CALIFORNIA DEPARTMENT OF TOXIC SUBSTANCES CONTROL
HUMAN AND ECOLOGICAL RISK DIVISION (HERD)

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ISSUE: Revised U.S. Environmental Protection Agency (USEPA) Region 9 Biological Technical Assistance Group (BTAG) Mammalian Toxicity Reference Value (TRV) for Lead: Justification and Rationale.

BACKGROUND

Assessing ecological risk to mammals and birds from contaminants involves comparison of exposure levels to an appropriate toxicity reference value (TRV). A TRV is the daily dose of a chemical (e.g., mg chemical /kg wet body weight/day) that elicits a particular biological effect (e.g., behavioral abnormality, reproductive failure, altered weight gain). In a cooperative effort, the U.S. Department of the Navy and the U.S. Environmental Protection Agency (USEPA) Region 9 Biological Technical Assistance Group (BTAG) developed mammalian and avian TRVs for a number of inorganic and organic chemicals of concern at military facilities in California (Engineering Field Activity West, 1997). The Navy/BTAG TRV Workgroup selected biological effects that primarily related to growth, reproduction, and development; however, all effects deemed ecologically relevant were considered when developing TRVs. TRVs were developed to represent no observed adverse effect levels (NOAELs; TRV-Low) and mid-range adverse effect levels (TRV-High). The TRVs were selected from the published literature via consensus among the Navy, Navy consultants, and several regulatory agency representatives within the BTAG, including the USEPA, Department of Toxic Substances Control, Human and Ecological Risk Division (DTSC, HERD), Regional Water Quality Control Board (RWQCB), Office of Environmental Health Hazard Assessment (OEHHA), National Oceanic and Atmospheric Administration (NOAA), U.S. Fish and Wildlife Service (USFWS), and the California Department of Fish and Game, Office of Spill Prevention and Response (DFG, OSPR). In 1997, the TRV Workgroup supported the adoption of a mammalian TRV-Low for lead (Pb) of 0.0015 mg/kg body weight (BW)/day based on the study of Krasovskii et al. (1979) that evaluated reproductive, hematological and neurological effects in rats.

In a letter dated January 29, 2001 (from Dr. Mark Johnson, U.S. Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, MD to Dr. Jim Polisini, DTSC, HERD and Dr. Clarence Callahan, USEPA Region 9 BTAG Coordinator), the Army requested, following guidelines outlined in EcoNOTE4 (DTSC, HERD, 2000), that the BTAG consider revision of the mammalian TRV-Low for Pb (U.S. Army, 2001). Following a meeting held May 16, 2001 and in a letter dated July 31, 2001 (letter from

Dr. Clarence Callahan to Dr. Mark Johnson), the BTAG concurred with the Army that the study (Krasovskii et al., 1979) used to set the original TRV-Low was inadequate for that purpose. The BTAG's decision was based on the following rationale:

- First, while the Army concluded that the Krasovskii et al. (1979) study was not appropriate for mammalian TRV derivation because of inadequate reporting and inconsistencies with the preponderance of other scientific information, the BTAG did not believe that the described reporting deficiencies were sufficient to justify exclusion of the study. Nevertheless, following a review of former and recent toxicological literature for Pb, the BTAG concurred that investigators evaluating similar endpoints (as cited in ATSDR, 1999), have generally not reproduced the Pb dose-response relationships reported by Krasovskii et al. (1979). For example, the Ronis et al. (1998) study is likely one of the better, recent, studies for identifying a NOAEL for the reproductive toxicity of Pb to rats.

- Second, the BTAG did not agree that the Army (2001) should limit a TRV-Low to reproduction, development, and mortality endpoints. The BTAG believes that behavioral and systemic effects should be considered in TRV development, in as much as these endpoints could potentially affect the survival and reproductive fitness of an animal. The BTAG suggested that a reevaluation of available Pb toxicity information [i.e., Agency for Toxic Substances Disease Registry (ATSDR), 1999], focusing on sensitive and ecologically relevant endpoints, was warranted.

On January 7, 2002, at the invitation of the Army, BTAG representatives from HERD and the DFG/OSPR participated in the review of Pb toxicity studies identified by the BTAG and the Army for consideration in the development of a revised TRV-Low for Pb. Studies included those from the ATSDR (1999), and those resulting from an independent literature review conducted by the Army.

On February 22, 2002, the Army submitted to the BTAG a second proposal for revising the mammalian TRV-Low for Pb to 13 mg/kg body wt./day (U.S. Army, 2002). The Army considered a total of 21 studies from the literature as acceptable for use in deriving a TRV-Low for Pb. Other studies were rejected from consideration, including those studies where (1) conclusions were drawn using inappropriate statistics, (2) endpoints were evaluated that had questionable ecological relevance or presented difficulty in interpretation [i.e., aminolevulinic acid dehydratase (ALAD) changes, hepatic glutathione levels, serum chemistry data, blood pressure changes], (3) a clear dose response relationship was not demonstrated, and/or (4) it was not possible to reconstruct or determine the dose or form of Pb administered. The Army stated that given the extensive nature of the mammalian literature for oral exposures to Pb, no single study could be found that would be definitive in terms of accurately characterizing the effects of oral Pb exposures for all mammalian wildlife. Therefore, to account for variation from differences among laboratories and laboratory methodology, differences in species susceptibility, and differences in effects and absorption for various forms of Pb, the Army proposed to average across NOAEL TRVs generated from multiple mammalian Pb studies to derive a TRV-Low.

BTAG'S RESPONSE TO THE ARMY'S REQUEST TO REVISE THE MAMMALIAN BTAG TRV-LOW FOR LEAD

Following the rationale presented in the original Navy/BTAG effort to set low TRVs (EFA West, 1997), the BTAG supports using the lowest credible, ecologically relevant, NOAEL from the literature. This approach is supported by the Superfund guidance for ecological risk assessment (USEPA 1997), and is protective of individuals that are potentially the most toxicologically sensitive to Pb. As such, the BTAG did not accept the Army's suggestion of using an average of literature NOAELs as a TRV, especially across species and across disparate toxicity endpoints. While the BTAG agrees with the Army that no one single study can account for differences in species susceptibility and differences in effects and absorption for various forms of Pb, a single study can be used to represent a dose that is protective for a variety of species and toxicological endpoints (i.e., protecting the most toxicologically sensitive small mammal species is protective of other small mammal species). To account for differences in field versus laboratory bioavailability of lead, the bioaccessibility of lead at a hazardous waste site can be compared to the bioaccessibility of lead acetate, the form of lead used in most laboratory toxicity studies. Please see EcoNOTE4 (DTSC, HERD, 2000) for a more detailed discussion of lead bioavailability/bioaccessibility.

In preparing a response to the Army (2002) proposal and in selecting a revised mammalian BTAG TRV-Low for Pb, the BTAG met over two one-day meetings held May 15, 2002 and July 17, 2002. During the May 15, 2002 meeting, BTAG members reviewed and discussed the mammalian Pb toxicity literature, including tabular summaries of secondary (i.e., ATSDR, 1999) and primary literature review sources. The outcome of the meeting was a list of studies deemed either acceptable (pending further review) or unacceptable for TRV-Low development. Members were each assigned a set of "further review" studies to critically evaluate and were asked to present their findings at the July 17, 2002 meeting. At the July 17, 2002 meeting, each "further review" study was discussed and debated, and following a consensus building process, the members agreed upon a revised mammalian BTAG TRV-Low for Pb. The selection process and rationale is described in detail below.

BTAG LITERATURE REVIEW IN SUPPORT OF REVISED TRV-LOW FOR LEAD

The BTAG reviewed the available, published Pb literature for small mammals (i.e., mostly laboratory rats and mice) where Pb, in various chemical forms, was administered orally over an intermediate (greater than 14 days) or chronic (greater than 365 days) exposure period (ATSDR, 1999). Acute exposure studies, and studies utilizing other exposure routes, including injection, dermal absorption, and inhalation were not evaluated. Small mammal studies, as opposed to large mammal studies (i.e., dogs, cats, lambs, cattle, pigs, monkeys, humans), were preferred. Small mammals are typically the most exposed receptor populations at hazardous waste sites because of their burrowing behavior and small foraging ranges.

Table 1 presents a summary of studies selected from the ATSDR Toxicological Profile for Lead (ATSDR, 1999) that are based on the oral administration of Pb to small mammals (i.e., laboratory rats and mice). Table 1 also includes the small mammal studies considered by the Army (2002) in its proposed revision of the Navy/BTAG TRV-Low. When the NOAEL and lowest observable adverse effects level (LOAEL) values from the ATSDR reported studies were plotted (Figures 1 and 2), it was apparent that the lowest NOAELs and LOAELs ranged primarily between 0.1 and 10 mg/kg body weight (BW)/day. As shown in the yellow highlights in Table 1, a number of these studies reported NOAELs $\leq$ 1 mg/kg BW/day and LOAELs $\leq$ 10 mg/kg BW/day. However, as previously reported by the Army (2002), many studies included endpoints that were of questionable ecological relevance or presented difficulty in interpretation. As shown in Table 1, the BTAG review eliminated these types of studies from further consideration. Studies selected for further review in the TRV-Low selection process (i.e., NOAEL $\leq$ 1; LOAEL $\leq$ 10 mg/kg BW/day) are highlighted in Table 1 and summarized in greater detail in Table 4.

Table 2 presents a list of 15 studies evaluated in the Pb Ecological Soil Screening Level (Pb EcoSSL) effort (USEPA, 2002) for TRV derivation, where a NOAEL dose was estimated as $\leq$ 1 mg/kg BW/day and a LOAEL dose was estimated as $\leq$ 10 mg/kg BW/day. Many of these studies were not reported by ATSDR (1999). Each of the identified EcoSSL studies was reviewed, and the no effects- or effects-based dose presented by USEPA (2002) was checked for comparability (i.e, did the USEPA, 2002 report an estimated dose within an order of magnitude of that calculated by the BTAG). Of the 15 studies reviewed, only six studies had a NOAEL or LOAEL dose that fell within the 0.1 to 10 mg/kg BW/day dose range. The Pb EcoSSL studies selected for further review are summarized in Table 4.

Table 3 presents the results of an independent literature review conducted by the USEPA Region 9 BTAG for the effects of Pb on small mammals. Based on dosing regimes, only two of these studies (McMurry et al., 1995; Khalil-Manesh et al., 1993) were selected for further review as potentially appropriate to set a TRV-Low. These studies are summarized in Table 4.

Copies of each study selected for further review (Table 4) were obtained and distributed among the BTAG and/or HERD members. The following information was evaluated:

- stated or estimated NOAEL or LOAEL
- experimental design and toxicity endpoint(s)
- exposure duration/frequency
- Pb form
- exposure medium
- organism
- observed effects (including statistical inferences)
- best professional judgement concerning the value of the paper, with focus on "fatal flaws".

SUMMARY OF MAMMALIAN LEAD STUDIES CONSIDERED IN TRV-LOW DEVELOPMENT

Following the BTAG's initial secondary literature review effort, 30 published mammalian toxicity studies were each given further scientific review (Table 4). The purpose of the review was to determine the best study, or best set of studies, to support and represent a revised BTAG mammalian TRV-Low for Pb. The conclusions of the scientific review are summarized in Table 4 and are discussed in more detail below.

Summary of the Study Selected for the TRV-Low

A series of papers was published that examined the effects on rats exposed to Pb during the same experiment. Effects on postnatal physical and behavioral development (Grant et al. 1980), maternal toxicity and perinatal effects (Kimmel et al. 1980), immunological effects (Luster et al. 1978; Faith et al. 1979) and renal effects (Fowler et al. 1980) were described. Of these studies, that of Fowler et al. (1980) was deemed to be the most appropriate for establishment of the TRV-Low for Pb.

Fowler et al. (1980) reported the adverse effects of Pb on renal structure and mitochondrial function. Male and female Sprague-Dawley rats were exposed to 0, 0.5, 5, 25, 50, and 250 mg Pb (as Pb acetate)/L in drinking water during gestation, lactation, and the first six or nine months of life. Tissue Pb concentrations and ALAD were increased in a dose-dependent manner. Renal tubule mitochondrial respiration was depressed in a dose-dependent manner by Pb treatment. Kidney weight and the incidence of histopathologic lesions in the proximal tubule were slightly increased (in males only) relative to controls in the 5 mg Pb/L treatment group. Histopathologic lesions included enlarged tubular lining cells (cytomegaly) with enlarged nuclei (karyomegaly). The decreases in mitochondrial respiration supported the observed cytomegaly and karyomegaly, as well as the fact that others have associated renal proximal tubular dysfunction with impairment of mitochondrial function (see Goyer et al., 1970). No statistical testing was conducted to evaluate the semi-quantitative histopathological scoring data; however, the data do suggest a dose-related increase in the severity of proximal tubule cytomegaly, inclusion bodies (primarily Pb precipitates), and hemosiderin content.

Fowler et al. (1980) concluded that the 5 mg Pb/L treatment group was the lowest Pb concentration that elicited a detectable effect (median blood concentration of 11 µg/dL). Co-authors Grant et al. (1980) considered the renal changes at 5 mg Pb/L as "subtle". Furthermore, Grant et al. (1980), Kimmel et al. (1980), and Fowler et al. (1980) considered 25 mg Pb/L as the lowest concentration that produced organ-specific toxicity (median blood concentration of 21 µg/dL). Given the uncertainty associated with changes in enzyme levels (i.e., mitochodrial respiration) as indicative of an adverse effect, the minimal cytomegaly reported in male kidneys after nine months, and lack of organ-specific or behavioral toxicity associated with the 5 mg Pb/L treatment group, the BTAG concluded that the 5 mg Pb/L drinking water concentration best represented a

NOAEL and the 25 mg Pb/L concentration best represented a LOAEL. Using female dosing information provided in Kimmel et al. (1980, Table 1 of the publication), the BTAG estimated a 95% upper confidence limit of the mean NOAEL (1 mg Pb/kg BW/day) as protective of potentially adverse renal effects, and a LOAEL of 5.6 mg Pb/kg BW/day as indicative of potentially adverse renal effects (see Table 5 for derivation). The BTAG considered the 1 mg Pb/kg BW/day dose as representative of a TRV-Low and, based on the strength of the study design, concluded that the findings of the Fowler et al. (1980) and associated studies should form the basis of the revised TRV-Low for Pb.

Summary of Studies Considered Supportive of a TRV-Low, by Toxicological Endpoint

The BTAG identified 19 additional studies that directly or indirectly support the development of a mammalian Pb TRV-Low. Doses near or below 10 mg/kg BW/day cause a variety of potentially adverse effects, including changes in bone density or structure (i.e., osteodystrophy), behavior, immune function, reproductive capacity, embryonic development, and renal ultrastructure. A maternal dose of 12.6 mg Pb/kg BW/day causes multiple biochemical and functional changes in the eye (i.e, ocular changes) of lactationally exposed pups, including degeneration of the retina. Each effect is discussed in more detail below.

Renal

Six additional renal studies support the 1 mg Pb/kg BW/day dose as protective of adverse kidney effects caused by low-level Pb exposure:

Dieter et al. (1993) exposed six to seven week old male F344/N rats to 0, 30, and 100 mg Pb (as Pb acetate)/kg food for 30 days. Renal lesions similar to those reported by Fowler et al. (1980) were seen in the 30 and 100 mg Pb treatment groups. A NOAEL of 0.5 mg Pb/kg BW/day was estimated for this study (Table 4). However, the data provided by Fowler et al. (1980) suggest that effects at this dose may be of passing significance. The Fowler et al. (1980) study was preferred for TRV-Low development because the study included multi-generation Pb exposures over more sensitive life-stages (i.e., fetal, weanling).

Hubermont et al. (1976) exposed adult female Sprague-Dawley rats to 0, 0.1, 1, and 10 mg Pb (as Pb nitrate)/L in drinking water three weeks before mating, during pregnancy, and 3 weeks after birth. Pb treatment at 10 mg Pb/L caused a decrease in ALAD activity in blood and kidney, and increased free tissue porphyrins in kidney of newborns (21 d old). The biological and ecological significance of these endpoints could not be established and therefore the study was inappropriate for developing a TRV-Low; however, the renal effects occurred near drinking water concentrations reported in Fowler et al. (1980) to alter renal ultrastructure .

Gupta et al. (1995) exposed two month old female mice (LACA strain) to daily doses of 0, 6.0, 14, and 28 mg Pb per kg BW by gavage through pregnancy. The highest doses

of lead (14 and 28 mg Pb [as Pb acetate]/kg BW/day) significantly reduced the trace mineral content (i.e., iron, copper, manganese), reduced ALAD activity, and increased glutathione levels in kidney. As stated for the Hubermont et al. (1976) study, the biological and ecological significance of these endpoints could not be established. Therefore the BTAG considered this study as inappropriate for developing a TRV-Low; however, the renal effects described occurred within dosing levels previously reported to alter renal ultrastructure.

Khalil-Manesh et al. (1993) exposed 2 month old Sprague Dawley rats to 0 and 55 mg Pb/L in drinking water for up to 12 months. Following exposure, animals were sub-sampled over 1, 3, 6, 9, and 12 month intervals. At 12 months, mild focal tubular atrophy, accompanied by interstitial fibrosis, was evident. The authors stated that Pb exposure produced no significant changes in renal function; however mild histopathologic lesions were evident at 12 months, suggesting incipient damage to the proximal tubules. Because the study was not as long in duration as Fowler et al. (1980), did not include a sensitive life-stage (e.g., fetal, weanling), and only evaluated two doses, the finding of no renal functional effect was, in the opinion of the BTAG, inconclusive.

McMurry et al. (1995) exposed adult wild cotton rats (*Sigmodon hispidus*) to 0, 55, and 550 mg Pb (as Pb acetate)/L in drinking water (ad libitum) for up to 13 weeks. Uniform alterations in the renal proximal tubular epithelium were observed in the 550 mg Pb /L treatment group. Cells were enlarged, occasionally necrotic, possessed irregular apical borders, and contained nuclear inclusion bodies. Animals in the 55 mg Pb/L treatment group showed similar lesions, but were free of inclusions. The 55 mg Pb/L treatment group was estimated to have received a dose of 11 mg Pb/kg BW/day (Table 4), which is within the same order of magnitude effects level reported by Fowler et al. (1980).

Osteodystrophy

Two studies, Escribano et al. (1997) and Gruber et al. (1997), demonstrated that Pb can effect both bone density and growth. Both studies were designed to explore whether Pb can contribute to bone disorders in humans. Escribano et al. (1997) exposed 50 day old female rats to 0 and 9.3 mg Pb (as Pb acetate)/kg feed (ad libitum) for 50 days. Lead was shown to affect the development of the axial skeleton (i.e., vertebrae) and produce a histomorphometric decrease in bone mass. No effect on the longitudinal growth of peripheral long bones (i.e. femur) was observed. Since one Pb concentration was tested (i.e., 9.3 mg Pb/kg), and a dose-response relationship was not established, limited inferences concerning the adverse effects of Pb on bones can be made, as well as the potential for adverse ecological effects. Gruber et al. (1997) exposed adult rats to 0, 55, and 2750 mg Pb/L in drinking water (ad libitum) for 365 days. A significant dose-dependent decrease in bone density was observed following one year exposure in the 55 mg Pb/L treatment group. Similar to Escribano et al. (1997), Gruber et al. (1997) reported that histomorphometric analysis of femur revealed significantly elevated osteoid and resorptive trabecular surface features.

Effects-level doses were estimated as 0.9 and 6 mg Pb/kg BW/day for each study, respectively (Table 4). The BTAG concluded that (1) the relationship between the endpoints evaluated and adverse ecological effects was unknown, (2) the three or less doses evaluated in each study did not present a robust dose-response relationship, and (3) the results were of limited usefulness because a NOAEL was not established. Hence, neither of these studies was used to develop a bone-specific TRV-Low. Nevertheless, the studies suggested that adverse effects on bone density were potentially significant at the 6 mg Pb/kg BW/day dose estimated from Gruber et al. (1997).

Neurobehavioral

Four studies, Bushnell and Levin (1983), Grant et al. (1980), Singh and Ashraf (1989), and Singh (1993), provide direct or indirect evidence that Pb causes neurobehavioral deficits in rats (e.g., learning behavior, reflex development), as observed in humans (ATSDR 1999), at low dose levels. Bushnell and Levin (1983) exposed postpartum male rats to 0, 11.4, and 99.7 mg Pb (as Pb acetate)/L in drinking water (ad libitum) for 28 days. The 11.4 mg Pb treatment group showed a significant reduction in choice behavior in a complex maze. The BTAG concluded that because the maze choice behavior effect was not dose-responsive, only three doses were tested, and a NOAEL dose was not determined, the study should only be considered as supporting evidence for establishing a TRV-Low.

Grant et al. (1980) investigated the effects of lead on rat postnatal physical and behavioral development. Weaned pups were exposed as described in Kimmel et al. (1980) to 0, 0.5, 5, 25, 50, and 250 mg Pb (as Pb acetate)/L drinking water (ad libitum) until sacrifice at 6 to 9 months of age. Food and water consumption was unchanged, but significant decreases in body weight were found in offspring exposed to 50 mg Pb/L and greater. The surface righting and air righting reflexes were significantly delayed in rats exposed to 50 mg Pb/L and unaffected at 5 mg Pb/L. Other reflex development landmarks, including auditory startle and visual placing were unaffected by Pb. Pb (at the highest concentration tested, 250 mg/L) had no effect on locomotor development, activity levels, and motor coordination (i.e., rotorod performance). The BTAG concluded that the NOAEL of 1 mg Pb/kg BW/day obtained in this study for behavioral effects is supportive of a TRV-Low; however the potential ecological significance of delayed surface and air righting reflexes is unknown.

At low doses, lead produces a variety of biochemical changes in the brain and neurons of small mammals. Singh and Ashraf (1989) and Singh (1993) exposed pregnant rats, 5 day old rats, or 5 week old rats to lead acetate (via gavage at 1.0 mg/kg/day, 5 days a week) for 10 or 20 weeks. Singh and Ashraf (1989) reported significant decreases in brain norepinephrine, GABA, and glutamate decarboxylase, and increases in brain glutamate, glutamine/asparagnine, tyrosine, and monoamine oxidase activity in exposed rats. Singh (1993) showed that chronic prenatal lead exposure delayed the age-dependant decrease in neuron mRNA expression, ADP-ribosylation, and photoaffinity labeling of the mRNA α_1 subunit. As presented in Table 1, several studies,

including Cory-Slechta et al. (1992), Kala and Jadhav (1995a,b), and Widzowki et al. (1994) also showed alterations in brain neurotransmitters (i.e., dopamine, seratonin), dopaminergic receptors, and neuroglial enzymes. While these effects occurred at doses between 1 and 10 mg Pb/kg BW/day, there were no concurrent functional tests to evaluate the significance of the alterations. As such, these studies were considered by the BTAG as inappropriate to set a TRV; nevertheless, they do suggest that lead begins to affect the nervous system at low doses, within the same range as functional effects (i.e., radial maze choice behavior; surface righting, air righting) described above.

Immune

Three studies, Luster et al. (1978), Faith et al. (1979), and McMurry et al. (1995) showed that low doses of Pb produced potentially adverse changes in the humoral and cell-mediated immune systems of small mammals. The Luster et al. (1978) and Faith et al. (1979) studies are companion studies to Kimmel et al. (1980) described previously. Luster et al. (1978) showed that 35 to 45 day old rats, exposed pre- and post-natally to 25 or 50 mg Pb (as Pb acetate)/L drinking water, had enlarged thymus, reduced circulating levels of immunoglobulin G (IgG), and depressed antibody response to sheep red blood cells (SRBCs). Faith et al. (1979) showed that similar aged and Pb exposed rats have suppressed lymphocyte responsiveness to mitogen stimulation and reduced delayed hypersensitivity responsiveness. While significant immunological effects were noted in both studies, a clear dose-response relationship and NOAEL were not established.

McMurry et al. (1995) exposed adult wild cotton rats (*Sigmodon hispidus*) to 0, 55, and 550 mg Pb (as Pb acetate)/L in drinking water (ad libitum) for up to 13 weeks. Exposure to the 55 mg Pb/L concentration caused a significant decrease in white blood cell, neutrophil, and eosinophil counts and splenocyte yield; however the same effects were not found at the higher dose (i.e., lack of dose-response). At the high drinking water concentration, Pb altered the proliferative responses of splenocytes to mitogenic stimulation and reduced thymus size, similar to effects reported by Faith et al. (1979). However, Pb did not affect the delayed-type hypersensitivity response or the metabolic activity of macrophages. Differences in species sensitivity and/or differences in exposure regimes (i.e., rats in the Faith et al. [1979] study were exposed for a much longer duration through sensitive life stages) likely accounted for the observed differences in Pb responsiveness.

The biological or ecological significance of the reported immunological effects was not evaluated in each aforementioned study. For example, in no study were concurrent functional tests performed (e.g., disease-challenge tests). As such, these studies were considered by the BTAG as inappropriate for TRV development. Nevertheless, the studies suggest that lead is potential immunotoxicant at concentrations above 25 Pb mg/L in drinking water (i.e., doses greater than 5.6 mg Pb/kg BW/day).

Reproductive/Developmental

Seven studies, Dilts and Ahokas (1979), Kimmel et al. (1980), Wiebe and Barr (1988), Sierra and Tiffany-Castiglioni (1992), Gupta et al. (1995), McMurry et al. (1995), and Junaid et al. (1997), suggest either directly or indirectly that low doses of Pb affect reproduction and sexual development in small mammals.

Dilts and Ahokas (1979) exposed pregnant female Sprague-Dawley rats to 0, 10, 50, 100, 200, or 500 mg Pb (as Pb acetate)/L in drinking water over a 21-day gestation period. There were dose-dependent decreases in food ingestion rate (50 mg Pb/L) and both total (50 mg Pb/L) and net (total minus conceptus) body weight (100 mg Pb/L), but drinking rate was not significantly different from control. There was no difference in live litter size, or number of litters with dead fetuses, but the number of dead fetuses increased with concentration. The live litter weight (50 mg Pb/L) and average fetal weight (100 mg Pb/L) deceased with increasing concentration. The adverse effects on food ingestion and net maternal weight at 50 mg Pb/L introduces a high degree uncertainty of the cause of fetal effects, since fetal nutritional status may have varied directly with maternal nutritional status. However, the lack of effects on placental weight suggests that Pb toxicity was the major determinant. No body weights were reported by the authors, but time-dependent maternal weight was presented in Figure 1 of the study. The maternal body weight at the start of the experiment for the 50 mg Pb/L treatment group was approximately 245 g. Using the water ingestion rates provided by the authors (34.2 mL/day), the LOAEL for reproductive effects is 7 mg Pb/kg BW/day. Using the water ingestion rate for the next lower dose (37 mL/day) yields a NOAEL for reproductive effects of 1.3 mg Pb/kg BW/day. Although these were short-term studies, they were undertaken during a critical life stage (days 1 to 21 of gestation) and may be considered short-term chronic, at least for these endpoints. The NOAEL of 1.3 mg Pb/kg BW/day supports the selected TRV-Low.

Kimmel et al. (1980) exposed Sprague-Dawley rats to 0, 0.5, 5, 25, 50, or 250 mg Pb (as Pb acetate)/L for 6-7 weeks pre-mating and continuously through gestation and lactation. No changes in food or water consumption were noted. No effects were found on the ability to conceive, carry normal litter to term, or deliver the young. No effects were found on the percentage of malformed fetuses, resorptions, or postpartum pup deaths; however, body lengths were significantly reduced in the 250 mg Pb/L treatment group. The reduction in body length without reductions in food or water consumption could not be explained, but may relate to findings of Escribano et al. (1997) and Gruber et al. (1997) described above. Vaginal opening was significantly delayed in the 25 mg Pb/L treatment group; however, there was a high degree of variability in the data and no link to an adverse biological effect (i.e., delay did not affect rats ability to reproduce). Furthermore, in a more recent two-generation Sprague-Dawley rat reproductive study, Ronis et al. (1998) showed that Pb-related differences in vaginal opening and prostate weight disappeared after 85 days. Ronis et al. (1998) determined that the likely cause of the effects was that Pb suppressed the normal sex steroid surges observed at birth and during puberty. The Army (2001), using body weight and intake rate information provided by the authors of the Ronis et al. (1998) study, calculated a NOAEL of 32 mg

Pb/kg BW/day for these effects. The BTAG estimated a NOAEL of 1 mg Pb/kg BW/day from the Kimmel et al. (1980) study. Both authors stated that the pH of the administered drinking water solution was adjusted such that Pb was not observed to precipitate from solution. Hence, the reason for the disparity in drinking water effect-levels for vaginal opening in the Kimmel et al. (1980) and Ronis et al. (1998) studies is unknown, but it may relate to differences in Pb adsorption, sequestration, or elimination among test animals used in each study. This hypothesis is supported by the fact that in both studies the lowest-effect blood Pb level for sexual maturation effects in juvenile rats was approximately 20 µg/dL. The ecological significance of delayed vaginal opening or sexual maturation, if it occurred in wild rats, is unknown.

Wiebe and Barr (1988) exposed Sprague-Dawley rats to three different Pb exposure regimes. Female rats were exposed to 0, 20, or 200 mg Pb (Pb as Pb chloride)/L in drinking water for 118 days prior to mating, and the offspring were sacrificed after 21 days (Experiment 1). There were no effects on the number of uterine estradiol (E2) receptors of 21 day old offspring, but the affinity of the receptors was reduced. Female rats were exposed to 0, 20, or 100 mg Pb/L beginning on day 7 of pregnancy and continuing until the offspring were weaned (Experiment 2). Half of the offspring from each group were exposed to 20 mg Pb/L and half received no additional Pb exposure. Exposures continued until the rats were 150 days old. A significant decrease in the number of uterine E2 receptors was observed. Twenty-one day old rats were exposed to 0, 20, or 200 mg Pb/L for 35 days (Experiment 3). There were no effects on uterine weight or, except for a brief period, whole body weight. Lead was associated with increases in receptor affinity for E2 (Experments 1, 2 and 3) and with either no change (Experiment 1) or a decrease in the number of E2 receptors (Experiments 2 and 3), regardless of age at exposure. However, variance was high and there was no dose response beyond that found in the 20 mg Pb/L treatment group. The authors stated that changes in uterine E2 receptor numbers and affinity may occur maximally at low, subclinical exposures to Pb. The BTAG did not consider that *ex vivo* estradiol-binding experiments could be readily used to evaluate the likelihood of adverse effects on wildlife. However, decreases in receptor number could eventually affect follicular responsiveness to estrogen, potentially resulting in an adverse reproductive effect. A LOAEL of 2.6 mg Pb/kg BW/day day was estimated for the study. The BTAG concluded that this study should not be used to set a TRV-Low; however, it was supportive of potential adverse reproductive effects resulting from low developmental Pb exposure.

Sierra and Tiffany-Castiglioni (1992) gave pregnant guinea pigs a daily oral dose of 0, 5.5, and 11 mg Pb (as lead acetate) per kg BW. Hypothalamic levels of gonadotropin releasing hormone and somatostatin were reduced in a dose-dependent manner in both dams and fetuses. However, neither litter size nor body and organ weights, including placental weights, of the dams and fetuses were affected. The authors postulated that a reduction in peptide hormone levels may alter *in utero* sexual development, resulting in developmental effects that do not become apparent until sexual maturity or breeding (i.e., F1 generation endpoints not evaluated in the study). The BTAG concluded that this study should not be used to set a TRV-Low; however, it was supportive of potential adverse effects resulting from low level maternal and developmental Pb exposure.

Gupta et al. (1995) exposed two month old female mice (LACA strain) to daily doses of 0, 6.0, 14, and 28 mg Pb per kg BW by gavage through pregnancy. Females were treated with human chorionic gonadotropin (hCG) and allowed to mate with non-Pb treated males. The number of living embryos conceived by the Pb treated females was significantly reduced (29%) from controls, but a weak dose-response relationship was demonstrated. The poor dose-response relationship may have been the result of the low numbers of animals in each treatment group (i.e., less than six animals). The BTAG considered this study as supportive evidence for the adverse reproductive effects of lead at low doses, but inappropriate to set a TRV-Low.

Junaid et al. (1997) exposed female Swiss albino mice to daily doses of 0, 2, 4, or 8 mg Pb (as Pb acetate)/kg BW/day for 60 days (5 days/week, gavage). A clear dose-response relationship was established. The lowest dose significantly reduced the number of small, medium, and large follicles present in ovaries. Rates of follicular atresia also were increased, but the effect was only observed at the highest dose for medium-sized follicles. Table 4 presents the effects-level of 2 mg Pb/kg BW/day reported by the authors. However, it was not clear whether the effects-level was expressed as elemental Pb and adjusted for the 5 days a week exposure protocol. The study is confounded by the fact that the control animals received significant Pb exposure (i.e., greater than 20 µg Pb/dL blood) from an unknown source (e.g., contaminated feed or drinking water). The BTAG considered this study as supportive evidence for the adverse reproductive effects of lead, but inappropriate to set a TRV-Low.

As previously described, McMurry et al. (1995) exposed wild adult male cotton rats to 0, 55, or 550 mg Pb/L in drinking water for 7 or 13 weeks. When rats were exposed over a 7 week period that included maturation of the gonads (i.e., breeding season), Pb at the highest dose reduced seminal vesicle and epididymis mass. Testicular and ovarian histological lesions were detected in animals exposed to 55 mg Pb/L or 550 mg Pb/L; lesions were usually more frequent and severe at the higher dose. Lesions included reductions in spermatogenesis in males and the lack of developing follicles in females. The BTAG estimated a lowest-effects level for adverse reproductive effects from this study at 12 mg Pb/kg BW/day. The BTAG considered this study as supportive of a TRV-Low in the range of 1 mg Pb/kg BW/day.

Ocular

Following a review of the literature, HERD identified a study by Fox et al. (1997; see related studies in Table 1, ATSDR references 23-26) that provides direct and indirect evidence that rat visual acuity is adversely effected by Pb. Fox et al. (1997) exposed lactating female Long-Evans rats to 0, 109, and 1090 mg Pb (as Pb acetate)/L in drinking water. Rat pups were exposed to Pb only via mother's breast milk for three weeks until weaning. After 90 days, rats, exposed as pups, showed marked retinal degeneration and thinning. Histologic and electron microscopic examination of the retina showed a 22% loss of rod cells and a 30% loss of bipolar cells, primarily in the

inferior retina. In addition, the authors reported a dose-dependent decrease in rod cell sensitivity; rhodopsin content; reduced cGMP phosphodiesterase activity, and cGMP concentration in retina. Loss of visual acuity, particularly night vision, was considered a significant adverse and ecologically-relevant effect. The lowest-effects dose estimated in dams that caused adverse effects in pups was 12.6 mg/kg BW/day (Table 4). The BTAG considers this study as supportive of a 1 mg lead/kg BW/day TRV-Low.

Summary of Studies Rejected as Supportive of a TRV-Low

Upon closer examination, many of the studies, including Skoczynska et al. (1993), Cory-Slechta et al. (1983, 1985), Cory-Slechta and Pokora (1995), Barratt et al. (1989), Hayashi (1983), Reiter et al. (1975), and Victery et al. (1982) were rejected by the BTAG from further consideration as supporting a TRV-Low. These studies either utilized toxicological or behavioral endpoints that have questionable ecological relevance, showed effects that were transitory or reversible, or failed to demonstrate a clear dose-response relationship (see summary statements in Table 4).

The BTAG concluded that the Al-Hakkak et al. (1988) study should not be used to support a TRV-Low for Pb. Al-Hakkak et al. (1988) investigated the effects of ingestion of lead monoxide alloy on male mouse reproduction. The authors exposed Balb-C albino Swiss mice to 0, 25, or 50 mg Pb monoxide alloy powder/kg diet for 35 days. The 25 mg alloy/kg diet caused an adverse effect on implantation and litter size. Neither body weights nor the lead content of the alloy were provided in the study. Therefore, it was not possible to estimate the total dose of elemental Pb ingested in the treatment groups. In addition, the alloy used in the study may have contained other metallic constituents that contributed to the observed toxicity.

The BTAG concluded that the Azar et al. (1973) study should not be used to support a TRV-Low for Pb. The Azar et al. (1973) study involved a three-generation, six-litter rat reproductive study with seven different dose levels. The reduction of weanling weight observed in the study has important implications for reproductive potential in the wild, but occurred at concentrations in the feed that generate an estimated dose outside of the 1 to 10 mg/kg BW/day range. At doses estimated to be less than 10 mg/kg BW/day, blood ALAD activity was reduced. At these doses, the adverse effects associated with reduced ALAD in blood are unknown, as well as the ecological relevance of reduced ALAD. For example, the ATSDR (1999) reports that the adverse effects of decreased ALAD (i.e., observed at doses of Pb below 10 mg/kg BW/day), in the absence of detectable effects on hemoglobin levels and erythrocyte function, are of questionable biological significance.

CONCLUSIONS

The USEPA Region 9 Biological Technical Assistance Group (BTAG) has reviewed the request and submittal of the U.S. Army for reconsideration of the current mammalian BTAG TRV for Pb. After consideration of the endpoints, dosing information, evaluation of the experimental results, and limitations of the experiments, the BTAG has agreed to

set the mammalian Pb NOAEL (TRV-Low) at 1 mg/kg BW/day, based primarily on the kidney toxicity data contained in Fowler et al. (1980) and supported by at least 19 other studies suggesting that a 1 mg/kg BW/day Pb dose would be protective of bone, behavioral, immune, reproductive, embryonic, renal, and ocular effects seen at doses within one order of magnitude higher. The decision to alter the BTAG TRV is based on the best available data developed after the initial determination of the BTAG mammalian TRV-Low in 1997. As new information becomes available, this TRV, or others, may be revised. The BTAG will not consider revising other TRVs without sufficient scientific justification and documentation, as provided in this EcoNOTE.

When Pb is shown to generate hazard during the initial predictive phase of the ecological risk assessment (i.e., screening phase) using the BTAG TRV-Low, the BTAG recommends that the bioavailability or bioaccessibility of site-derived Pb be compared with that of lead acetate (i.e., test material used in most laboratory Pb toxicity studies). Please see EcoNOTE 4 (DTSC, HERD, 2000) for further information.

Finally, the BTAG and Army literature reviews suggest that blood Pb levels should be considered as a line of evidence in characterizing ecological risk. It is recognized that these levels are variable during different life stages (Kimmel et al. 1980); however, they appear to be more reliable in terms of predicting adverse effects (U.S. Army, 2002). The BTAG and the Army both recommend that the efficacy of blood Pb levels be further investigated to determine the relevance of developing site-specific blood Pb NOAEL and LOAEL values for wildlife.

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Table 1. Small Mammal Lead Toxicity Studies Reported in ATSDR (1999)*

Exposure Level	NOAEL - Toxicity Reference Value (mg/kgBW/day)	LOAEL - Toxicity Reference Value (mg/kgBW/day)	Endpoint	Exposure/Duration/Frequency	Lead Form	Medium	Organism	Effects	BTAG Review Conclusions	Reference	ATSDR Reference #
Acute		17.5	systemic	one dose	PbAc	gavage in water	Wistar Rat	increased activity of ALA-S in liver and kidney		Chmielnicka et al. 1994	3
Acute		17.5	growth/development	10 days, ad libitum	PbAc	water	Sprague-Dawley Rat	approx. 19% decrease in body wt.; approx. 18% and 27% reduction in food and water intake, respectively		Minnema and Hammond 1994	4
Acute		146	systemic	6 days, ad libitum	PbAc	water	Fischer-344 Rat	decreased erythrocyte ALAD activity; increase urinary coproporphyrins		Simmonds et al. 1995	5
Acute		734.7	systemic	1-2 week, ad libitum	PbAc	food	Holtzman Rat	blockage of calcium intestinal transport response to vitamin D		Smith et al. 1981	6
Acute		2.6	systemic	14 days, 7 days a week, once per day	Pb(NO3)2	gavage	Swiss-Webster Mouse	decrease spleen and thymus weight, leukopenia	Acute Study, inappropriate for setting chronic TRV; however, supportive of other studies with similar endpoints and longer duration	Hillam and Ozkan 1986	7
Acute		50	behavioral	ppd 9-18, once per day	PbAc	gavage in water	Wistar Rat	impaired latent learning		Massaro and Massaro 1987	8
Acute	39	390	reproductive	gestational day 6-16, 11day, once per day	PbAc	gavage in water	COBS Rat	decreased number of pregnancies		Kennedy et al. 1975	9
Acute	39	390	reproductive	gestational day 5-15, 11day, once per day	PbAc	gavage in water	CD-1 Mouse	decreased number of pregnancies		Kennedy et al. 1975	10
Acute	39	390	growth/development	gestational day 6-16, 11day, once per day	PbAc	gavage in water	COBS Rat	increased fetal resorptions, retarded skeletal development		Kennedy et al. 1975	11
Intermediate		605	mortality	multigenerational	PbAc	water	HET Mouse	increased fatality rates		Rasile et al. 1995	12
Intermediate		873	systemic	6 weeks, ad libitum	PbAc	water	Sprague-Dawley Rat	myofibrillar fragmentation, mitochondrial swelling		Asokan 1974	16
Intermediate	0.5	1.5	systemic	30 days	PbAc	food	Fischer-344 Rat	mild to moderate enlargement of nuclei in renal tubules	**Further review (1)**	**Dieter et al. 1993**	**17**
Intermediate	1.5	5	systemic	30 days	PbO	food	Fischer-344 Rat	mild to moderate enlargement of nuclei in renal tubules	**Further review (1)**	**Dieter et al. 1993**	**18**
Intermediate	1.5	5	systemic	30 days	PbAc	food	Fischer-344 Rat	increased urinary excretion of aminolevulinic acid and 14-20% reduction in weight gain	**Further review (1)**	**Dieter et al. 1993**	**17,18**
Intermediate	5		systemic	30 days	PbAc, PbO, PbS, and Pb Ore	food	Fischer-344 Rat	NOAEL value		Dieter et al. 1993	17,18, 19, 20
Intermediate		1	systemic	50 days	PbAc	food	Wistar Rat	decreased trabecular bone mass and thickness	**Further review (2)**	**Escribano et al. 1997**	**21**
Intermediate		109	systemic	4 weeks, ad libitum	PbAc	water	Albino Rat	decreased ALAD activity and hemoglobin; increased urinary excretion of ALA and increased blood zinc protoporphyrin; increased hepatic lipid peroxidation; decreased body weight gain, but not quantitated		Flora et al. 1993	22
Intermediate		0.5	systemic	3 weeks, ad libitum	PbAc	water	Hooded Rat	rod degeneration	Dose based on concentration pups receive from breast milk; dose given to dames 25 to 250 X greater	Fox and Chu (no date)	23

Yellow and green highlights show studies considered in TRV-Low Development

Table 1. Small Mammal Lead Toxicity Studies Reported in ATSDR (1999)*

Exposure Level	NOAEL - Toxicity Reference Value (mg/kgBW/day)	LOAEL - Toxicity Reference Value (mg/kgBW/day)	Endpoint	Exposure/Duration/Frequency	Lead Form	Medium	Organism	Effects	BTAG Review Conclusions	Reference	ATSDR Reference #
Intermediate		0.5	systemic	3 weeks, ad libitum	PbAc	water	Hooded Rat	alterations in rod photo-receptors	Dose based on concentration pups receive from breast milk; dose given to dames 25 to 250 X greater.	Fox and Farber 1988	24
Intermediate		0.08	systemic	21 days - 1-21 lactational day	PbAc	water	Long-Evans Rat	decreased rod sensitivity and range of dark adaptation	Dose based on concentration pups receive from breast milk; dose given to dames 25 to 250 X greater (see text).	Fox and Katz (no date)	25
Intermediate		0.5	systemic	3 weeks, ad libitum	PbAc	water	Hooded Rat	decreased retinal sensitivity, rhodopsin, and rod outer segment length	Dose based on concentration pups receive from breast milk; dose given to dames 25 to 250 X greater (see text).	Fox and Rubinstein 1989	26
Intermediate		0.9	systemic	44 days, ad libitum	PbAc and Pb Soil	food	Fischer-344 Rat	reduction in blood ALAD activity	Changes in enzyme levels not necessary linked to adverse functional or ecological effects.	Freeman et al. 1996	27,29
Intermediate		6.4	systemic	44 days, ad libitum	PbS	food	Fischer-344 Rat	reduction in blood ALAD activity	Changes in enzyme levels not necessary linked to adverse functional or ecological effects.	Freeman et al. 1996	28
Intermediate		7.5	systemic	1-12 months	PbAc	water	Sprague-Dawley Rat	decreased femur density	**Further review (3)**	**Gruber et al., 1997**	**30**
Intermediate		145	systemic	26 days	PbAc	water	Long-Evans Rat	altered bone development; 13% reduced weight relative to controls; decreased food intake		Hamilton and O'Flaherty 1995	31
Intermediate		11.1	systemic	20 days, ad libitum	PbAc	water	Wistar Rat	36% decrease in ALAD activity in erythrocytes on day 20		Hayashi et al. 1993	32
Intermediate	0.9		systemic	63 days, ad libitum	Pb(NO3)2	water	Sprague-Dawley Rat	NOAEL value	**Further review (4)**	**Hubermont et al. 1976**	**33**
Intermediate	38		systemic	90 days, ad libitum	PbAc	water	Long-Evans Rat	NOAEL value		Kala and Jadhav 1995a	34
Intermediate	0.005	0.05	systemic	20-30 days, once per day, ad libitum	PbAc	water	Rat	decreased RNA, glycogen; pyknosis of Kupffer cells; increased liver weight	Reject, see text	Krasovskii et al. 1979	35
Intermediate	0.0015	0.005	systemic	6-12 months, ad libitum	PbAc	water	Rat	impaired heme synthesis assessed by increased excretion of ALA and porphobilinogen; decreased glycogen, RNA, sulfhydryl groups, alterations in activities of oxidizing enzymes	Reject, see text	Krasovskii et al. 1979	36
Intermediate	6.4	19.2	systemic	18 days, once per day	PbAc	gavage in water	Long-Evans Rat	decreased hematocrit		Overmann 1977	37
Intermediate	0.03	0.3	systemic	159 days, ad libitum	PbAc	water	Long-Evans Rat	increased systolic blood pressure	Changes in blood pressure not necessary linked to adverse functional or ecological effects.	Perry and Erlanger 1978	38
Intermediate		502	systemic	14-50, ad libitum	PbAc	water	Sprague-Dawley Rat	24% reduction in weight gain; 17-20% reduction in water intake		Ronis et al. 1996	39
Intermediate		14.6	systemic	10 weeks, ad libitum	PbAc	water	Fischer-344 Rat	decreased erythrocyte ALAD activity and ZPP/heme ratio; increase urinary coproporphyrins		Simmonds et al. 1995	40
Intermediate	0.64		systemic	20 weeks, five times per week	PbAc	gavage in water	Rat	NOAEL value	**Further review (5)**	**Singh 1993**	**41**

Yellow and green highlights show studies considered in TRV-Low Development

Table 1. Small Mammal Lead Toxicity Studies Reported in ATSDR (1999)*

Exposure Level	NOAEL - Toxicity Reference Value (mg/kgBW/day)	LOAEL - Toxicity Reference Value (mg/kgBW/day)	Endpoint	Exposure/Duration/Frequency	Lead Form	Medium	Organism	Effects	BTAG Review Conclusions	Reference	ATSDR Reference #
Intermediate		64	systemic	4 months, once per day	PbAc	gavage	Porton Rat	significant reduction in hepatic AST, ALT and Ap activities		Singh et al. 1994	42
Intermediate		5	systemic	7 weeks, 1-2 times per week	PbAc	gavage	Buffalo Rat	atrophy of the elastic fibers of the aorta; 24% increase in serum triglycerides	**Further review (7)**	**Skoczynska et al. 1993**	**43**
Intermediate	414	828	systemic	2-3 months, 7 days per week, ad libitum	PbAc	water	Wistar Rat	proximal tubular dysfuntion; increased urinary excretion of B2-microglobulin		Vyskocil et al. 1989	44
Intermediate	81	320	systemic	2-4 months, ad libitum	PbAc	water	Wistar Rat	tubular dysfunction as indicated by 2-3-fold increase in urinary excretion of B2-microglobulin; water intake reduced by half		Vyskocil et al. 1995	45
Intermediate	320		systemic	2-4 months, ad libitum	PbAc	water	Wistar Rat	NOAEL value		Vyskocil et al. 1995	45
Intermediate		318	systemic	7-8 weeks, 7 days per week	PbAc	food	Wistar Rat	decreased hematocrit; increased kidney weight; 18% reduction in body weight gain		Walsh and Ryden 1984	46
Intermediate		77	systemic	13 weeks, ad libitum	PbAc	water	Wistar Rat	15% reduction in final body weight		Yokoyama and Araki 1992	47
Intermediate	17	42	systemic	31 days	PbAc	water	Fischer-344 Rat	decrease in blood total leukocyte count in offspring		Miller et al. 1998	48
Intermediate		1.6	behavioral	35 days, ad libitum	PbAc	water	Rat	reduced radial maze accuracy	**Further review (8)**	**Bushnell and Levin 1983**	**54**
Intermediate		4.2	behavioral	less than 50 days, ad libitum	PbAc	water	Long-Evans Rat	increased sensitivity to muscarinic cholinergic agonists	**Further review (9)**	**Cory-Slechta and Pokora 1995**	**55**
Intermediate		9.5	behavioral	335 days, ad libitum	PbAc	water	Wistar Rat	increased fixed interval response rates to level press	**Further review (10)**	**Cory-Slechta et al. 1983**	**56**
Intermediate		2.1	behavioral	186 days, ad libitum	PbAc	water	Long-Evans Rat	higher response rate for operant learning tests	**Further review (11)**	**Cory-Slechta et al. 1985**	**57**
Intermediate		8.3	behavioral	21 days	PbAc	water	Long-Evans Rat	increased sensitivity of D2-D3 receptor subtype to dopamine agonists	Changes in neurotransmittor levels not necessarily linked to adverse functional or ecological effect. However, supportive of potential functional effects occuring at this or higher doses.	Cory-Slechta et al. 1992	58
Intermediate		2.2	behavioral	90 days, ad libitum	PbAc	water	Long-Evans Rat	reduction in dopamine in nucleus accumbens and in seratonin in brain stem and frontal cortex	Changes in neurotransmittor levels not necessarily linked to adverse functional or ecological effect. However, supportive of potential functional effects occuring at this or higher doses.	Kala and Jadhav 1995a	59
Intermediate		4	behavioral	90 days, ad libitum	PbAc	water	Long-Evans Rat	reduced basal and potassium induced release of dopamine from the nucleus accumbens	Changes in neurotransmittor levels not necessarily linked to adverse functional or ecological effect. However, supportive of potential functional effects occuring at this or higher doses.	Kala and Jadhav 1995b	60

Yellow and green highlights show studies considered in TRV-Low Development

Table 1. Small Mammal Lead Toxicity Studies Reported in ATSDR (1999)*

Exposure Level	NOAEL - Toxicity Reference Value (mg/kgBW/day)	LOAEL - Toxicity Reference Value (mg/kgBW/day)	Endpoint	Exposure/Duration/Frequency	Lead Form	Medium	Organism	Effects	BTAG Review Conclusions	Reference	ATSDR Reference #
Intermediate	0.0015	0.005	behavioral	6-12 months, ad libitum	PbAc	water	Rat	disruption of conditioned responses and motor activity	Reject, see text	Krasovskii et al. 1979	61
Intermediate	14.3		behavioral	112 days, ad libitum	PbAc	water	Wistar Rat	NOAEL value		Massaro and Massaro 1987	62
Intermediate	6.4	19.2	behavioral	18 days, once per day	PbAc	gavage in water	Long-Evans Rat	increased motor activity and operant delayed response; impaired motor coordination		Overmann 1977	63
Intermediate		0.64	behavioral	20 weeks, 5 times per week	PbAc	gavage in water	Rat	altered normal developmental pattern of proteins in neurons of young exposed prenatally and continued postnatally	**Changes in neurotransmittor or protein levels not necessarily linked to adverse functional or ecological effect. However, supportive of potential functional effects occuring at this or higher doses. Further review (5)**	**Singh 1993**	**64**
Intermediate		0.64	behavioral	10 weeks, 5 days per week, once per day	PbAc	gavage in water	Rat	altered levels of neurotransmitters in the brain after pre- and postnatal exposure	**See Singh 1993. Further review (6)**	**Singh and Ashraf 1989**	**65,66**
Intermediate		8.3	behavioral	21 days	PbAc	water	Long-Evans Rat	increased number of D2 dopaminergic receptors in striatum and nucleus accumbens	Change in receptor levels not necessarily linked to adverse functional or ecological effect. However, supportive of potential functional effects occuring at this or higher doses.	Widzowski et al. 1994	67
Intermediate		89.6	behavioral	15 weeks, ad libitum	PbAc	water	Wistar Rat	decrease in motor nerve conduction velocity		Yokoyama and Araki 1986	68
Intermediate		77	behavioral	13 weeks, ad libitum	PbAc	water	Wistar Rat	decreased slow axonal trasport of proteins		Yokoyama and Araki 1992	69
Intermediate		0.19	reproductive	9 weeks, 7 days per week, once per day	PbAc	gavage in water	Wistar Rat	decreased number of spermatozoa	**Further review (12)**	**Barratt et al. 1989**	**70**
Intermediate	22	45	reproductive	60 days, ad libitum	PbAc	water	Albino Rat	partial inhibition of spermatogenesis		Chowdhury et al 1984	71
Intermediate		90	reproductive	60 days, ad libitum	PbAc	water	Albino Rat	testicular atrophy; cellular degeneration		Chowdhury et al 1984	71
Intermediate	34		reproductive	312 days, 7 days per week, ad libitum	PbAc	water	Rat	NOAEL value		Fowler et al. 1980	72
Intermediate		0.013	reproductive	30 days, once per day	PbAc	gavage	Rat	increased prostate weight	Reject, form of lead administered and dose cannot be determined. See Army (2002)	Hilderbrand et al. 1973	73
Intermediate		0.014	reproductive	30 days, once per day	PbAc	gavage	Rat	impotence; hyperplasia; increase prostate weight	Reject, see above	Hilderbrand et al. 1973	73
Intermediate		0.26	reproductive	30 days, once per day	PbAc	gavage	Rat	irregular estrus cycles	Reject, see above	Hilderbrand et al. 1973	73
Intermediate		0.28	reproductive	30 days, once per day	PbAc	gavage	Rat	ovarian cysts; persistent vaginal estrus	Reject, see above	Hilderbrand et al. 1973	73
Intermediate	0.9		reproductive	63 days, ad libitum	Pb(NO3)2	water	Sprague-Dawley Rat	NOAEL value	**Further review (4)**	**Hubermont et al. 1976**	**74**

Yellow and green highlights show studies considered in TRV-Low Development

Table 1. Small Mammal Lead Toxicity Studies Reported in ATSDR (1999)*

Exposure Level	NOAEL - Toxicity Reference Value (mg/kgBW/day)	LOAEL - Toxicity Reference Value (mg/kgBW/day)	Endpoint	Exposure/Duration/Frequency	Lead Form	Medium	Organism	Effects	BTAG Review Conclusions	Reference	ATSDR Reference #
Intermediate	0.0015	0.05	reproductive	6 to 12 months, ad libitum	PbAc	water	Rat	decreased activity of AIDH, SDH, NAD, and NADPH-diaphorase in spermatogenic epithelium and swelling of follicular epithelial cells in males	Reject, see text	Krasovskii et al. 1979	75
Intermediate	0.0015	0.005	reproductive	20 to 30 days, ad libitum	PbAc	water	Rat	dystrophy of Leydig cells	Reject, see text	Krasovskii et al. 1979	76
Intermediate		0.05	reproductive	20 to 30 days, ad libitum	PbAc	water	Rat	decreased motility of spermatozoa; acid phosphatase activity increased	Reject, see text	Krasovskii et al. 1979	76
Intermediate		502	reproductive	14-50, ad libitum	PbAc	water	Sprague-Dawley Rat	decreased testicular weights; delayed vaginal opening and disruption of estrus cycling		Ronis et al. 1996	77
Intermediate		42	reproductive	gestational day 5-21, postnatal day 21-85, ad libitum	PbAc	water	Sprague-Dawley Rat	reduced plasma testosterone and 17B-estrdiol at birth		Ronis et al. 1998b, 1998c	78
Intermediate		40	reproductive	30 day, ad libitum	PbAc	water	Rat	decreased LH and prolactin levels		Sourgens et al. 1987	79
Intermediate		141	reproductive	12 weeks, 7 days per week, once per day	PbCl2	water	NMRI Mouse	decreased number of implantations		Johansson and Wide 1986	80
Intermediate	176		reproductive	6 weeks, ad libitum	PbCl2	water	NMRI Mouse	NOAEL value		Kristensen et al. 1995	81
Intermediate		166	growth/development	34 days, gestational days 16-21, postnatal days 1-28, ad libitum	PbAc	water	Sprague-Dawley Rat	30-40% reduction in ChAT activity in septum and hippocampus from pups and 30-40% decrease in cholinergic muscarinic receptors in septum		Bielarczyk 1994	85
Intermediate		25	growth/development	56 days, ad libitum	PbCl2	water	CD Rat	delayed synthesis of cytochrome C in cerebral cortex in male pups neonatally exposed		Bull et al. 1979	86
Intermediate		3.5	growth/development	gestational days 1-21, 105-115 days, ad libitum	PbAc	water	Sprague-Dawley Rat	suppression of delayed hyper-sensitivity response and lymphocyte responsiveness to mitogen stimulation; decreased thymic weight in pups	**Further review (13)**	**Faith et al. 1979**	**87**
Intermediate	0.07	0.7	growth/development	gestational days 1-21, 312 days, ad libitum	PbAc	water	Rat	elevated kidney weight; cytomegaly in male pups	**Further review (14)**	**Fowler et al. 1980**	**88**
Intermediate	0.7	3.5	growth/development	201-291 days, ad libitum	PbAc	water	CD Rat	delays in vaginal opening in pups	**Further review (15)**	**Grant et al. 1980**	**89**
Intermediate		7	growth/development	201-291 days, ad libitum	PbAc	water	CD Rat	delayed righting reflex in pups	**Further review (15)**	**Grant et al. 1980**	**89**
Intermediate		38	growth/development	70 days	PbAc	water	Sprague-Dawley Rat	decreased body weight and tail length in pups		**Hamilton and O'Flaherty 1994**	**90**
Intermediate		0.45	growth/development	gestational days 1-21, ad libitum	PbAc	water	Wistar Rat	decreased erythrocyte ALAD activity in pups; lower fetal weights	**Further review (16)**	**Hayashi 1983**	**91**
Intermediate	0.09	0.9	growth/development	63 days, ad libitum	Pb(NO3)2	water	Sprague-Dawley Rat	decreased ALAD activity; increased protoporphyrins in pups	**Further review (4)**	**Hubermont et al. 1976**	**92**
Intermediate	0.7	3.5	growth/development	84-91 days, ad libitum	PbAc	water	CD Rat	delayed vaginal opening	**Further review (17)**	**Kimmel et al. 1980**	**93**

Yellow and green highlights show studies considered in TRV-Low Development

Table 1. Small Mammal Lead Toxicity Studies Reported in ATSDR (1999)*

Exposure Level	NOAEL - Toxicity Reference Value (mg/kgBW/day)	LOAEL - Toxicity Reference Value (mg/kgBW/day)	Endpoint	Exposure/Duration/Frequency	Lead Form	Medium	Organism	Effects	BTAG Review Conclusions	Reference	ATSDR Reference #
Intermediate		2.24	growth/development	gestational days 1-21, 105-112 days, once per day	PbAc	water	Sprague-Dawley Rat	immune suppression; decreased thymus weight in pups	**Further review (18)**	**Luster et al. 1978**	**94**
Intermediate		28	growth/development	56 days, ad libitum	PbCl2	water	CD Rat	delayed cortical development in pups		McCauley et al. 1979	95
Intermediate	48	64	growth/development	gestational days 1-21, 41 days, once per day	PbAc	gavage in water	Long-Evans Rat	decreased fetal weight		Miller et al. 1982	96
Intermediate		0.7	growth/development	138-145 days, two generations	PbAc	water	Sprague-Dawley Rat	impaired righting reflex in pups	**Further review (19)**	**Reiter et al. 1975**	**97**
Intermediate	18	36	growth/development	77 days, mating gestation, lactation, ad libitum	PbAc	water	Wistar Rat	increased activity in open field; failure to habituate to environment		Rodrigues et al. 1993	98
Intermediate		17.5	growth/development	94 days, mating gestation, lactation, ad libitum	PbAc	water	Wistar Rat	increased relative kidney weight in 6-month-old rats; increased ALAD reactivation index in kidney from 6-month-old rats		Rodrigues et al. 1996	99
Intermediate		502	growth/development	gestational days 5-21, lactational days 1-21, postnatal days 21-85, ad libitum	PbAc	water	Sprague-Dawley Rat	19% incidence of stillbirth vs Ronis et al. 1996, 2% in controls; reduced weight gain of pups; decreased serum testosterone		Ronis et al. 1996	100
Intermediate	42	126	growth/development	gestational days 5-21, postnatal days 21-85, ad libitum	PbAc	water	Sprague-Dawley Rat	reduced birth weight, crown-to-rump length, and anogenital distance		Ronis et al. 1998b, 1998c	101
Intermediate		377	growth/development	gestational days 5-21, postnatal days 21-85, ad libitum	PbAc	water	Sprague-Dawley Rat	28% rate of stillbirth compared to 4% in controls		Ronis et al. 1998b, 1998c	101
Intermediate		15	growth/development	3 weeks, 7 days per week, ad libitum	PbAc	water	Wistar Rat	increase in volume of mossy fiber zone, granule cell layer, and commissural association zone in hippocampus of offspring		Slomianka et al. 1989	102
Intermediate		28	growth/development	gestational days 1-21, 56 days, ad libitum	PbAc	water	Sprague-Dawley Rat	slower extinction of acquired response when reward no present relative to controls		Taylor et al. 1982	103
Intermediate		2.2	growth/development	gestational days 1-21, 5 months	PbAc	water	Charles River Rat	inhibit renin synthesis and release	**Further review (20)**	**Victery et al. 1982a**	**104**
Intermediate		608	growth/development	gestational days 1-21, 41 days, ad libitum	PbAc	water	HET Mouse	altered measures of square crossing and standups in open field, and in time to return to home cage		Draski et al. 1989	105
Intermediate		5.5	growth/development	gestational days 22-52 and 22-62	PbAc	gavage in water	Guinea Pig	reduced levels of gonadotropin-releasing hormone and somatostatin in hypothalamus from 52- and 62-day-old fetuses	**Changes in gonadotropin levels not necessary linked to adverse functional or ecological effect. However, supportive of potential adverse reproductive effects occurring at this or higher doses. Further review (21)**	**Sierra and Tiffany-Castiglioni 1992**	**106**

Yellow and green highlights show studies considered in TRV-Low Development

Table 1. Small Mammal Lead Toxicity Studies Reported in ATSDR (1999)*

Exposure Level	NOAEL - Toxicity Reference Value (mg/kgBW/day)	LOAEL - Toxicity Reference Value (mg/kgBW/day)	Endpoint	Exposure/Duration/Frequency	Lead Form	Medium	Organism	Effects	BTAG Review Conclusions	Reference	ATSDR Reference #
Intermediate		5.5	growth/development	gestational days 22 to 52 or 22 to 62, once per day	PbAc	gavage in water	Guinea Pig	decrease in the neuroglial enzymes GPDH and glutamine synthetase, decrease blood ALAD and increase ZPP levels in pups and dams	Changes in enzyme levels not necessarily linked to adverse functional or ecological effect. However, supportive of potential adverse behavioral effects occurring at this or higher doses.	Sierra et al. 1989	107
Chronic	0.9	3.1	systemic	2 years, ad libitum	PbAc	food	Rat	decreased ALAD activity	**Changes in enzyme levels not necessarily linked to adverse functional or ecological effect; however, further review because study has been used by others to support a TRV for lead. (22)**	**Azar et al. 1973**	**111**
Chronic	27	56.5	systemic	2 years, ad libitum	PbAc	food	Rat	unspecified decrease in weight gain		Azar et al. 1973	111
Chronic	1.4	2.8	systemic	18 months, 7 day per week, once per day	PbAc	water	Sprague-Dawley Rat	increased systolic and diastolic pressure	Changes in blood pressure not necessarily linked to adverse functional or ecological effect.	Carmignani et al. 1988a	112
Chronic	5.6		systemic	18 months, 7 day per week, once per day	PbAc	water	Sprague-Dawley Rat	NOAEL value		Carmignani et al. 1988a	112
Chronic		371	systemic	76 weeks, ad libitum	PbAc	water	Sprague-Dawley Rat	necrotic and dilated cortical tubules, tubular protein casts		Koller et al. 1985	113
Chronic	0.71	0.014	systemic	less than 18 months, 7 days per week, once per day	PbAc	water	Long-Evans Rat	increase in systolic blood pressure	Changes in blood pressure not necessarily linked to adverse functional or ecological effect.	Perry et al. 1988	114
Chronic		27	systemic	2 years, 7 days per week, ad libitum	PbAc	food	Rat	Cancer Effect Level: 5/50 renal tubular adenomas in males		Azar et al. 1973	131
Chronic		371	systemic	76 weeks, ad libitum	PbAc	water	Sprague-Dawley Rat	Cancer Effect Level: renal tubular carcinomas in 13/16		Koller et al. 1985	132
Chronic		83.2	systemic	2 years, ad libitum	PbAc	food	Swiss Mouse	Cancer Level Effect: renal tubular adenomas and carcinomas in 7/25		Van Esch and Kroes 1969	133

* Agency for Toxic Substances and Disease Registry (ASTDR). 1999. Toxicological Profile for Lead. U.S. Department of Health and Human Services. Atlanta. pp.587. All doses reported are as listed in the ATSDR document.

Yellow and green highlights show studies considered in TRV-Low Development

Table 2. Draft Lead EcoSSL (USEPA 2002) Literature Citations with NOAEL or LOAEL Reported as at or Below 1 or 10 mg/kg BW/day, Respectively

Study Number[1]	Reference	No- or Effects-Dose Reported by USEPA (mg/kg BW/day)	BTAG Review Conclusions
2509	al-Hakkak, Z. S., Zahid, Z. R., Ibrahim, D. K., al-Jumaily, I. S., and Bazzaz, A. A. 1988. Effects of ingestion of lead monoxide alloy on male mouse reproduction. Arch. Toxicol. 62(1):97-100.	2.4	Further Review
2593	Dilts Jr., P. V. and Ahokas, R. A. 1979. Effects of dietary lead and zinc on pregnancy. Am. J. Obstet. Gynecol. 135(7):940-946.	1.2	Further Review
2876	Sierra, E. M. and Tiffany-Castiglioni, E. 1992. Effects of low-level lead exposure on hypothalamic hormones and serum progesterone levels in pregnant guinea pigs. Toxicology 72(1):89-97.	5.5	Further Review
2666	Gupta, G. S. , Singh, J., and Parkash, P. 1995. Renal toxicity after oral administration of lead acetate during pre- and post-implantation periods: effects on trace metal composition, metallo-enzymes and glutathione. Pharmacol. Toxicol. 76(3):206-211.	6.4	Further Review
2930	Wiebe, J. P. and Barr, K. J. 1988. Effect of prenatal and neonatal exposure to lead on the affinity and number of estradiol receptors in the uterus. J. Toxicol. Environ. Health 24(4):451-460.	2.4	Further Review
2725	Junaid, M., Chowdhuri, D. K., Narayan, R., Shanker, R., and Saxena, D. K. 1997. Lead-induced changes in ovarian follicular development and maturation in mice. J. Toxicol. Environ. Health 50(1):31-40.	4.0	Further Review
2634	Fox, D. A., Wright, A. A., and Costa, L. G. 1982. Visual acuity deficits following neonatal lead exposure: cholinergic interactions. Neurobehav. Toxicol. Teratol. 4(6):689-693.	0.041	**
2751	Lorenzo, A. V., Gewirtz, M., and Averill, D. 1978. CNS lead toxicity in rabbit offspring. Environ. Res. 17(1):131-150.	1.8	**
2767	McConnell, P. and Berry, M. 1979. The effects of postnatal lead exposure on Purkinje cell dendritic development in the rat. Neuropathol. Appl. Neurobiol. 5(2):115-132.	0.21	**

Table 2. Draft EcoSSL Reported Studies with NOAEL or LOAEL Listed as at or Below 1 or 10 mg/kg/day, Respectively

Study Number[1]	Reference	No- or Effects-Dose Listed by USEPA (mg/kg body wt./day)	BTAG Review Conclusion
2774	Michaelson, I. A. and Sauerhoff, M. W. 1974. An improved model of lead-induced brain dysfunction in the suckling rat. Toxicol. Appl. Pharmacol. 28(1):88-96.	2.72	**
2781	Murthy, R. C., Saxena, D. K., Gupta, S. K., and Chandra, S. V. 1991. Lead induced ultrastructural changes in the testis of rats. Exp. Pathol. 42(2):95-100.	0.27	**
2857	Saxena, D. K., Murthy, R. C., Singh, C., and Chandra, S. V. 1989. Zinc protects testicular injury induced by concurrent exposure to cadmium and lead in rats. Res. Commun. Chem. Pathol. Pharmacol. 64(2):317-329.	1.9	**
2704	Hsu, J. M. 1981. Lead toxicity as related to glutathione metabolism. J. Nutr. 111(1):26-33.	2.9	**
2711	Jacquet, P. 1977. Early embryonic development in lead-intoxicated mice. Arch. Pathol. Lab. Med. 101(12):641-643.	6.5	**
2850	Rosenblum, W. I. and Johnson, M. G. 1968. Neuropathologic changes produced in suckling mice by adding lead to the maternal diet. Arch. Pathol. 85(6):640-648.	10	**

1. As referenced in USEPA (2002).

**Based on the BTAG's review of the study, the dose(s) reported in USEPA (2002) could not be reproduced or verified, and were outside the range to be evaluated (i.e., NOAEL > 1 mg/kg BW/day; LOAEL > 10 mg/kg BW/day).

Table 3. U.S. Environmental Protection Agency Region 9 Lead Toxicity Literature Review: Summary of Findings							
Concentration in Medium Representing No Adverse Effect	**Other Concentrations**	**Chemical Form**	**Test Species**	**Exposure Duration**	**Effects**	**BTAG Review Conclusions**	**Reference**
None	300 ppm (LOAEL)	Pb acetate in water	Wistar rat	gestation through 5 days	neurological	NOAEL TRV estimated > 1	Antonio et al. (1996)
0.1% (1000 ppm)		Pb acetate in water	male Wistar rat	30 days	reproductive	NOAEL TRV estimated > 1	Apostoli et al. (1998)
None	17.6 ppm, 42.8 ppm, 127 ppm	Pb acetate, Pb sulfide, Pb-contaminated soil	male Fischer 344 rat	7, 15, or 44 days	hematological	Study endpoint is ALAD inhibition; not relevant endpoint	Freeman et al. (1996)
No NOAEL	1000 ppm (LOAEL)	Pb chloride in water	male NMRI mice	12 weeks	reproductive	NOAEL TRV estimated > 1	Johansson et al. (1986)
No NOAEL found	100 ppm (LOAEL)	Pb acetate in water	male Sprague-Dawley rat	1, 3, 6, 9, 12 months	renal	Further Review	Khalilmanesh et al. (1993)
0.125% (growth), 0.25% (reproduction)	0.5%	Pb acetate in water	Swiss CD-1 mice	3 generation	growth, reproduction	NOAEL TRV estimated > 1	Lamb et al. (1997)
No NOAEL found	1000 ppm	Pb acetate in water	pregnant Sprague-Dawley rat	gestation through 83 days	reproduction	NOAEL TRV estimated > 1	McGivern et al. (1991)

Table 3. U.S. Environmental Protection Agency Region 9 Lead Toxicity Literature Review: Summary of Findings							
Concentration in Medium Representing No Adverse Effect	**Other Concentrations**	**Chemical Form**	**Test Species**	**Exposure Duration**	**Effects**	**BTAG Review Conclusions**	**Reference**
No NOAEL found	100, 1000 ppm	Pb acetate in water	cotton rat	7 or 13 weeks	reproduction, hematological, immunological	Further Review	McMurry et al. (1995)
1500 ppm	3500, 5500 ppm	Pb acetate in water	male Sprague-Dawley rat	18 weeks	reproduction, growth	NOAEL TRV estimated > 1	Piasek and Kostial (1987)
No NOAEL	7500 ppm	Pb acetate in water	female Wistar rat	20 weeks	reproduction	NOAEL TRV estimated > 1	Piasek and Kostial (1991)
3000 ppm	NONE	Pb acetate in water	Sprague-Dawley rats	70 days	reproduction	NOAEL TRV estimated > 1	Pinon-Latillade et al. (1993)
No NOAEL	5000 ppm	Pb acetate in water	NMRI mice	2 generations	reproduction, growth	NOAEL TRV estimated > 1	Pinon-Latillade et al. (1995)
No NOAEL	0.6% (6000 ppm)	Pb acetate in water	pregnant, prepubertal, and postpubertal Sprague-Dawley rats	14-68 days depending on developmental stage	growth/devel-opment (prepubertal), reproduction (pregnant)	NOAEL TRV estimated > 1	Ronis et al. (1996)
500 ppm	1500, 4500 ppm	Pb acetate in water	weaned Sprague-Dawley rat	gestation through 85 days	growth (at lowest dose) reproduction (at highest dose)	NOAEL TRV estimated > 1	Ronis et al. (1998)

Table 3. U.S. Environmental Protection Agency Region 9 Lead Toxicity Literature Review: Summary of Findings							
Concentration in Medium Representing No Adverse Effect	**Other Concentrations**	**Chemical Form**	**Test Species**	**Exposure Duration**	**Effects**	**BTAG Review Conclusions**	**Reference**
5-18 ppm	30-60 ppm (LOAEL)	Pb acetate in water (lab), Pb-cont. soil (wild)	various, lab and wild	varied	growth, reproduction	Review Paper	Shore and Douben (1994)
No NOAEL	2500, 5000 ppm	Pb acetate in water	male CF-1 mice	6 weeks	reproduction (reduced sperm count)	NOAEL TRV estimated > 1	Wadi and Ahmad (1999)
0.05 ppm	0.1, 0.2, 0.5, 1 ppm	Triethyl Pb	weanling male Sprague-Dawley rat	90 days (gavage)	neural lesions	Organic form of lead; not relevant to TRV selection	Yagminas et al. (1992)

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Table 4. Small Mammal Lead Toxicity Studies Selected by the BTAG for Further Review

Test Species[1]	Elemental Pb Conc. in Food or Water[2]	Body Weight of Test Species	Consumption Rate of Food or Water	Duration of Exposure	Chemical Form	MOA	Oral Dose[3] (mg/kg BW/day) LOAEL	NOAEL	Toxicity Endpoint	Notes/Professional Judgement	Reference
Rat (42 to 49 day old males, F344/N)	0, 10, 30, and 100 mg/kg	0.206 kg[a]	0.011 kg/day	30 days	Pb Ac	Feed	5[b]	0.5[b]	Body weight loss, urinary aminolevulinic acid excretion, kidney histopathological lesions	Effects of Pb Acetate on body weight loss and kidney consistent with findings of Fowler et al. (1980) and Khalil-Manesh et al. (1993). Calculation of dose is subject to uncertainty because body weights of tested rats are not reported. Study shows that chemical form of Pb (i.e., Pb Ac, Pb S, Pb Ore) clearly affects bioavailability. The BTAG concluded that this study supports a 1 mg Pb/kg BW/day TRV-Low for kidney effects.	Dieter et al. 1993 (1)
Rat (100 day old females, Wistar)	0, 9.3 mg/kg[c]	0.224 kg[d]	0.022 kg/day[e]	50 days	Pb Ac	Feed	0.9[b]	ND	Bone structure, density, length	Only one dose was tested and the relationship between the toxicity endpoint and an adverse ecological effect is not strong. The BTAG concluded that the study should not be used to set a TRV, however it does support other studies that show more relevant effects at similar dose levels.	Escribano et al. 1997 (2)
Rat (Adult)	0, 55, and 2750 mg/L[c]	0.350 kg[f]	0.038 kg/day[j]	365 days	Pb Ac	Drinking water	6[b]	ND	Bone density and histology	Decrease in bone density noted in the lowest treatment group (55 ppm Pb) after 12 months exposure. Relationship between toxicity endpoint and adverse ecological effect not strong. The BTAG concluded that the study should not be used to set a TRV, however it does support other studies that show more relevant effects at similar dose levels.	Gruber et al. 1997 (3)
Rat (female, Sprague-Dawley)	0, 0.1, 1 and 10 mg/L[g]	0.279 kg[h]	0.031 L/day[j]	3 wks before mating, during pregnancy and 3 wks after birth = 63 days	Pb N	Drinking water	1[b,j]	0.1[b,j]	Decrease in ALAD activity in blood and kidney. Increase in free tissue porphyrins in kidney of newborns (21 d old)	Only 4 rats per dose level. No effects on fertility, gestation, viability, lactation or blood biochemistry observed in adult females. No behavioral, morphologic, or histologic endpoints evaluated, so there are limited inferences that can be made about functional effects. The BTAG concluded that the study should not be used to set a TRV, however it does support other studies that show kidney effects at low dose levels.	Hubermont et al. 1976 (4)
Rat (35 days old)	N/A	N/A	N/A	20 wks	Pb Ac	Gavage	0.4[k]	ND	Neurological: changes in G Protein signal transduction	Only prenatal effects observed; no adult effects. See below for Singh and Ashraf, 1989.	Singh 1993 (5)
Rat (35 days old)	N/A	N/A	N/A	10 wks	Pb Ac	Gavage	0.4[k]	ND	Neurological: changes in amino acid & neurotransmitter concentrations	Methods not rigorously presented. Effects more pronounced in developing young, however difficult to equate changes in neurotransmittor levels with ecological relevance. The BTAG concluded that the study should not be used to set a TRV, however it does support other studies that show behavioral effects at low dose levels.	Singh and Ashraf 1989 (6)
Rat (35 to 42 days old, male Buffalo)	0, 19 mg/kg BW once a week, 39 mg/kg BW twice a week[c]	N/A	N/A	7 wks	Pb Ac	Gavage	5	ND	Atrophy of the elastic fibers of the aorta, decrease in serum cholesterol, and 24 % increase in serum triglycerides	Study was designed to investigate the effects of Pb on the development of atherosclerosis in humans. No dose produced clinical signs of Pb poisoning. The BTAG concluded that the study should not be used to set a TRV because there is questionable ecological relevance of the endpoints considered.	Skoczynska et al. 1993 (7)

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Rat (21 to 56 days postpartum males, Sprague-Dawley)	0, 11.4, 99.7 mg/L[m]	0.172 kg[l]	0.020 L/day[j]	28 days	Not reported[m]	Drinking water	1.3[b]	ND	Increase in tissue lead retention; significant reduction in choice behavior in a complex maze	Sensitive life stage with ecologically relevant endpoints. Single generation study with no maternal exposure; really a study of zinc deficiency. The BTAG concluded that because the maze choice behavior effect was not linear, only 3 doses were tested, and because a NOAEL dose was not determined, the study should only be considered as supporting evidence for establishing a TRV-Low near 1 mg Pb/kg BW/day.	Bushnell and Levin 1983 (8)
Rats (weanling male and female, Long-Evans)	0, 28, 83 mg/L[c]	0.350 kg[f]	0.038 kg/day[j]	up to 365 days	Pb Ac	Drinking water	3[b]	ND	Altered cholinergic sensitivity in response to lead.	Study was designed to investigate the effects of various muscarinic agonists and antagonists on rats chronically exposed to Pb. The BTAG concluded that the study should not be used to set a TRV because there is questionable ecological relevance of the endpoints considered.	Cory-Slechta and Pokora 1995 (9)
Rats (weanling male and female, Long-Evans)	0, 28, 55, 275 mg/L[c]	0.300 kg	0.033 L/day[j]	255 days	Pb Ac	Drinking water	3[b]	ND	Increases in the rate of fixed-interval lever-response and running time.	Marked individual differences in susceptibility to Pb-induced increases in performance on a fixed interval 1-min schedule of food reinforcement. The BTAG concluded that the study should not be used to set a TRV because there is questionable ecological relevance of the endpoints considered.	Cory-Slechta et al. 1985 (10)
Rats (weanling male and female, Long-Evans)	0, 14 mg/L[c]	0.300 kg	0.033 L/day[j]	136 days	Pb Ac	Drinking water	1.5[b]	ND	Increases in the rate of fixed-interval lever-response and running time.	See Cory-Slechta et al. 1985 above.	Cory-Slechta et al. 1983 (11)
Rats (70 days old male Wistar)	0, 0.2, 18, 182 mg/kg[c] BW	N/A	N/A	9 weeks	Pb Ac	Gavage	0.2	ND	Reduction in the total number of spermatozoa in testes. Decrease in body weight gain and % normal spermatozoa.	The decrease in sperm numbers was not dose related and only statistically different from the control at the lowest dose tested. Decrease in body weight and % normal spermatozoa only found at the highest dose tested. The BTAG concluded that the study should not be used to set a TRV because of the lack of a dose response relationship for the most sensitive endpoint examined (i.e., number of spermatozoa).	Barratt et al. 1989 (12)
Rat (F1, 40 days old, Sprague-Dawley)	0, 25, 50 mg/L	N/A	N/A	F0 weaning - F1 9 months	Pb Ac	Drinking water	5.6	ND	Immunotoxicity, including negative effects on cell-mediated immune function and reduced thymus weight	Dose estimated from companion study Kimmel et al. 1980 (see Table 5 herein). The BTAG concluded that the Fowler et al. (1980) study should be used to set the TRV in absence of NOAEL for this study. Study supports a 1 mg Pb/kg BW/day NOAEL.	Faith et al. 1979 (13)

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Rat (F1, 270 days old, males, Sprague-Dawley)	0, 0.5, 5, 50, 250 mg/L	N/A	N/A	F0 weaning - F1 9 months	Pb Ac	Drinking water	5.6	1**	Adverse histologic lesions in male kidney (cyto- and karyo-megaly)	Doses estimated from companion study Kimmel et al. 1980 (see Table 5 herein). Viral infection in one replicate, however data are excluded from analysis. The BTAG concluded that this study (and associated companion studies, including Luster et al. 1978, Faith et al. 1979, Grant et al. 1980, and Kimmel et al. 1980) provides a representative of a NOAEL for kidney related adverse effects, as well as representative of a number of other studies (i.e., reproductive, behavioral, immunologic, ocular, bone) where no observable adverse effect is expected.	Fowler et al. 1980 (14)
Rat (F1, 30 to 60 days old, Sprague-Dawly)	0, 0.5, 5, 50, 250 mg/L	N/A	N/A	F0 weaning - F1 9 months	Pb Ac	Drinking water	5.6	1	Physical and behavioral development, delayed surface and air righting	Doses estimated from companion study Kimmel et al. 1980 (see Table 5 herein). Study supports a 1 mg Pb/kg BW/day NOAEL for behavioral adverse effects.	Grant et al. 1980 (15)
Rat (F0, F1 fetuses, Wistar)	N/A	N/A	N/A	F0 through F1 - GD 21	Pb Ac	Drinking water	0.5[n]	ND	Decreased erythrocyte ALAD activity in pups; lower fetal weights.	Changes in ALAD activity not ecologically relevant. Reduced body weight of fetuses or pups not reported in other studies utilizing a similar low dose of Pb Ac. The BTAG concluded that this study should not be used to generate a TRV.	Hayashi 1983 (16)
Rat (F1, 30 to 60 days old, females, Sprague-Dawley)	0, 0.5, 5, 25, 50, 250 mg/L	N/A	N/A	F0 weaning - F1 9 months	Pb Ac	Drinking water	5.6	1	Maternal toxicity and perinatal growth, delayed vaginal opening	See Table 5 (herein) for dose estimation. High variability of vaginal opening data and inconclusive link to adverse effect (see study). The BTAG concluded that the Fowler et al. 1980 companion study should be used to set the TRV.	Kimmel et al. 1980 (17)
Rat (F1, 40 days old, Sprague-Dawley)	0, 25, 50 mg/L	N/A	N/A	F0 weaning - F1 9 months	Pb Ac	Drinking water	5.6	ND	Immunotoxicity, including negative effects on antigen stimulation, antibody production, and thymus weight	Dose estimated from companion study Kimmel et al. 1980 (see Table 5 herein). The BTAG concluded that the Fowler et al. 1980 study should be used to set TRV in absence of NOAEL for this study.	Luster et al. 1978 (18)
Rat (2 generations, Sprague-Dawley)	0, 5, 50 mg/L	N/A	N/A	F0 weaning - F2 pups	Pb Ac	Drinking water	0.7	ND	Delayed eye opening and righting reflex development, and transient decreased exploratory activity in treatment groups.	The ecological relevance of the endpoints measured is questionable. Similarly, the biological significance of the minimal delays and transient hypoactivity is also questionable. The BTAG concluded that this study should not be recommended as the basis for setting the Pb TRV.	Reiter et al. 1975 (19)

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Rat (F1, 150 days old, males, Charles River)	0, 5, 25 mg/L	N/A	N/A	F0 pregnant females - F1 5 months	Pb Ac	Drinking water	2.2	ND	Basal decreases in plasma renin concentration (highest dose) and in renal renin concentrations (low and high doses). No effects on systolic blood pressure.	Author states that the most biologically significant effects occurred in the 25 ppm exposure group (LOAEL shown). The BTAG concluded that this study should not be recommended as the basis for setting the Pb TRV because the linkage between altered sensitivity of the renin-angiotension system and ecologically relevant effects is tenuous. Functional tests of or histopathological lesions in the kidney were judged to be more significant, ecologically relevant effects (i.e., Fowler et al. 1980).	Victery et al. 1982 (20)
Rats (male and female)	0, 10, 50, 100, 500, 1000, 2000 mg/kg	N/A	N/A	2 years	Pb Ac	Feed	10 mg/kg increased stippled cell; 50 mg/kg decreased ALAD; 500 mg/kg increased kidney tumors in male; 1000 mg/kg reduced weight gain; 1000 mg/kg reduced weanling weight	10 mg/kg no effect on ALAD; 500 mg/kg no effect on weanling weight	Growth and mortality; blood parameters, ALAD; microscopic examination for kidney tumors; Number of pregnancies, pups; fertility, gestation, viability, and lactation indices; weanling weight and kidney histology	Adverse effects associated with reduced ALAD are unknown, as well as ecological relevance. The strength of this study is that it involves a 3-generation, 6-litter reproductive study with 7 different dose levels. Reduced weanling weight has important implications for reproductive potential in the wild, however effects on body weight were only apparent at doses estimated to be greater than 10 mg Pb/kg BW/day. Because of uncertainties in estimating a daily dose and the ALAD lowest effects endpoint, the BTAG did not consider this study appropriate for calculating a defensible TRV-Low.	Azar et al. 1973 (21)
Guinea pig (females at days 22 - 62 of pregancy)	0, 5.5, and 11 mg/kg/d	N/A	N/A	40 days	Pb Ac	Gavage	5.5	ND	Reduction in hypothalamic levels of GnRH and SRIF.	The ecological relevance of the endpoints measured is questionable. No function tests were performed to assess significance of changes in peptide hormone levels. The BTAG concluded that this study should not be used to set the Pb TRV-low; however, it is supportive of adverse reproductive effects occurring at similar or higher doses.	Sierra and Tiffany-Castiglioni 1992 (22)
Mouse (male weanlings, Balb-C albino Swiss)	Unknown	N/A	N/A	35 days	Pb Monoxide Alloy	Feed	0.1 mg/animal/day	ND	Decreased litter size and numbers of spermatogenic cells in seminiferous tubules	Neither body weights nor alloy composition were provided. The Pb alloy caused decreased reproductive performance in male mice with some evidence of a dominant lethal effect at the highest dose. However, the lack of analysis of the test article leaves uncertain which other metals might have been present in the diets of the test animals. The lower dose also caused an adverse effect on implantation and litter size. The lack of chemical analysis of the alloy precludes assigning this toxicity to Pb. The BTAG concluded that this study cannot be used to set a TRV-Low for Pb.	Al-Hakkak et al. 1988 (23)

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Rat (female, through pregancy, Sprague-Dawley)	0, 10, 50, 100, 200, 500 mg/L	0.25 kg[o]	0.037 L/day[p]	21 days	Pb Ac	Drinking water	7[b]	1.3[b]	Maternal weight gain, feeding efficiency, litter size, and fetal weight	Short-term study undertaken during a critical life stage (days 1 to 21 of gestation) and may be considered short-term chronic, at least for these endpoints. The BTAG concluded that the NOAEL for reproduction supports the proposed 1 mg Pb/kg BW/day TRV-Low.	Dilts and Ahokas 1979 (24)
Rat (female, F0 - 150 day old F1, Sprague-Dawley)	0, 20, 200 mg/L	0.078 kg[q]	0.010 L/day[i]	F0 weaning - F1 5 months	Pb Cl	Drinking water	2.6[b]	ND	Reduction in uterine estradiol receptors and increases in receptor affinity.	The BTAG did not consider that ex vivo estradiol-binding experiments can be readily used to evaluate the likelihood of adverse effects on ecological receptors. However, decreases in receptor number could eventually affect follicular responsiveness to estrogen, potentially resulting in an adverse reproductive effect. The BTAG concluded that this study should not be used to set a TRV low, however it is supportive of potential adverse reproductive effects occuring at these and higher dose levels.	Wiebe and Barr 1988 (25)
Mouse (female adult, albino Swiss)	0, 2, 4, and 8 mg/kg/d	N/A	N/A	60 days	Pb Ac	Gavage	2	ND	Number of small, medium, and large follicles reduced in ovary.	Pb was detected in the control group (21.7 ug/dl blood, see Table 3 in the study), which limits inferences that can be made from the study. Exposure period was 60 days, but gavages were administered only 5 days per week. Large ovarian follicles showed a statistical effect (ANOVA) at 4 mg/kg BW/day, but small and medium ovarian follicles showed a statistical effect at 2 mg/kg BW/day. Given the short, and irregular, exposure period it is likely that the LOAEL would be lower if dosing were continued for a longer period on a daily basis. The BTAG concluded that this study is supportive of adverse reproductive effects caused by low level exposure to Pb, but inappropriate to set a TRV-Low.	Junaid et al. 1997 (26)
Mouse (adult males and females, through pregancy, LACA strain)	0, 6.0, 14, and 28 mg/kg[c]	N/A	N/A	28 or 56 days	Pb Ac	Gavage	6	ND	Living embryos per mother significantly reduced, kidney activity of glutathione increased and alkaline phosphatase significantly decreased from control levels in pregnant mice, kidney accumulation of lead greater in non-pregnant females.	The small number of animals used in this study limits its usefulness as a primary source for setting a Pb TRV. Renal effects reported were not related to functional deficits in the kidney. However, based on the reproductive effects observed, the BTAG concluded that the study supports a 1 mg Pb/kg BW/day TRV-Low.	Gupta et al. 1995 (27)

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Cotton Rat (adult males & females, wild)	0, 55, 550 mg/L[c]	0.190 kg[r]	2.1 mg Pb/day via drinking water	49 or 91 days	Pb Ac	Drinking water	11[b]	ND	Compromized cellular immune and hematological responses, kidney lesions, reduction in liver, seminal vesicle mass, testes sperm content and ovarian follicles.	Histopathologic lesions consistent with Pb toxicosis, including altered renal proximal tubular epithelium, renal intranuclear inclusions, and at the highest dose, lowered numbers of sperm and developing follicles. The BTAG concluded that this study is supportive of a 1 mg Pb/kg BW/day TRV-Low.	McMurray et al. 1995 (28)
Rat (60 days old, male, Sprague-Dawley)	0, 55 mg/L[c]	0.395 kg[s]	0.043 L/dayi	30, 90, 180, 270, or 365 days	Pb Ac	Drinking water	6[b]	ND	Transient increase in glomerular filtration rate, increase in urinary n-acetyl-[beta]-D-glucosaminidase, tubular atrophy and interstitial fibrosis (at 365 days).	Authors state that exposure produced no significant changes in renal function; however mild histopathologic lesions were evident at 12 months, suggesting incipient damage to the proximal tubules. Study was not as long in duration as Fowler et al. (1980), did not include a sensitive life stage (e.g., fetal, weanling), and only two doses were evaluated. The BTAG concluded that this study supports a 1 mg Pb/kg BW/day TRV-Low.	Khalil-Manesh et al. 1993 (29)
Rat (55-60 days old, pregnant, Long-Evans; pups exposed via breast milk until weaning)	0, 109, 1090 mg/L[t]	0.225 kg[u]	0.026 L/day[j]	Parturition (day 0) - weanling (day 21). Pups exposed via breast milk and effects followed through 90 days in age	Pb Ac	Drinking water	12.6[b]	ND	Most significant effects found in pups, including retinal degeneration; loss of rod cells; reduction in rod cell sensitivity; reduced rhodopsin content; reduced cGMP phospohodiesterase activity; and reduced cGMP concentration in retina	Loss of visual acuity, particularly night vision, seen as a significant adverse ecologically-relevant effect. Lowest effects dose estimated in dames that causes adverse effects in pups is slightly greater than 10 mg/kg BW/day. The BTAG determined that this study supports a 1 mg Pb/kg BW/day TRV-Low.	Fox et al. 1997 (30)

FOOTNOTES

Pb Ac = lead acetate
Pb S = lead sulfate
Pb N = lead nitrate
Pb O = lead oxide

BW = body weight
GD = gestational day
MOA = Mode of administration
LOAEL = lowest observable adverse effect level
NOAEL = no observable adverse effect level
N/A = not applicable or not available.
N/D = not determined.

1. Parenthetical comments include age of test species when significant effects were observed, gender, and strain of test species evaluated.
2. Elementation concentrations of lead in food or water tested in the study, unless otherwise noted.
3. Dose reported in the study or estimated using average body weight and intake rates provided in the study.

a. Average of initial six week old male rat BW (0.112 kg; http://www.criver.com/techdocs/tech_pdf/weightstudy.pdf) and eleven week old male rat BW (0.300 kg; http://ehp.niehs.nih.gov/ntp/hcrs/growth/grorafee.gif).
b. Dose estimated because BWs, drinking water rates, and/or feed intake rates are not reported in the study.

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c. Elemental concentration of lead determined assuming atomic weight of Pb is 207.2 and molecular weight of Lead(II) Acetate Trihydrate (commercially available form of lead) is 379.33. Therefore, elemental concentration of lead administered assumed as 55% of the total mass of lead acetate trihydrate.
d. Average of experimental group initial (0.173 kg) and final (0.276 kg) BWs.
e. Food intake rate estimated by Nagy (2001), where $0.332(\text{g BW})^{0.774}$ = g food/day.
f. Default BW for rat (USEPA 1988).
g. Elemental concentration reported by the authors; however it is not clear in the methods whether concentration reported reflects elemental Pb or Pb nitrate. Therefore, elemental concentration of lead administered assumed as 63% of the total mass of lead nitrate.
h. Estimated BW of 14 week old Sprague-Dawley rat in study (see: http://www.taconic.com/addinfo/sdweight.htm).
i. Drinking water intake rate estimated by Calder and Braun (1983), where 0.099(kg BW)0.9 = L water/day
j. Maternal dose through pregnancy resulting in adverse effects on pup.
k. Dose reported in the study, converting lead acetate dose to elemental lead dose as described in footnote c above and assuming that doses were administered 5 days per week.
l. Average of initial (assuming 3 week old male weanling rat = 0.033 g; see http://www.criver.com/techdocs/tech_pdf/weightstudy.pdf) and final mean BW of 10 ppm treatment group reported in the study (0.310 kg).
m. Form of lead administered not reported, however actual concentrations of elemental lead (by atomic absorption assay) in drinking water were reported.
n. Dose reported by ATSDR (1999).
o. Maternal BW at gestational day 11 (approximate midpoint of exposure regime).
p. Average water consumption rate in 10 mg/L dosage group.
q. Average BW of five week old female in-bred rat (see: http://www.criver.com/techdocs/tech_pdf/weightstudy.pdf)
r. Estimated average adult cotton rat BW over duration of exposure (average of initial body weight = 0.170 kg and maximum adult body weight reported in Silva and Downing [1995] = 0.211 kg).
s. Estimated average BW of male Sprague-Dawley rat over duration of exposure (8 to 52 weeks in age; see: http://www.taconic.com/addinfo/sdweight.htm).
t. Elemental Pb concentration reported in the study.
u. Estimated average body weight of 55-75 day old female Long-Evans rat (from control group reported in http://web6.duc.auburn.edu/~newlamc/personal/ResearchWarehouse/aging_unmasks_adverse.pdf).

Table 5. Estimated Lead Dose (mg/kg BW/day) Consumed by Females[1] Exposed via Drinking Water as Reported by Kimmel et al. (1980)[2]

Pb Exposure Group (mg/L)	Wean-ling	Prepregnancy Period (Weeks)					Pregnancy (Weeks)			Postpregnancy (Weeks)		Estimated 95th UCL of the Mean Pb Dose Over Entire Exposure Period
		1	2	3	4	5	1	2	3	1	2	
5 (Group A)	1.62	1.27	1.18	0.79	0.71	0.59	0.80	0.79	0.71	0.73	0.96	
5 (Group B)	1.08	1.43	0.78	0.85	0.86	1.29	0.74	0.62	0.64	1.00	0.85	1.0[3] NOAEL
25[4] (Group B)	5	5	5	4	4	5	4	4	3	4	9	5.6 LOAEL

1. No dosing data are presented for males in the study, therefore the BTAG assumed that male and female exposure was equivalent.
2. Values presented are the median dose level (mg/kg BW/day) calculated for each treatment group (see Kimmel et al. [1980], Table 1 and second paragraph of Results on pg. 32 of the publication).
3. Value listed is the 95th upper confidence limit on the arithmetic mean combining Groups A & B dose levels.
4. The 25 mg/kg BW/day dose group was only represented by Group B.

NOAEL = No Observable Adverse Effects Level for renal effects
LOAEL = Lowest Observable Adverse Effects Level for renal effects

Figure 1. Lead Toxicity Reference Values for Intermediate Oral Exposure to Small Mammals based on a combined plot of NOAEL and LOAEL (ATSDR 1999*)

* Agency for Toxic Substances and Disease Registry (ASTDR). 1999. Toxicological Profile for Lead. U.S. Department of Health and Human Services. Atlanta. pp. 587.

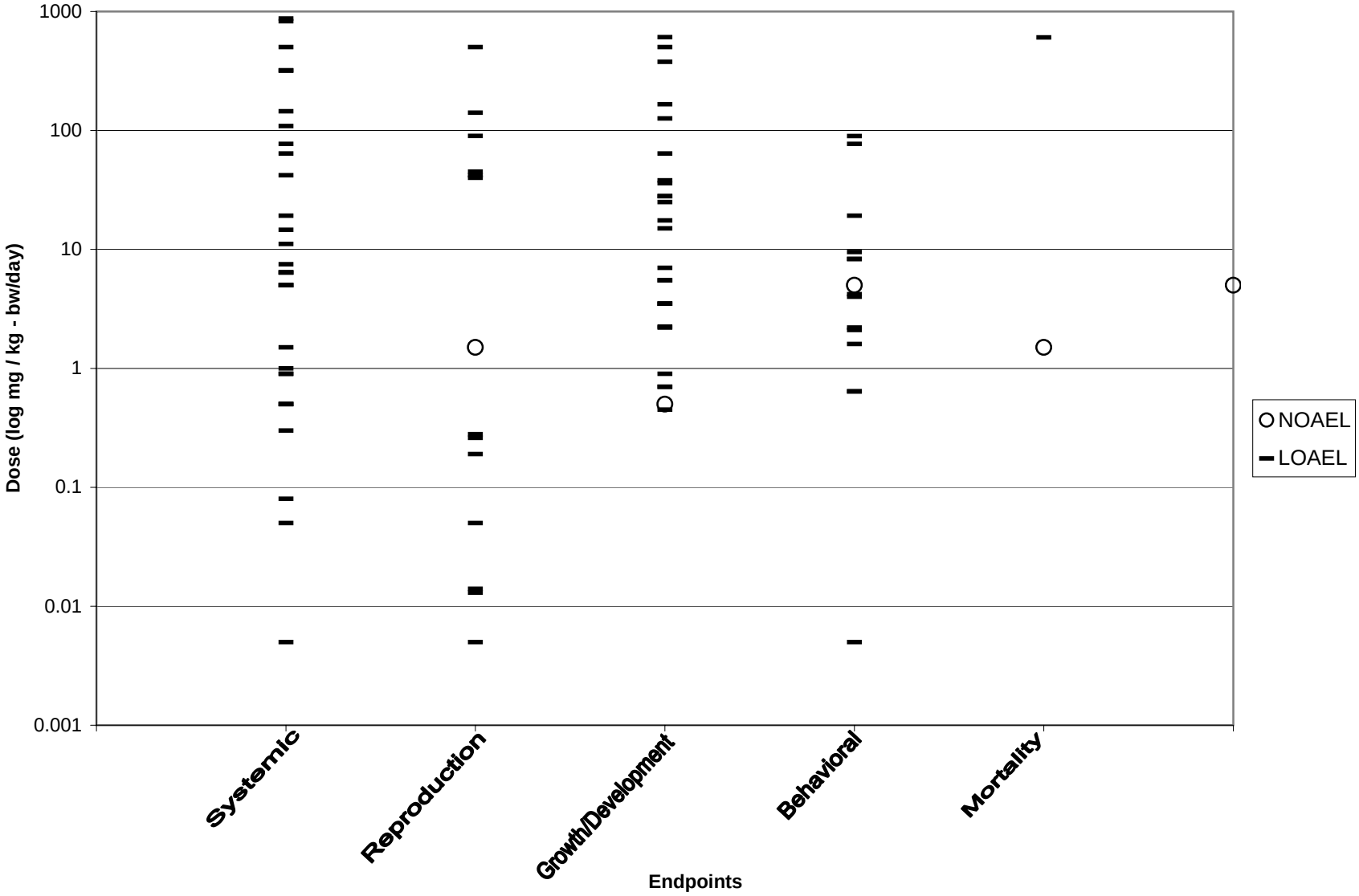

Figure 2. Lead Toxicity Reference Values for Chronic Oral Exposure to Small Mammals (ATSDR 1999*)

* Agency for Toxic Substances and Disease Registry (ASTDR). 1999. Toxicological Profile for Lead. U.S. Department of Health and Human Services. Atlanta. pp. 587.