alternative approach for estimation of human biliary clearance of Pb is potentially the stable isotope approach, such as that used by Gulson et al. (1995, 1997, 1998, 1999). Subjects who have bone Pb isotopically distinct from Pb in their external contact environment release that isotopically distinct bone Pb into blood and eventually into urine and into the biliary tract with endogenous fecal excretion. Therefore, some fraction of this Pb is added to unabsorbed fecal Pb having a different, external Pb isotopic composition.

5.4. Bone Pb releases in adult workers including pregnancy

A second physiological factor that affects both stable and altered Pb exposure assessments is the

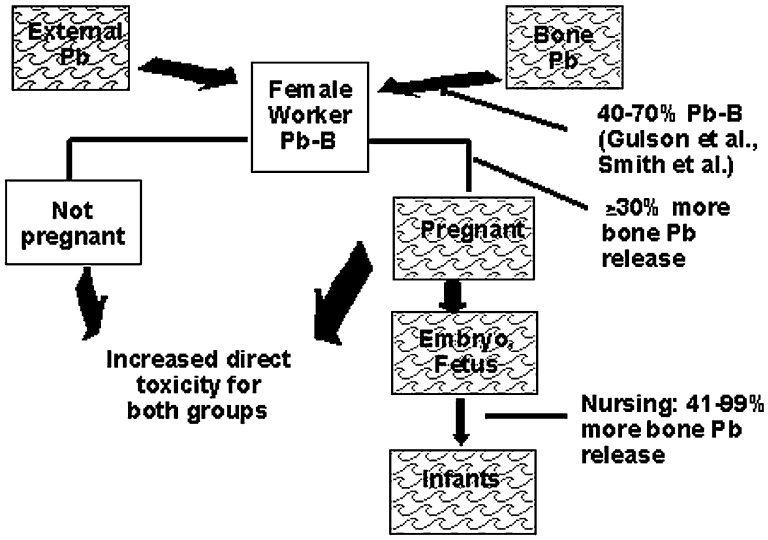

Fig. 4. Bone lead releases in non-pregnant and pregnant women.

extent to which skeletal resorption in pregnancy and nursing or in menopause, the latter representing osteoporotic release, affects how one estimates the effectiveness of lead remediation.

The notion that bone Pb is not static is not new, contrary to some impressions. For example, the German pathologist Gusserow (cited in Aub et al., 1925) strongly hinted at potential Pb releases, observing that, in his studies of Pb-dosed rabbits, the largest fraction was in bone. Furthermore, there was a Pb–calcium association. Aub et al. (1925) clearly expressed the likelihood that Pb in bone is to be considered a toxicologically active store of the toxicant.

Fig. 4 depicts the steps in Pb release from bone with some attached estimates of fractional releases compared to a basal state. It can readily be seen that any predictive modeling or even poorly timed serial Pb-B screenings can be affected by this metabolic phenomenon. Of particular concern would be those women who have had an extended Pb exposure history from early childhood years, permitting sizeable bone stores to arise (e.g. NAS/NRC, 1993; Mushak, 1998b).

A number of factors affect the degree of bone Pb resorption, some of these being intrinsic and some being extrinsic. The former may potentially include the degree of bone density. Bone density differs along racial lines. Afrocentric populations tend to have bones of greater mineral density and the extent to which this produces a differing mineral resorption rate may affect endogenous lead releases (O'Flaherty, 1993, 1995, 1998). Dietary adequacy, specifically adequate calcium intakes during pregnancy, will affect the extent of bone Pb release (e.g. Gulson et al., 1998). Those with adequate calcium diet release less bone elements than those who are calcium-deficient. The reproductive history of pregnant women is also a factor in predicting how much resorption will occur (Gulson et al., 1998). Each new pregnancy appears to alter the extent of skeletal Pb release.

6. Interactions of Pb sources and remediation effectiveness

6.1. Accounting for all Pb sources

Lead remediation can differ in the extent to which it addresses all Pb sources and pathways. Typically, when Superfund sites are involved, remediation is confined to cleaning up Pb in soil and associated dusts and perhaps other media such as contaminated sediments and groundwater.

Remediations done only for these media but where paint Pb may also be present require some assessment of the contribution of the latter to population exposures before and after the usual remediation efforts. Statistical methodologies exist to tease out a paint Pb contribution, including structural equation modeling, a form of multiple regression, inferential statistics (USEPA, 1996b; Succop et al., 1998; Marcus, 1995).

Succop et al. (1998), in their investigations of statistical modeling approaches to assessing Pb exposures at Western US extractive industry sites, noted that paint Pb had a range of fractional contributions to overall children's Pb-B levels, from statistically insignificant to a statistically significant contribution. Furthermore, paint Pb can affect Pb-B by either a direct contribution or via the dust pathway, in a fashion similar to interior and exterior dusts from leaded soils. In their investigations of almost a dozen Western sites, interior paint Pb was less frequently a statistically significant contributor to children's Pb-B than was soil Pb. These findings indicate that for those communities around waste sites where Pb paint may potentially be a problem, any a priori assumption that Pb paint is actually a contributing factor must in fact be confirmed empirically. Marcus (1995), in a statistical reanalysis of soil, dust and paint Pb at a Superfund community in Madison County, IL, using structural equation modeling, reported that an earlier crude analysis done by others using environmental data from this site had produced an inaccurately high impact of Pb paint on children's Pb-B values and an equally inaccurate underestimate of soil lead inputs to children's Pb-B.

6.2. Accounting for all changing Pb sources in Pb remediation efforts

Post-remediation statistical assessment of any effectiveness of Pb remediation in soils, dusts, sediments, etc. at some hazardous waste site can potentially require that other sources and pathways of Pb be considered as contributors to exposure changes, e.g. declines in Pb-B levels post-remediation. For example, nationwide declines in the use of leaded gasoline and Pb levels in the diet have been claimed to contribute to any declines in exposure where the remediation effectiveness is indexed by the extent of Pb-B decline.

Claims that national trends in declines in other Pb sources will somehow significantly affect declines seen within community site-specific remediations are often incorrectly drawn. First, national depictions of such changes do not quantitatively apply to specific communities. That is, we cannot statistically disaggregate the national picture for source trends into identical trends for each and every community that may have Pb remediation done. A national statistical picture incorporates all geographic and demographic strata and would not be theoretically comparable to a single, specific site (USATSDR, 1988).

The extent to which leaded gasoline phase-out that was essentially complete in the early-mid 1990s will impact a community in recent years will obviously depend on the extent to which leaded gasoline was a major factor to begin with and how long the phase-out had already been in place. Any recent Pb remediation efforts in lightly populated, highly rural areas with stationary Pb sources such as Pb mining, milling and smelting operations would be minimally impacted, overall, by leaded gasoline consumption changes. Leaded gasoline contributions to ambient air and dust Pb fallout is directly proportional to population and traffic density (USEPA, 1986, 1995).

Similarly, it is unlikely that dietary Pb changes in the most recent years will effectively confound the effectiveness of site-specific Pb remediation. This largely owed to the fact that typical diet Pb intakes were already quite low by the early 1990s and further changes downward would minimally affect measurement or modeling of population Pb-Bs. For example, the default diet Pb intake in the 1994 IEUBK model had already declined to approximately 5–6 $\mu g/d$ and less (USEPA, 1994). It is unlikely there would be much further decline, the level already being close to zero Pb in diet. A decline to less than this diet Pb daily value would also constitute a trivial contribution to Pb-B relative to site soil and dust Pb concentrations.

6.3. Cumulative beneficial impact of permanent Pb remediation at waste sites

The extent of reduction of Pb exposures with a permanent Pb remediation associated with such actions as residential and community soil Pb removal differs with populations in a number of ways, and consequently the overall health benefits vary as well. A quantitative comprehension of the magnitude of such benefits is necessary before one can draw any conclusions as to the cost-effectiveness of such actions. Permanent forms of Pb remediation in a community, such as when contaminated soils are removed and exposures are lowered, affect not only the current community residents but future ones as well. This impact is especially amplified with rental housing, where one can consider successive groups of such risk groups as very young children moving into and out of remediated rental properties. While the first wave of such children, those residing at sites before remediation was completed, have only a body Pb burden reduction after some Pb accumulation, future groups of children moving into remediated properties are spared the initial Pb accumulation in the body and thereby have maximum protection from Pb toxicity.

What is the magnitude of the cumulative beneficial impact of a permanent remediation on mobile child populations in rental housing within a community? ATSDR estimated (USATSDR, 1988) that where Pb in rental housing is abated in a residential area with a remaining residential life of 50 years, then 10 successive waves of pre-school children, each residing for 5 years therein, are protected from Pb toxicity. Prevented childhood Pb toxicity and its attendant societal and medical resource costs are therefore much greater than one calculates by simply using just the current tally of residents at remediated sites. The ATSDR estimate permits one to distribute remediation costs vs. benefits over 10 sets of children, not merely the current set of child residents.

7. Summary and overview

The point of Pb remediation is to lower Pb exposures in various populations at risk. The extent to which various remediation strategies achieve this goal requires a rather comprehensive grasp of the myriad of environmental, biological, and biokinetic factors that are at work to influence estimates of exposure reduction. Without such awareness, one cannot readily conclude that some particular level of exposure reduction has been or will be achieved. Superfund site remediation actions typically involve removing soil (and dust) Pb when some action level is reached or exceeded from both residential and common use areas.

This paper identified whom we evaluate for the highest risk among populations affected by remediation and post-remediation, how we evaluate Pb exposures at the outset and with alterations (reductions) in exposure, and the various dimensions biologically and biokinetically to this evaluation of exposure reduction.

Groups at highest risk for Pb exposure and toxicity and those to be protected are fetuses of industrial site workers who are pregnant, infants, and toddlers. Remediation workers and non-resident workers employed in industrial activities at some post-remediation site are, of course, themselves at risk for toxic effects, the risk being compounded by any pre-existing body burdens from prior high Pb exposures. All of these groups in turn have biological and biokinetic dimensions to their lead exposure that require understanding before one can determine exposure changes during or after Pb remediation.

The discussion on exposure assessment identified three ways one could measure the effectiveness of Pb remediation in lowering exposures. The first is empirical, measurement of some biomarker of exposure or early biochemical effect. The second method is a predictive mathematical modeling approach, whereby inputs of measured environmental Pb levels are employed to estimate a measure of exposure, a Pb-B value. Finally, one could use combinations of measurement and modeling data.

Biomarkers of exposure are more commonly used in lead risk assessment than measures of early biochemical effect, although the use of one such early effect measure, the free erythrocyte protoporphyrin or more correctly zinc protoporphyrin test, can be quite useful in early screening or

fixing the temporal Pb exposure pattern (NAS/NRC, 1993). The use of the Pb-B measurement has a number of virtues: it is readily related to toxic effect thresholds or frequencies via dose–response relationships; it can be readily measured within known and available QA/QC protocols: and it is a measure of ongoing exposure, i.e. exposure in real time. The last-named is of particular concern for risk managers and health protection policy makers.

Pb-B in those risk subjects with variable pre-existing body Pb burdens will respond in complex ways to changes in external Pb contact occasioned by remediation actions, such as removal of contaminated soils and dusts in and around a Superfund site. Two major factors affecting this response and its implications for judging clean-up effectiveness are the behavior of lead in components of the blood compartment and the role of a mobile bone reservoir in the skeleton of exposed subjects. This article and earlier articles discussed in detail the various biokinetic sequences that govern Pb movement in and out of the blood compartment, to include such factors as genetic polymorphism as a contributing factor and the interplay of lead removal rates from the plasma sub-compartment versus Pb removal from the erythrocyte during cell turnover and biochemical degradation.

The cardinal assumption when monitoring exposure changes from Pb remediation is that Pb-B will decline. This assumption prompts some key questions. How much will Pb-B decline and how long will it take to maximize the decline? Who among the affected risk populations should be particularly evaluated for any Pb-B? That is, should we look at mean or median Pb-B group declines or is it more toxicologically and medically important to examine downward shifts in the overall distribution of community Pb-B values, particularly those high Pb-B levels in the upper tail of the original Pb-B distribution?

The use of Pb-B changes in response to Pb remediation actions is affected by endogenous factors, such as the rate of Pb-B decay and the time interval used to assess Pb-B decline, and such external factors as persistence or preservation of the extent of the clean-up. This article showed that with both young children and older individuals Pb-B decline rates, to include the half-life of decline, vary considerably and can take extended time to show maximal response to remediation. Simultaneously, we can potentially be faced with the problem of difficult-to-quantify recontamination, which would externally attenuate an otherwise more robust decline that would occur with preserved clean-up conditions. Quantification of clean-up effectiveness also requires that we rule out potentially unrecognized additional sources or pathways contributing to Pb-B decline.

A good example of the above caveats in actual practice is the finding by Aschengrau et al. (1994) that soil Pb abatement in a Boston study required at least 2 years to show maximal decline in Pb-B. Had someone not waited for 2 years but used a 1-year post-remediation cutoff the observed Pb-B decline would have only been approximately 50% of the cumulative 2-year decline.

Recontamination can readily occur even with areal and zonal remediations, and this is certainly a risk with spot remediations in the presence of adjacent or nearby unremediated tracts. As noted by EPA in its assessment of the Three-City Soil Lead Abatement Demonstration Project (USEPA, 1996b), the Cincinnati component of the project involved comprehensive clean-up of the neighborhood but leaded dustfall from farther way still introduced Pb in dusts. Remediation must therefore be a macro-scale, not a micro-scale, effort.

Trends in source levels other than those media being abated will probably not affect current or very recent remediation–Pb-B relationships. As noted above, national trends in such sources and pathways as leaded gasoline and diet Pb content will have little relevance for site-specific conditions. First, national trends by definition are not site-specific trends, although this fact is often ignored. One must evaluate the site specifically for additional source changes being operative to begin with. Second, diet and gasoline lead declines, even factoring in air Pb fallout to soils, had largely run their course by the early 1990s. US air lead levels for 1994 compared to earlier years are seen in one of EPA's air quality trend reports (USEPA, 1995) to bear this out. Dietary Pb with reference to centralized food supplies is arguably not a confounding factor for current

remediation assessments since the diet Pb is already quite low and any downward trends would be quantitatively minimal compared to soil and dust remediations involving hundreds or thousands of parts-per-million changes.

Localized, ethnic dietary practices involving, for example, high-lead canned foods in lead-seamed cans as well as other idiosyncratic Pb sources (NAS/NRC, 1993) actually take the issue the opposite way, in that continuing or increasing Pb exposures of this type mask an actual decline in body Pb burden from media being remediated. Home remedies favored by certain ethnic groups can also be a real confounder for children's Pb-B changes.

Lead remediation, at least ideally, is a permanent reduction in the body lead burdens of infants, toddlers, and other high risk groups. There are therefore obvious positive contributions to risk population health that go beyond merely the current residential or community populations. This benefit affects successive groups of individuals in remediated residential areas and impacts them increasingly more beneficially.

In physiological and biokinetic terms, the impacted population living in some community where remediation is being carried out sustains a body lead burden decline from a higher level that existed pre-remediation and that was due to the contaminated media undergoing remediation. That is, the contaminated media that are to be remediated had already contributed to a bone, soft tissue and blood Pb burden. Future groups of such populations as infants and toddlers who then move into these units will be spared such elevated body lead burdens at the outset.

The above interplay of Pb biokinetics and physiology with remediation costs and benefits is particularly evident in rental housing with its populations of mobile tenant children, notably preschool children, The 1988 ATSDR report to Congress on childhood Pb poisoning in America (USATSDR, 1988) noted that where remediated and rehabilitated residential rental units have a 50-year remaining lifetime, ten waves of pre-school children will pass through this housing and ten waves of children will benefit by avoidance of toxic lead exposures. Consequently, risk managers and regulatory policy makers must average out such benefits across cumulative risk populations as done in the ATSDR report. It is quite incorrect in econometric terms to merely relate costs to current site populations. For example, a Superfund site remediation costing $30 million to permanently remove Pb, and using the ATSDR figures for the next 50 years of rental unit remaining life, entails factoring this cost over 10 groups of children. This roughly decreases the remediation cost per child an order of magnitude.

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